

# A Comprehensive Review on Adenoviruses Infections in Fowl: Epidemiology, Forms, Diagnosis, and Control

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## ABSTRACT

Fowl Adeno Viruses (FAdVs) are non-enveloped and double-stranded DNA viruses. They include eight species (FAdVs A-E) and 12 serotypes (FAdVs-1 to -8a and -8b to -11). Strains of FAdVs have been widely distributed in different countries all over the world. Most avian species are susceptible to FAdVs infections. Vertical, horizontal, and mechanical infections and transmissions have been recorded in different forms of FAdVs infection. There are many forms of FAdVs infections according to the groups (including three groups) of the virus. Group I usually causes inclusion body hepatitis, hydropericardium syndrome, quail bronchitis, pancreatic erosions, gizzard erosion, cardiovascular, hematopoietic, and respiratory systems disorders. Group II is incriminated in diseases, such as turkey hemorrhagic enteritis, marble spleen disease in pheasants, and splenomegaly in chickens. In addition, group III is responsible for egg drop syndrome in laying chickens. Diagnosis of FAdVs infections is not based on the signs and lesions. However, microscopic detection of specific lesions and inclusion bodies may be suggestive. Diagnosis is mainly based on the conventional traditional isolation in embryonated eggs of different avian species as well as on tissue culture of avian origin. Molecular diagnostic techniques are now widely used for rapid and confirmative detection of FAdVs. The application of sanitary and hygienic measures in poultry farms is very important to prevent FAdVs outbreaks. However, different types of inactivated, living attenuated as well as recombinant vaccines have been developed and used in several countries to overcome different forms of FAdVs. Therefore, this review article deals with the FAdVs susceptibility and transmission, the etiological agent, forms of infections, and diagnosis as well as different methods of prevention and control.

**Keywords:** Egg drop syndrome, Fowl adenoviruses, Hydropericardium syndrome, Inclusion body hepatitis, Quail bronchitis, Turkey hemorrhagic enteritis.

## INTRODUCTION

During the last decade, the incidence of viral diseases of poultry has been increased. Adenoviruses isolated from poultry are termed as Fowl Adenovirus(s) (FAdVs). These viruses are a diverse group of pathogens that cause a variety of important infections in poultry (Fadly and Winterfield, 1973). Reduced humoral and cell-mediated immune competence to various antigens and vaccines is the immunosuppressive potential of FAdVs (Singh et al., 2006; Schonewille et al., 2008).

Avian adenoviruses are non-enveloped and double-stranded DNA viruses (Hess, 2000; Zhao et al., 2015). There are eight species (FAdVs A to E) (Hess, 2000) and 12 (FAdVs-1 to -8a and -8b to -11) serotypes of FAdVs

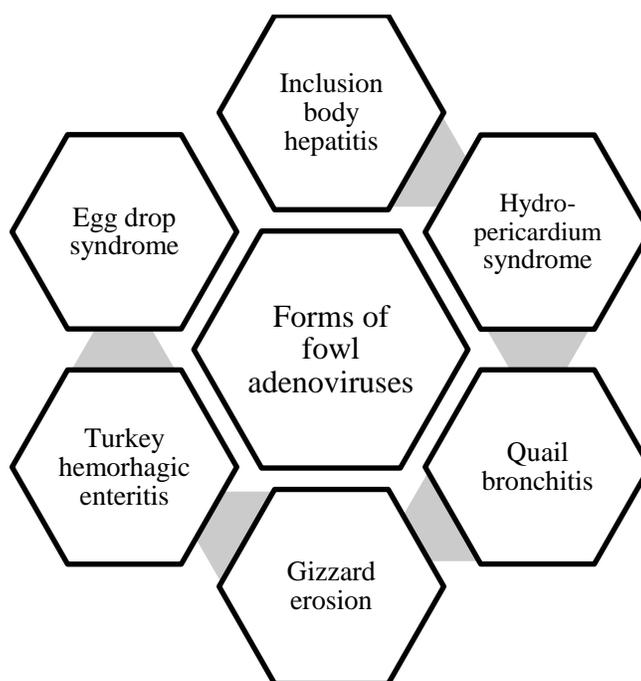
(Meulemans et al., 2004). Several outbreaks of FAdVs infections have been demonstrated in poultry farms worldwide as in the USA, Europe, Australia, and Asia. For example, strains of FAdVs-2, -11, -7, and -8 have been detected in Europe and FAdVs -7 in North America (Grgic et al., 2011; Kajan et al., 2013; Schachner et al., 2016), FAdVs-4 in Asia (Park et al., 2017; Niu et al., 2018) and FAdV-2 and FAdV-8b in South Africa (Joubert et al., 2014; Maartens et al., 2014).

The pathogenesis of FAdVs infection is affected by the serotypes or genotypes of the virus. The pathogenicity of FAdVs varies from 10-90% depending on the virulence of the virus strain (Li et al., 2017; Schachner et al., 2018). The disease conditions associated with FAdVs infections can vary based on the group of the virus. Group 1 may

cause Inclusion Body Hepatitis (IBH, Zhao et al., 2015), Hydropericardium Syndrome (HPS, Schonewille et al., 2008; Zhao et al., 2015), Quail Bronchitis (QB, Olsen, 1950), pancreatic erosions (McFerran and Smyth, 2000; Nakamura et al., 2002), Gizzard Erosion (GE, Blicharz et al., 2011; Mase and Nakamura, 2014) and cardiovascular, hematopoietic and respiratory systems disorders (Cheema et al., 1989; Erny et al., 1995). Group II is considered as the cause of diseases like Turkey Hemorrhagic Enteritis (THE), Marble Spleen Disease (MSD) in pheasants, and

splenomegaly in chickens. In addition, group III is responsible for Egg Drop Syndrome (EDS) in laying chickens (McFerran et al., 1978; Del Valle et al., 2020). Different forms of FAdVs infections in poultry are summarized in Figure 1.

Accordingly, the present review article focused on FAdVs infections regarding susceptibility and transmission of infection, causative agent, different forms of infections, diagnosis along with prevention and control methods.



**Figure 1.** Different forms of fowl adenoviruses infections in poultry

### **Susceptibility to fowl adenoviruses**

Fowl adeno viruses are heterogeneous and have been detected in at least 40 species of vertebrates, including mammals, birds, amphibians, reptiles, and fish (Benko and Harrach, 2003; Ko, 2005). Infections with FAdVs are known as ubiquitous primary or secondary pathogens and have been isolated from either healthy or diseased birds (Toro et al., 2000; Niczyporuk et al., 2012; Niczyporuk et al., 2013). Fowl adeno viruses have been commonly identified in different avian species such as chickens, turkeys, ducks, and geese (Hess, 2013; Pan et al., 2017a). About 31 wild bird species have been reported to have a role in the distribution of FAdVs outbreaks (Hess, 2000). It has been recorded that falcons (Singh et al., 2002; Mohamed et al., 2018), pigeons (Steer et al., 2009), wild black kites (Kumar et al., 2010), guinea fowl (Zellen et al., 1989), raptors (Ramis et al., 1992), parrots (Bradley et al.,

1994), kestrels (Schelling et al., 1989), tawny frogmouths (Rosen et al., 1965), and common buzzards (Frolich et al., 2002) are susceptible to FAdVs infections. It is clear that, as the age of the host increases, the degree of FAdVs multiplication in the host decreases, and consequently the losses also decrease (Rahimi and Minoosh, 2015).

### **Transmission of fowl adenoviruses**

The transmission of FAdVs may occur vertically through eggs as the virus can spread from the dam to the offspring (Grgić et al., 2006; Philippe et al., 2007; Hafez, 2011, Hess, 2012). Viruses of adeno groups are rapidly transmitted among flocks (Cowen, 1992) through both oral-fecal (lateral) and mechanical means of infections. Airborne infection is a possible means of transmission, especially in QB infection (DuBose, 1967). Moreover,

wild birds have a role in the spread of FAdVs infections as a mechanical means of FAdVs transmission.

Experimental inoculation of FAdVs liver homogenate using subcutaneous route succeeded in the induction of typical disease conditions (Asrani et al., 1997; Chandra et al., 1997). However, the induction of FAdVs was also reported by the route of oral inoculation (Naem et al., 2001).

### The etiological agent

Adenoviruses belong to the family Adenoviridae which is classified into five genera; *Atadenovirus*, *Siadenovirus*, *Mastadenovirus*, *Aviadenovirus*, and *Ichtadenovirus* (Davison et al., 2003). Avian adenoviruses belong to group I Aviadenovirus genus and family Adenoviridae. Group I includes 12 serotypes of FAdVs that are isolated from a variety of avian species with a common group of antigens (Kawamura et al., 1964; McFerran et al., 1975; Toro et al., 2000). Moreover, the viruses in group II share a common group of antigens that differentiates them from other groups (Domermuth et al., 1980).

By electron microscopy, FAdVs have been found to be non-enveloped, and contain linear 35-36 kbp double-stranded DNA with icosahedral morphology and a diameter of 70-90 nm (Nicklin et al., 2005; Steer et al., 2009; Robinson et al., 2011). The guanine/cytosine content of the viral DNA is 53–59%. The genome of the virus encodes 40 proteins, and the ends of the viral genome are attached to terminal proteins. The genome of FAdVs consists of 13 structural proteins. The primary major structural viral proteins capsid include hexon, knobbed fiber, and penton (Russell, 2000; Russell, 2009) while the other minor structural proteins are cement proteins (VI, VIII, IX, IIIa) and core proteins (V, VII, Mu, terminal protein, IVa2, protease). The viral capsid consists of subunits of 720 hexon set as 240 trimers and 12 triangular penton capsomers with one or two protruded fibers (Viralzone, 2015). It has been demonstrated that penton and fiber interact with the receptors of infected cells during the viral penetration (Jucker et al., 1996; Fingerut et al., 2003).

The size of the hexon gene is different among the viruses according to the serotype, as the largest one contains 967 amino acids. There are four types of hexon; H1, H2, H3, and H4 (Burnett, 1985). The type H1 hexons are peripentonal, 60 in number, and associated with pentons at the 12 apices. The other hexons are a group of 9 on the 20 faces of the icosahedra. However, types H2 and H3 hexons are on the twofold and on the threefold axes,

respectively, and the remaining ones are H4. There are nine hypervariable regions at the top of the hexon molecule (Saban et al., 2006). Hexons are highly susceptible to mutations due to the presence of these hypervariable regions. In addition, these hexons could be used for serotyping as they carry the major neutralizing epitope (Rux et al., 2003; Roberts et al., 2006; Matsushima et al., 2011).

The fiber contains receptors of cell surface binding and virulence epitopes. Thus, fiber protein is responsible for the attachment of the viral capsid to the host cell surface by its interaction with cellular receptors (Nicklin et al., 2005; Russell, 2009). It has been found that FAdVs have one long and other short fibers with different receptors. Thus, one fiber is responsible for virus attachment and the others are for internalization (Hess et al., 1995; Tan et al., 2001). The fiber consists of the knob, shaft, and tail. The fiber knob determines the haemagglutinating characters of the virus that are used for the classification of the viral species (A-F) (Pehler-Harrington et al., 2004). Moreover, the knob plays an important role in the synthesis of fiber protein and encapsidation (Henning et al., 2006). It has been documented that the fiber comprises about 582 amino acids that bind to the penton base (Zubieta et al., 2005).

The penton consists of base and fiber protein. It has been documented that the penton base is sensitive to heat, trypsin, pH, and changes in ionic strength (Wiethoff et al., 2005). The penton plays an important role in the penetration of the virus into the host cell (Fender et al., 2005), and interacts with cellular contents, as neutralizing antibodies against the penton have been detected in the sera (Hong et al., 2003). Furthermore, the penton interacts with capsomers, hexons, and other proteins for stabilization of the capsid.

There are some types of important non-structural proteins named 100K and 33K. The 100K protein helps intracellular transport and folding of hexon during the replication of the viruses of groups B and C in insects (Hong et al., 2005). Antibodies against these proteins have been used to differentiate the vaccinated infected from non-vaccinated infected birds with FAdVs (Shah et al., 2015), as antibodies were detected in challenged chickens, but not vaccinated ones (Xie et al., 2013). It has been shown that FAdVs are resistant to dryness (Domermuth and Gross, 1971; Domermuth and Gross, 1972), as they can remain viable in contaminated carcasses or droppings for up to seven weeks. Accordingly, it is clear that FAdVs can survive among production cycles thorough out the cleaning and disinfection processes.

## Forms of fowl adenovirus infections

### *Inclusion body hepatitis*

Inclusion body hepatitis is an economically important acute disease affecting poultry worldwide (Schachner et al., 2016; Schachner et al., 2018). There are some other synonyms of IBH like Angara disease, Litchi heart disease, and infectious hydropericardium (Abdul-Aziz and Hassan, 1995; Mazaheri et al., 1998). The disease was first described in chicken flocks in the USA in 1963 (Helmboldt and Frazier, 1963), and then rapidly spread over the world, including Australia, Europe, Canada, India, Turkey, Saudi Arabia, and Egypt.

First, IBH is classified as group I FAdVs-8 (Reece et al., 1987; Erny et al., 1991). Later on, it has been found that all IBH virus strains isolated from chickens were assigned to FAdVs-1-8a,8b-12 serotypes, and species FAdVs-D and/or E (Morshed et al., 2017; Schachner et al., 2018). It has been shown that FAdV-4 is closely related to FAdV-10 using immunological and molecular techniques (Erny et al., 1991). A closer genetic relationship has been confirmed in FAdVs species D and E (Marek et al., 2013). Moreover, FAdVs-2, -3, -9 and -11 (D) as well as -6, -7 and 8 a, b (E) are considered as the causative agents of IBH (Ojkic et al., 2008; Steer et al., 2011; Schachner et al., 2016). Based on the genomic sequence of a non-pathogenic strain of FAdVs-11 and the pathogenic one, only 0.8% differences have been found among the non-pathogenic strains and the virulent ones (Absalón et al., 2017).

Epidemiological investigations on IBH outbreaks in Canada revealed that FAdVs-2, -6, -7, -8 a,b, and -11 (D) have been discovered in broiler flocks (Gomis et al., 2006; Ojkic et al., 2008; Grgic et al., 2011). In Japan, FAdVs-2 (D) strains were isolated from outbreaks in broiler farms in 2010 (Nakamura et al., 2011; Mase et al., 2012). Furthermore, FAdVs-8b (E) (Zadravec et al., 2013) and FAdVs-7 (Niczyporuk, 2017) in broiler chickens were confirmed to be the causative agent of IBH in Slovenia and Poland, respectively. Outbreaks caused by FAdVs-2, -4, -8a, b, and -11 have been reported in New Zealand (Christensen and Saifuddin, 1989), Korea (Choi et al., 2012), Hungary (Kajan et al., 2013), and China (Zhao et al., 2015). Similarly, outbreaks of IBH in broiler chickens caused by FAdVs-8b or -11 have been recorded in Australia, Austria, Spain, and South Africa (Maartens et al., 2014; Schachner et al., 2016; Oliver-Ferrando et al., 2017). During 2012 in Iran, the virus has been demonstrated in an outbreak in a 21-day-old broiler chicken farm with 14% mortalities (Rahimi and Minoosh, 2015). In addition, two FAdVs-11 and -8b (D and E) were

related to Iranian outbreaks of IBH that occurred from 2013 to 2016 (Hosseini and Morshed, 2012; Nateghi et al., 2014; Morshed et al., 2017). Moreover, the first case report of isolation and identification of FAdVs-8b from an outbreak of IBH in broiler farms in Turkey was detected by Cizmecigil et al. (2020). Radwan et al. (2019) and El-Tholoth and Abou El-Azm (2019) detected the presence of FAdVs-8a (E) in Egyptian broiler chicken flocks, while Elbestawy et al. (2020) have recently isolated 17 strains of FAdVs-2 and -11 (D) from chickens. Mohamed et al. (2018) molecularly characterized FAdVs-2 (D) and -6 (E) as the causative agents of IBH in both broiler chickens and falcon in Saudi Arabia.

It has been suggested that immunosuppressive diseases like infectious bursal disease (Fadly et al., 1976), chicken infectious anemia (Markowski-Grimsrud and Schat, 2003), and Marek's disease (Niczyporuk et al., 2012) may play a role in the transmission of IBH and its increasing mortalities (El-Tholoth and Abou El-Azm, 2019). However, it has been recorded that IBH could induce independent mortalities without the presence of other immunosuppressive factors (Christensen and Saifuddin, 1989; Gomis et al., 2006; Ojkic et al., 2008).

The course of IBH occasionally continues for two to three weeks. In broiler chicken flocks up to five weeks old, the mortality rate of IBH varies from negligible to 5-10% (McFerran and Smyth, 2000), and may reach 30% for a short time (average five days) (Alvarado et al., 2007). Very high mortality rates (60-70%) have been recorded in outbreaks associated with IBH in India and Canada (Dahiya et al., 2002; Gomis et al., 2006, respectively). Some outbreaks have been reported in layers and broiler breeders (McFerran and Adair 2003; Hess, 2013; Schachner et al., 2016). The variable mortalities may be related to the pathogenicity of the virus strain, the host's age and susceptibility, and the presence of concurrent immunosuppressive diseases (Grgic et al., 2011).

In post-mortem lesions, broiler and layer chickens infected with IBH virus revealed swollen, pale, necrotic and friable, and hemorrhagic livers as well as petechial and ecchymotic hemorrhages on the skeletal muscles (McFerran et al., 1976; Mase et al., 2012; Ahamad et al., 2016). Splenomegaly and moderate to severe lymphoid atrophy in the bursa of Fabricius were also recorded in falcons with IBH (Schrenzel et al., 2005). A pale and enlarged pancreas could also be observed (Pilkington et al., 1997). Infection with IBH has been represented in three stages based on the hepatic lesions' severity; the incubation stage (one to three days of infection), the degeneration stage (four to seven days of infection), and

the convalescence stage (14 days pos-infection) (Steer et al., 2015).

The histopathological examinations of the affected liver with IBH showed variable areas of multifocal hepatocellular necrosis and vacuolar degeneration as well as lymphoid infiltration (Wilson et al., 2010; Schachner et al., 2018). In the degenerated hepatocytes, big, circular, or irregular-shaped intranuclear basophilic inclusion bodies could be detected (Grimes et al., 1977; Steer et al., 2015; Matos et al., 2016). However, acidophilic inclusion bodies that contained few or no virus particles, and corresponded to fibrillary and granular material have also been detected (Itakura et al., 1974). Inclusion bodies could be observed also in the liver, pancreas, and spleen indicating the replication of adenovirus in these organs (Cook, 1983). Matos et al. (2016) recorded that these inclusions could be mostly detected from six to nine days after infection

#### ***Hydropericardium syndrome***

Hydropericardium Syndrome (HPS) was first reported in Karachi, Pakistan in 1987 in three to six-week-old broiler chickens (Khawaja et al., 1988), then it was spread in different areas of the country (Anjum et al., 1989; Khan et al., 2005). Several outbreaks of HPS have been recorded in many countries, including India (Dahiya et al., 2002; Rahul et al., 2005; Mittal et al., 2014), Iraq (Abdul-Aziz and Al-Attar, 1991), Hungary (Kajan et al., 2013), Canada (Grgic et al., 2011), Poland (Niczyporuk, 2016), Mexico, Peru, Chile and Ecuador, Russia, Korea (Kim et al., 2008; Choi et al., 2012), China (Liu et al., 2016; Pan et al., 2017b), and Japan (Abe et al., 1998; Mase et al., 2012).

The main causative agent of HPS is FAdVs-4 (C) (Nakamura et al., 2000; Mase et al., 2010; Asthana et al., 2013). Although HPS is a disease of chickens, it has also been detected in ducks, pigeons, and quails in rare cases (Cowen, 1992; Naeem and Akram, 1995; Lobanov et al., 2000). Hydropericardium syndrome is an infectious and highly pathogenic disease that primarily occurs in young broiler chickens (Khawaja et al., 1988; Akhtar, 1994), and is characterized by a low morbidity rate. The mortality rate is variable (Shane, 1996; Mansoor et al., 2011), ranging from 20% to 75% (Cheema et al., 1989), 30-80% (Ahmad et al., 1989; Kumar et al., 1997), or 30-60% (Zhao et al., 2015) in broiler chickens starting at the third week of age, and peaks for four to eight days. Sometimes, adult broiler breeders could be affected (Asrani et al., 1997) with mortalities reached up to 6.4% (Abe et al., 1998). Deaths may be due to pericardial effusion, and lung and kidney edema (Niu et al., 2019).

Gross lesions of HPS have been manifested as clear, straw-colored watery or jelly-like fluid in the pericardial sac with the misshapen and flabby heart as well as hemorrhages on the heart muscles and other organs (Asrani et al., 1997; Kumar et al., 1997). Congestion and edema of lungs, enlarged, pale and friable liver, pale kidneys, and swollen bursa of Fabricius have been also observed (Cheema et al., 1989; Ganesh and Raghavan, 2000; Ahmad et al., 2011).

#### ***Quail bronchitis***

Quail bronchitis is an acute fatal and highly contagious respiratory disease of young bobwhite quails (*Colinus virginianus*) with severe economic losses (Barnes, 1987). Chicken Embryo Lethal Orphan Virus (CELOV) virus is an endogenous virus that was isolated from embryonated chicken eggs, and it is similar to QB Virus (QBV) in serological characteristics, in the lesions and death pattern induced in chicken embryos (Yates and Fry, 1957; DuBose and Grumbles, 1959). Accordingly, both QBV and CELOV are considered the same type of strain for group I and serotype 1 of FAdVs (Calnek and Cowen, 1975). Both viruses could cause bronchitis after experimental inoculation in quails (DuBose and Grumbles, 1959). However, neither CELOV nor QBV has been found to induce diseases in species other than quails.

Quail Bronchitis was first detected by Olsen (1950) from an epornitic on a game farm in 1949 in West Virginia, United States. Later on, respiratory diseases have been discovered on quail farms in Taxes (DuBose et al., 1958; DuBose and Grumbles, 1959). The QBV belongs to FAdVs-1 group A (DuBose et al., 1958). In Minnesota, the United States, Singh et al. (2016) reported the isolation and molecular identification of QBV-positive cases from five to eight-week-old bobwhite quails suffering from respiratory signs and lesions as well as elevated mortalities. In the present study, the nucleotide sequences of the four isolates of FAdVs showed 99% identity with CELO strain of FAdVs group A. In addition, QBV isolates clustered closely with FAdVs group A and were different from FAdV groups B-E and FAdVs of turkeys, ducks, geese, and pigeons.

Captive quail chickens (less than three weeks of age) are severely affected with a morbidity rate approaching 100% and a mortality rate of more than 50% (Jack and Reed, 1990). Young chickens and turkeys could be naturally or experimentally infected with QBV without apparent clinical signs (Olsen, 1950; Yates and Fry, 1957). The disease incubation period is about two to seven days. Sudden onset of tracheal rales, coughing, sneezing, and

high mortalities are the most pronounced signs in the affected quails (DuBose et al., 1958; DuBose, 1967). Swelling of the infraorbital sinuses, conjunctivitis, and other general signs have also been reported (DuBose and Grumbles, 1959). The course of the disease takes one to three weeks (Olsen, 1950). Post-mortem lesions of QBV appear as tracheitis with a severe amount of mucus, lung congestion, fibrinous airsacculitis, liver necrosis, spleen enlargement, and accumulation of urates on the internal organs (Chew-Lim, 1980). Histopathological examination revealed "round-cell" infiltration with follicle formation and intact overlying ciliated epithelium in the trachea with the presence of basophilic intranuclear inclusions in the affected epithelium (Jack and Reed, 1990; Singh et al., 2016). Dhillon et al. (1982) observed leukocytic transmigration and exudation in the bronchi, trachea, and pulmonary parenchyma with diffuse bronchiolitis and pneumonia. Intranuclear inclusion bodies have been seen in the tracheal mucosa two days post-QBV challenge and deciliation and desquamation of epithelium on days four and five post-challenge, respectively (Jack et al., 1994).

#### ***Gizzard erosion***

The first detection of gizzard erosion was in 1993 by Tanimura et al. (1993). The main causes of GE are FAdVs-1 (S) and FAdVs-8 (E) as recorded in Japan, England, Italy, Germany, Korea, Poland, and Iran (Manarolla et al., 2009; Grafl et al., 2015), however, experimental infection with other serotypes as FAdVs-4, 8b, and 11 have been implicated in GE (Okuda et al., 2004; Okuda et al., 2006; Steer et al., 2015). Although the CELO (FAdV-1) strain does not induce GE in chickens (Marek et al., 2010), some strains can induce this lesion in Specific Pathogen Free (SPF) chickens and commercial layer chickens (Ono et al., 2004; Manarolla et al., 2009).

Broiler and layer chickens are the natural host of GE (Tanimura et al., 1993). However, bobwhite quails showed GE in North America (Goodwin, 1993).

Affected gizzards showed variable sizes of brown to black erosion areas (Manarolla et al., 2009). Recently, a post-mortem examination of 48 gizzards collected from seven broiler chicken farms in Iran revealed the presence of perforation, roughening, and discoloration of the koilin layer of gizzard (Mirzazadeh et al., 2019).

Manarolla et al. (2009) demonstrated microscopically multifocal or extensive degeneration of the cuticle's koilin layer with entrapped erythrocytes, ulcers, or sloughing/flattening of glandular epithelium of the gizzards and the presence of heterophils, lymphocytes, macrophages, and plasma cells as well as intranuclear

basophilic inclusion bodies. Ono et al. (2003) observed typical microscopic lesions after experimental oral and ocular inoculations of one, three, and five-week-old broiler chickens with FAdV-1 strain. In Korea, experimental oral inoculation of one-week-old SPF chickens with FAdV-1 indicated no signs, but the gizzard showed severe degeneration and necrosis of glandular epitheliums with eosinophilic inclusion bodies in histopathological examination (Lim et al., 2012). Similarly, dissociation of cellular debris in the koilin layer, mild to severe inflammatory cells infiltration of the mucosa, submucosa, and musculosa with inflammatory cells as well as desquamation of epithelial cells in the glandular mucosa (Mirzazadeh et al., 2019).

#### ***Turkey hemorrhagic enteritis***

Turkey Hemorrhagic Enteritis (THE) is a viral disease in turkeys characterized by acute signs of depression, bloody diarrhea, increased mortalities, and transient immunosuppression (Saif, 1998; Hoerr, 2010). The disease causes severe economic losses due to acute sudden deaths up to 80%, blood loss, and anemia as well as immuno-suppression with secondary bacterial or parasitic infections in sub-clinical conditions (Chandra and Kumar, 1998; Koncicki et al., 2012). This immunosuppression is expressed by decreasing the immune response to various vaccines as Newcastle disease (Nagaraja et al., 1985) and Metapneumo viruses vaccines (Chary et al., 2002).

The first distinguishing of THE was earlier in the USA without the identification of the exact causative agent (Pomeroy and Fenstermacher, 1937; Gale and Wyne, 1957). After that, the researchers supposed that the cause of THE could be filtrated through a 0.22-micron filter (Gross and Moore, 1967), and that result proved that the cause of THE is a virus (Domermuth and Gross, 1971). In 1974, adeno-like virus particles were detected in the spleen and intestine of the affected turkeys (Carlson et al., 1974). Then, THE has been discovered in different parts all over the world as Canada (Itakura et al., 1974), Japan (Fujiwara et al., 1975), England (Arbuckle et al., 1979), Australia (Tham and Critchley, 1981), the USA (Ianconescu et al., 1985) and Spain (Gomez-Villamandos et al., 1994).

The THE virus (THEV) is postulated as *siadenovirus* A, a member of the family Adenoviridae, genus *Siadenovirus* (Pierson and Fitzgerald, 2013). The results of molecular characterization of hexon gene revealed that the THEV is related to FAdV-3 which is closely related to that of penguin adenovirus (Lee et al., 2016). However, data

about the phylogenetic analysis and the sequence data of THEV are limited and scarce. The same virus was related to three to eight months old pheasants with MSD (Fitzgerald and Reed, 1989) and avian adenovirus splenomegaly in broiler chickens. This virus is serologically indistinguishable from THEV with diversity only at the genomic level.

Although turkey is the natural susceptible host, antibodies against THDV have been found in other species as chickens (Domermuth et al., 1979), quails, peafowl, and chukars (McFerran and Smyth, 2000). The disease is more pronounced in six to 11 weeks old turkeys. Birds younger than four weeks old are less susceptible which may be due to the presence of maternal antibodies that protect turkeys in the first week of life (Fadly and Nazerian, 1984).

Following entering of THEV to the body of the bird, the virus multiplies in the gastrointestinal tract, then migrates to the blood inducing primary viremia, and spreads to some immune organs like the spleen and bursa of Fabricius where Immunoglobulin (Ig) M bearing B-lymphocytes (Rautenschlein et al., 1998). So, THEV is regarded as a lymphotropic and lymphocytopathic (Fitzgerald and Reed, 1991) as well as macrophages target the virus (Suresh and Sharma, 1995). In the stage of transient immunosuppression, there is a reduction in antibody production and phagocytosis process, as well as the release of prostaglandins and histamine by mast cells (Rautenschlein, 2000). Due to the presence of a high level of the virus in the intestine, intestinal congestion and hemorrhages can be observed (Hussain et al., 1993; Dhama et al., 2017).

Affected turkeys with THE manifest general signs with severe bloody diarrhea as the skin and feathers around the vent are soaked with blood. Deaths usually occur five to six days after the onset of bloody diarrhea. The mortality rate may reach up to 60% (Pomeroy and Fenstermacher, 1937; Gale and Wyne, 1957). Signs usually subside within five to 10 days post-infection, and survived turkeys show permanent immunosuppression. Recovered birds from THE may show persistent infection, and become chronic carriers (Beach et al., 2009). In addition, these birds become highly susceptible to secondary diseases like colibacillosis, bordetellosis, mycoplasmosis, clostridia, turkey rhinotracheitis, and coccidiosis (Giovanardi et al., 2014). Avirulent strains of THEV can enhance sub-clinical infections inducing strong immunosuppression and losses due to secondary infections (Tykałowski and Koncicki, 2017; Tykałowski et al., 2019).

Dead birds show severe hemorrhagic enteritis and typhlitis with the pale anemic carcass. The gastrointestinal tracts of turkeys are severely distended with blood (Gross and Moore, 1967). The lesions of the intestines consist of congestion, petechial hemorrhages, and sometimes the presence of the fibrino-diphtheritic membrane. Other characteristic lesions like severely enlarged and mottled or marbled spleen (Itakura and Carlson, 1975; Cobb and Smith, 2015), congested lungs, enlarged liver, and petechial hemorrhages all over the organs are also recorded.

### ***Egg drop syndrome***

The first description of a syndrome causing low egg production and soft-shelled or shellless eggs in a laying fowl flock was in the Netherlands in 1967 (Van Eck et al., 1976). In Northern Ireland, haemagglutinating FAdVs were isolated from laying hens (McFerran et al., 1977; McFerran et al., 1978; McCracken and McFerran, 1978). Later, the disease has been termed Egg Drop Syndrome (EDS) and discovered in many countries all over the world (Firth et al., 1981; Lu et al., 1985). However, antibodies against the EDS virus (EDSV) have been detected in chickens in Denmark, Brazil, Mexico, Nigeria, and New Zealand (Nawathe and Abegunde, 1980; Howell, 1982).

It has been recorded that EDSV is designated as duck adenovirus 1 belonging to *Atadenovirus* genus of the Adenoviridae family (Hess et al., 1997; Dán et al., 1998). Recently, FAdVs-4 has been molecularly detected and isolated from the oviduct of layer chicken flocks with poor egg production in Eastern Japan (Del Valle et al., 2020).

Although waterfowl as ducks and geese are the most common natural hosts for EDSV infections (Schlör, 1980; Zsak et al., 1982; Bartha and Mészáros, 1984). Turkeys can get the infection with ESDV after an experimental infection (Parsons et al., 1980) but without clinical signs. Besides, antibodies against EDSV have been found in wild birds (Malkinson and Weisman, 1980), wild waterfowl (Schlör, 1980; Gulka et al., 1984), and pigeons (Durojaiye et al., 1992). Pheasants, guinea fowls, and quails can take the infection from infected chicken flocks, and transmit it by contact.

Outbreaks of EDS are characterized by a drop in egg production up to 50%, and last for four to 10 weeks (Van Eck et al., 1976; McFerran et al., 1978; Alam et al., 2009). In Japan, Yamaguchi et al. (1981) reported the first outbreak of EDS in a 30-55 weeks old broiler breeder farm with a 20-25% fall in egg production that continued for three to seven weeks. However, Alam et al. (2009) and Biswas et al. (2009), in Bangladesh, detected seropositive

cases of EDSV in layer flocks showing a decrease in egg production and soft-shelled or shell-less eggs. Furthermore, [McFerran and Adair \(2003\)](#) demonstrated that EDS usually happens when egg production is between 50% to the peak level and lasts for four to 10 weeks with a 40% drop in egg production. Infected quail flocks showed a fall in egg production, an increase in the number of soft-shelled eggs as well as a development of haeminhibiting antibodies to EDSV ([Das and Pradhan, 1992](#)). The respiratory manifestation was also reported in goslings EDSV ([Ivanics et al., 2001](#)).

The main site for the virus replication is the eggshell gland region of the oviduct causing oedema ([Taniguchi et al., 1981](#); [Lu et al., 1985](#)), consequently, abnormal eggs are produced ([Smyth et al., 1988](#)). Abnormal external egg quality in the form of discoloration and soft thin or shell-less eggs are common in cases of EDS infection ([Yamaguchi et al., 1981](#)). Moreover, deterioration of the internal egg quality can be affected by the virus as an adverse effect on albumin quality could be observed ([Cook and Darbyshire, 1981](#)). Only slight diarrhea could be detected after natural or experimental infection with the virus ([Higashihara et al., 1987](#)).

### Diagnosis of fowl adenoviruses

Clinical diagnosis based on the observation of specific signs and lesions is difficult and non-confirmative. Microscopic detection of specific lesions, as well as inclusion bodies, may be diagnostic for FAdVs infections ([Anjum et al., 1989](#)). Electron microscopy is successfully used for the detection of the virus morphology after staining of tissue homogenates ([Cheema et al., 1989](#); [Chandra et al., 1997](#); [Ganesh et al., 2002](#)).

The laboratory diagnosis of FAdVs infections is based on the use of recent conventional and molecular techniques for virus detection. Fowl adenoviruses could be propagated in the yolk sac or chorioallantoic membrane of embryonated chicken eggs as well as duck eggs. Inoculated embryos showed deaths, stunted growth, curling, and hemorrhages as well as the presence of inclusion bodies in their tissues. The virus can cause latent infection of the embryos till hatching indicated infections in the next generation of birds ([Fadly and Winterfield, 1973](#); [McFerran and Adair, 1977](#); [Toro et al., 2001](#)). The type and species of birds vary according to the type of the inoculated eggs (chickens, turkeys, and ducks). This type of latent infection has been recorded as FAdVs-1 ([Grgić et al., 2006](#)).

Homogenates of 11 or 19 days old FAdVs infected chicken embryos could be successfully inoculated on

tissue culture lines ([Chandra et al., 2000](#); [Balamurugan et al., 2002](#); [Ahmad et al., 2011](#)). These viruses are propagated on the chicken embryo, liver, kidney, fibroblast, and Vero cell lines with positive reaction (areas of cytopathic effects) that appeared within five to six days. The cytopathic effect appears as detachment of the cell surface with the presence of inclusion bodies ([Khawaja et al., 1988](#)). Sometimes, these viruses require adaptation by serial passages on cell lines to induce cytopathic effects ([Roy et al., 2001](#)). However, some research failed in the propagation of the viruses on tissue culture like the Japanese quail fibrosarcoma cell line (QT 35) ([Afzal and Ahmad, 1990](#)).

It has been documented that FAdVs could be easily detected using virus isolation and real-time PCR rather than using conventional Polymerase Chain Reaction (PCR) ([Günes et al., 2012](#)). Nowadays, it is molecular techniques are commonly used for viral genes. Diagnosis of FAdVs is based on the detection of the hexon gene loop 1 (Hex L1) of a major capsid protein gene using PCR ([Xie et al., 1999](#); [Raue et al., 2005](#); [Mase et al., 2009](#)). Hexon gene is amplified at the 700-bp fragment and is used as a probe for the dot blot hybridization technique ([Ganesh et al., 2002](#)). In addition, sequencing of the DNA-dependent polymerase gene or detection of 52K gene has also been used for detection of FAdVs ([Kajan et al., 2011](#); [Günes et al., 2012](#); [Kajan et al., 2013](#)). Differentiation of FAdVs to different species and serotypes could be carried out through amplification of specific regions on hexon gene, and then specify the product using restriction enzyme digestion or nucleotide sequencing ([Meulemans et al., 2001](#)). Moreover, serotyping of FAdVs is based on the presence of neutralizing epitope in the hexon gen which is serotype-specific ([Hess, 2000](#); [Russell, 2009](#); [Liu et al., 2016](#); [Niczyporuk, 2016](#)).

Restriction Fragment Length Polymorphism (RFLP) grouped FAdVs into five diverse species (A-E) ([Hess, 2000](#)), and used HpaI enzymes for the digestion of the PCR product ([Raue and Hess, 1998](#)). To distinguish various FAdVs-4 strains, PCR-RFLP analysis of the short fiber gene using the enzyme AluI was useful ([Mase et al., 2010](#)).

Detection of antibodies against FAdVs has been applied using some serological methods like agar gel precipitation test, enzyme-linked immunosorbent assay, haemagglutination assay for rat and rhesus erythrocytes, dot immunobinding assay, immunoperoxidase test, and virus neutralization test ([Saifuddin and Wilks, 1990](#); [Manzoor and Hussain, 2003](#)). Using serological tests may face some obstacles like the presence of antibodies in both

healthy and diseased birds (Hafez, 2011; Thakor et al., 2012).

#### **Prevention and control of fowl adenoviruses**

Reducing the incidence of FAdVs infections can be based on maintaining good management and husbandry practices. Thorough cleaning and disinfection, strict biosecurity measures as well as proper ventilation may significantly reduce the chances of infection (Poss, 1998). Reducing the movement of visitors, wearing special clothes and footwear, and shower-in-and-shower-out facilities are advised in breeder farms. Prevention of mechanical transmission of infections through efficient eradication of rodent and insects are also suggested. A concentration of 0.07-0.1% iodophor solution in the drinking water proved efficiency against FAdVs (Abdul-Aziz and Al-Attar, 1991; Abdul-Aziz and Hassan, 1995). Antibiotics could be used in a case of infection to avoid secondary bacterial infection. Suppling birds with vitamins and minerals to improve immunity is also important. In case of THEV infection, passive protection of turkey poults with antiserum of recovered flocks has been studied. Recovered turkeys from THEV infection showed persistent immunity, accordingly, antibodies in the serum of these birds could be used for the protection of unvaccinated young turkeys. Infections with different forms of FAdVs resulting from shortages in the application of hygienic and biosecurity measures in the farms (Elbestawy et al., 2020).

Vaccine administration is essential to combat FAdVs infections. Three types of vaccines including inactivated whole-cell live attenuated, and recombinant vaccines have been developed against the different forms of such infections (Shah et al., 2017). In areas where the adenovirus infections are endemic, FAdVs infections have been controlled using formalin-inactivated cell culture and live vaccines (Schachner et al., 2016; Schachner et al., 2018). These vaccines proved efficacy against natural and experimental FAdVs infections, and significantly reduced mortality (Balamurugan and Kataria, 2004). The protection level of the prepared vaccines was estimated based on the reduction of the severity of clinical signs, mortality rate, post-mortem lesions in the organs, and the characteristics of histopathological findings (Mansoor et al., 2011).

It has been proved that inactivated cell culture vaccine type is easier and faster in preparation than other types and effectively controlled FAdVs infections (Chandra et al., 2000; Kim et al., 2014). An inactivated liver homogenate vaccine was successfully used for the

prevention of HPS (Chishti et al., 1989; Akhtar et al., 2000; Ahmad and Hassan, 2004). The studies of Ahmad et al. (1990) proved that vaccination of broiler chickens at 15-18 days old was more effective than vaccination at 10-12 days of age to give vaccination to give the best protection against HPS. Subcutaneous inoculations of inactivated liver homogenate or cell culture vaccines for 10-15 days old broiler chickens have been found to bring HPS under the control in terms of reduction of mortalities (Chandra et al., 2000). In comparison with the inactivated liver homogenate vaccine, a living egg-adapted attenuated vaccine against HPS infection was prepared (Mansoor et al., 2011). The results showed higher antibody titers in broiler chickens that were immunized orally or parentally with a sixteenth-passage attenuated virus at 7, 14, and 21 days post-immunization with a protection rate reaching 95% compared with the only 55% in liver homogenate vaccine.

In Peru, the oil-adjuvanted cell culture IBH vaccine provided better protection to the vaccinated birds in comparison with the autogenous vaccine. Moreover, inactivated oil emulsion cell culture FAdVs-4 vaccines induced serotype homologous and heterologous cross-protection for the vaccinated breeders as well as their progeny (Kim et al., 2014). In China, a strain of FAdVs-4 was used for the preparation of inactivated oil-emulsion vaccine, and the results showed that a single dose was effective, and gave good protection against homologous virulent FAdVs-4 and heterologous virulent FAdVs-8b strains challenges (Xia et al., 2017). However, in Pakistan, Khan et al. (2005) and Mahmood et al. (2011) demonstrated outbreaks of the disease after vaccination, so they recommended propagation of the virus on SPF embryonated eggs and cell cultures to produce killed and live attenuated vaccines.

Earlier, Fadly and Nazerian (1984) demonstrated that THEV vaccines prepared by propagation in turkey origin Marek's disease which produced B-lymphoblastoid cell line have elicited effective protection against THEV without adverse effects. Maternal immunity can protect turkey poults against THEV infections in the first weeks of life, and also can interfere with vaccination protocols. But, earlier vaccination is very important to prevent exposure to virulent field THEV strains. Some vaccines have been produced from avirulent THEV strains after propagation in turkeys' leukocytes culture (Van den Hurk, 1990), and they are taken either 18-19-day-old embryos (*in-ovo* vaccination) or for three to six-week-old turkey poults through drinking water route. Vaccinated birds by these types of vaccines need a booster dose to gain complete

protection. Cell culture live vaccines prepared from avirulent strains of THEV or MSD virus could be effectively used to control the infections (Fadly et al., 1985; Sharma, 1994).

Live vaccines of THEV are prepared either by mixing of 6-week-old turkeys' splenic homogenates with avirulent THEV isolate or by inoculation of RP19 cell cultures. However, cell culture-prepared vaccines are only commercially available. Barbour et al. (1993) found that cell culture liquid vaccines are more effective than frozen ones in provoking seroconversion and antigen clearance from splenic tissue. Vaccinated birds showing more than 60% seroconversion with splenic homogenate indicate good protection. Good protection could be obtained if the inoculated splenic homogenates vaccines give more than 60% seroconversion rate in the vaccinated birds.

In addition to the traditionally used vaccine, other types of recombinant vaccines like hexon protein-based subunit or virus-vectored vaccines using fowl poxvirus expressing the native hexon of THEV have been developed (Cardona et al., 1999). This monoclonal vaccine does not associate with any immunosuppression. The containing protein of this vaccine should not be denatured, and also it should retain its native structure to give the desired results

The recombinant fowl poxvirus vaccine should co-express the hexon and a 100 kDa folding protein to elicit the best humoral immune response (Cardona et al., 2001). Another type of THEV sub-unit vaccine has been produced from capsid protein (knob protein) of THEV expressed in *Escherichia coli* (Pitcovski et al., 2005). This type of vaccine also showed safety, efficacy, and adequate protection against the THEV challenge. Rautenschlein and Sharma (1999) demonstrated that a combined vaccine of THEV and Newcastle disease virus failed to induce protection against both infections.

Commercially, three types of vaccines are used to prevent THE worldwide, the first type is live autogenous "splenic" vaccines, the second type includes live, tissue culture-derived vaccines, and the third type encompasses inactivated vaccines (Giovanardi et al., 2014). In comparison with tissue culture-derived vaccine, the splenic vaccine is considered more potent and requires fewer revaccinations to induce protective immunity (Weier, 2013). The tissue culture vaccine for THE is used to control infection in Canada, and it may be applied once at 3.5 to six weeks of age, or twice at 25 and 35 days of age. Passive or maternal immunity is transferred from vaccinated turkey breeder hens to their progeny to protect the poults for the first two to three weeks of life (Weier,

2013). The severity of clinical signs of THEV decreased due to vaccination and the circulation of avirulent virus strains in the field (Giovanardi et al., 2014). In a recent study by Palomino-Tapia et al. (2020), in Canada, the researchers found circulation of wild-type THEV in vaccinated flocks, so they developed a novel procedure that allows whole-genome sequencing of THEV from spleens, without passaging in cell culture or passaging *in vivo*.

Recombinant or sub-unit vaccine has been developed to overcome FAdVs infections. The effectiveness of this type of vaccine against EDSV in chickens (Fingerut et al., 2003), THEV (Pitcovski et al., 2005), and HPS virus in broiler chickens (Shah et al., 2012) have been determined. In the recombinant vaccine of HPS, the penton base protein of the FAdVs-4 was cloned and expressed in *Escherichia coli* in chickens, as it conferred a protection rate of 90% after the viral challenge. In addition, the role of fiber proteins type 1 and 2 was also tested as a candidate for the preparation of subunit vaccine (Schachner et al., 2014), and the results revealed that the recombinant fiber-2 was protective against signs but not the viral fecal excretion. The subunit vaccine is recommended over other types due to the elimination of the outbreaks caused by incomplete attenuation or inactivation (Fingerut et al., 2003). Moreover, the application of modern practices of recombinant DNA technology should be essential for the diagnosis and prevention of FAdVs infections (Balamurugan and Kataria, 2004; Khan et al., 2005).

## CONCLUSION

Further surveillance studies on FAdVs affections in different avian species as well as the geographic distribution of these viruses in different regions all over the world should be given into consideration. In addition, the pathogenicity of the FAdVs strains and their potential risks are needed. Researches regarding the preparation and production of FAdVs vaccines should be regularly updated to overcome such infections.

## DECLARATIONS

### Competing interests

The author has not declared any conflict of interest.

### Ethical considerations

Plagiarism, consent to publish, misconduct, data fabrication and/or falsification, double publication and/or

submission, and redundancy have been checked by the author.

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