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A Comprehensive Review on Angara Disease in Poultry

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A B S T R A C T

Hepatitis-hydropericardium syndrome (HHS) or Angara disease is an immunosuppression and contagious disease that often occurs in broiler poultry farms with a high mortality rate and sudden death. Furthermore, weight loss and sudden death have a significant and apparent economic impact on poultry farms, especially in fast-growing countries. Fowl adenovirus (FAdV) is a causative agent of HHS found in various animals, such as chicken. It causes rapid death and outbreak in young broiler farms, with an accumulation of jelly-like and straw-colored liquid in the heart pericardium, swollen and pale liver, heart muscles petechial and ecchymosis hemorrhages, swollen and pale kidneys, and atrophy thymus seen in gross pathology. Age, host, farm management, biosecurity plan, co-infectious, and level of immunity are risk factors for HHS. Angara is mainly found in Asian countries in Central and South America. The disease is transmitted vertically, like egg-transmitted, and horizontally by oral-fecal route. Rapid diagnostics and active monitoring systems in poultry farms can prevent and control Angara disease in farms. Vaccination and farm-specific biosecurity strategies reduce the initiation of outbreaks in farms. Treatment is based on activating humoral immunity against the virus, similar to vaccination.

Keywords: *Angara, Hepatitis Hydropericardium Syndrome, Poultry, Poultry Viral Disease*

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1 Introduction

Viral epidemics in poultry industries and farms have increased in recent decades, especially in developing countries (1). Adenovirus infections in poultry farms are significant in viral outbreaks (2). Hepatitis-hydropericardium syndrome (HHS), to distinguish it from IBH, is one of the most severe adenovirus diseases in poultry farms. Usually seen in broilers and layers between the ages of 3 and 6 weeks, HHS is an immunosuppressive infection that can lead to hydropericardium, hepatic necrosis, and sudden death. This causes a mortality rate of 75% for breeders and 10% for layers (3, 4). Weight loss and sudden death cause economic loss on poultry farms (2, 5, 6). Because it was first reported in Pakistan in 1987, Angara goth near Karachi, the disease is commonly called Angara disease. The disease was also called Leechy disease in India (3, 7). An early report of the disease revealed that healthy broiler flocks at age 3 to 5 weeks demonstrated sudden mortality lasting for 10 to 15 days and accumulation of straw coloured and watery fluid in the pericardium, and discolored livers with focal eosinophils and basophilic inclusions encumbered in the kidney (8) and weight loss in chickens. Weight loss can also affect the feed conversion ratio (9).

An isolate from Pakistan called K31 (Mazaheri, Prusas, et al. 1998) spread to Jammu, Kashmir, India (10), and Iraq. Many outbreaks of HHS were reported in South American countries like Mexico, Ecuador, and Peru simultaneously (11). Then, north Indian poultry industries (12), Chile (13), Russia (14), Japan (15), Korea (16) and rest of the world have reported the disease. Epidemiological studies applied to isolated cases in Mexico, Ecuador, Peru, Chile, Kuwait, Pakistan, and India showed that isolates belong to DNA group C and FAdV serotype four and strain KR5 (11, 17). FAdV is a causative agent of Angara disease. Angara disease should be monitored and controlled by detecting specific serotypes. Prevention depends on vaccination of suspected poultry farms, although co-infection with different fowl adenovirus serotypes has been reported (18). This review describes the etiology, epidemiology, pathogenesis, clinical pathology, treatment, and prevention of Angara disease in poultry farms.

2 Etiology

The cause of this syndrome was unknown for some years (19). The fowl adenovirus-C type 4 strain was found in the late 1990s (20, 21). The family Adenoviridae contains more than 100 serotypes, half of which are human adenoviruses. Adenoviridae genome is a single linear of double-strand DNA; this family is divided into two genera, Aviadenovirus and Mastadenovirus. Aviadenovirus is separated into three groups (group I, II, and III). Group I includes avianadenvirus, as FAdV is a causative agent of HHS (22, 23). There are five species of adenoviruses (A-E) and 12 serotypes (FAdV-1 to 8a and 8b to 11) (24). FAdVs are classified into five species (A-E) and 12 serotypes (FAdV-1 to 8a and 8b to 11) (25). The avian adenovirus has been found in a variety of poultry species, including ostriches, falcons, raptors, psittacine, and parrots. Several diseases can be caused by avian adenovirus, such as inclusion body hepatitis (IBH), hepatitis hydropericardium syndrome (HHS), adenoviral gizzard erosion (AGE), avian adenoviral splenomegaly (AAS), and egg drop syndrome (EDS). FAdV is emerging in some countries (26, 27).

Antigenic determinants are specific to FAdV types, groups, and subgroups encoded by the Hexon gene (24). The Hexon gene is used for detection by PCR extraction. Penton is another structural protein that consists of an icosahedral capsid and is responsible for attaching to the host cell, called a knob (28), as well as virulence (29). Virus morphology was detected by electron microscopy from liver extract (30). The non-enveloped capsid consists of Hexon, Peripentonal Hexon, and Penton shape protein, in which each fiber originates separately from the penton base (31). Which guanine/cytosine nucleotides is 53-59%. The genome encodes approximately 40 proteins, and the Terminal protein is covalently attached to the end of each genome (32) (Figure 1).

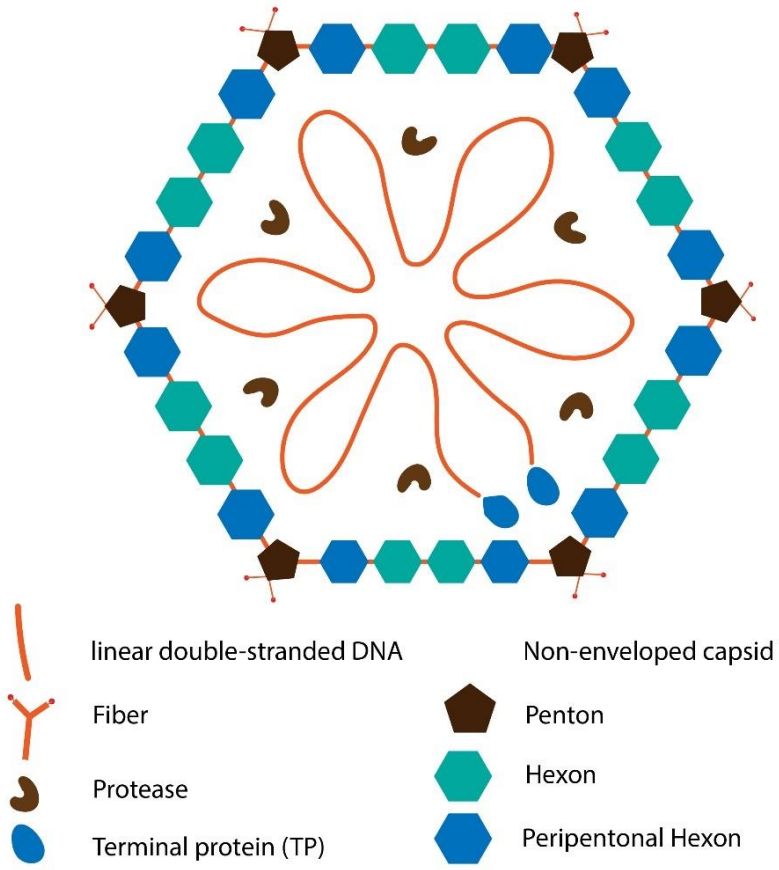

Figure 1. Fowl adenovirus structure

3 Pathogenesis and virology

The pathogenesis of fowl adenovirus serotype 4 depends on several factors such as the species and age of the host, the immune system and the level of the host's maternal antibody, viral proteins, and the presence of co-infections, which are described in detail below (33).

3.1 Viral proteins

Studies have shown that virus proteins can use the host's intracellular facilities to their advantage and for more infectivity (34). The capsid of FAdV-4 is made of three structural proteins named hexon, fiber, and penton base, which effectively bind the virus to the host, tissue tropism, and virulence of the virus (35). Hexon and fiber proteins play a crucial role in the virulence and tropism of the virus (36).

There are two fiber genes in FAdV-4 (fiber-1 and fiber-2) that differ in the number of amino acids and size. Since they are the first component of the virus that is in contact with the host, they have an influential role in the replication of the virus and its virulence (32, 37). Research showed that substituting amino acids of the fiber-2 gene and hexon can be one of the virulence factors of FAdV-4 compared to non-pathogenic strains (38). Fiber protein 2 plays a more critical role in the pathogenesis of FAdV-4 than hexon and can cause up to 100% mortality. In comparison, the maximum loss caused by hexon protein has been reported to be only 50% (39). Also, the gene coding for fiber protein 1 is necessary for the binding of the virus to the host receptors and the replication of the virus (40).

The function of the penton base has not been thoroughly studied, but together with other proteins, it is used in the penetration and entry of the virion into the host cell (41).

Compared with non-pathogenic strains, hypervirulent FAdV-4 isolated in China lacks ORF48, ORF27, and ORF19 due to 1966 bp nucleotide deletions on the right genome region. Additionally, fiber-1, fiber-2, hexon, and penton have been shown to have a variety of amino acid substitutions (42). When the 1966 bp deletion region of FAdV-4 was seamlessly replaced with its non-pathogenic counterpart, the hypervirulent characteristics of the virus did not change; however, viruses with substituted fiber-2 or hexon genes had a significant change in pathogenicity as

compared to the parental strain. Based on these results, hypervirulent FAdV-4 exhibited increased virulence independent of the 1966 bp deletion but was closely related to fiber-2 and hexon (39, 43).

In an earlier study, it was found that the chicken embryo lethal orphan (CELO) virus, which belongs to the FAdV-1, might bind to coxsackievirus and adenovirus receptor (CAR) via fiber-1 but initiate accessory infection via fiber-2 (44), suggesting fiber-2 might play a crucial role in early virus-host interactions.

According to the previous model, fiber proteins have an N-terminal tail that binds to the penton base, a C-terminal knob region, which binds to the host receptor, and a shaft region that connects the N-terminus tail to the knob, which influences the knob interaction with the cell receptor (45).

The sequence analysis of fiber-2 revealed that several mutations, including G219D, A380T, V319I, and P307A, are conserved in all hypervirulent FAdV-4 strains, and some may contribute to virulence. The crystal structure of fiber-2 has not yet been determined, so how fiber-2 participates in hypervirulent FAdV-4 infection is unknown. In addition, mutant amino acid positions and their effects on pathogenicity need to be clarified.

Numerous studies have demonstrated that viral proteins can utilize host factors during infection to facilitate pathogenicity and replication. Several studies have shown that hexon hijacks the T-complex polypeptide one subunit eta (CCT7) to contribute to the hypervirulent replication of FAdV-4 in immortalized chicken liver cells and LMH cells. CCT7 may function as a cytosolic chaperone protein for hexon protein folding or FAdV-4 capsid assembly (46). Moreover, hexon interacts with scavenger receptor II of Kupffer cells to facilitate infection with HADV-5 (47); the penton base interacts with Bcl-2-associated athanogene 3 to facilitate HADV-2 internalization (48). Although FAdV-4 is known to cause hemorrhagic and acute hepatitis, it is unknown whether hexon contributes to liver injury after hypervirulent infection or whether the penton base influences virus pathogenicity.

Nonstructural proteins also play a crucial role in virus pathogenicity, stability, and assembly. It is believed that the late phage nonstructural protein 100K facilitates the trimerization of chimeric hexon to improve proliferation efficiency and produce recombinant HAdV-5 vectors (49); this protein also forms a complex with poly(A)-binding protein and initiation factor eIF4G for enhanced protein synthesis (50).

In summary, viral proteins can utilize various host factors to impact the virus life cycle positively. Research is still needed to determine the exact role of viral proteins in hypervirulent FAdV-4 pathogenesis.

3.2 Mixed Infections:

Concurrent involvement with immunosuppressive viruses such as Newcastle virus, infectious bursal, chicken infectious anemia, and Mark's disease reduces maternal antibodies and makes chickens susceptible to other pathogens, and causes diseases such as hydropericardium syndrome and hepatitis (51, 52). Furthermore, it has been stated that mycotoxin, chicken infectious anemia virus, and infectious bursal disease can increase the pathogenicity of fowl adenovirus (53).

3.3 Immune system responses:

The host tries to identify and neutralize the virus with different methods. On the other hand, the virus, with its mechanisms, reduces the effects of the immune system on its reproduction and pathogenicity (33). The immune system's suppression occurs due to adenovirus's affinity to lymphoid organs such as the spleen, thymus, bursa of Fabricius, and intestinal tonsils (42). Infection with FAdV-4 affects both the humoral and cellular immune systems, as a severe decrease in lymphocytes in the bursa of Fabricius and a decrease in CD4+ and CD8+ cells in the thymus and spleen have been reported (54). Initially, acute FAdV-4 infection is recognized by pattern recognition receptors (PRRs) (55). Also, adenoviruses stimulate the host's production of inflammatory cytokines and chemokines (56).

Following viral infection, macrophages, monocytes, epithelial cells, and hepatocytes produce inflammatory mediators such as IL-1β and MIP-2, which can ultimately cause severe liver damage (57). One of the typical symptoms caused by the Angara virus is hydropericardium. Previous studies have reported apoptosis of heart cells following the increase in virus titer and the expression of inflammatory cytokines, especially IL-1β, in chicken hearts (58, 59).

Notably, chickens are also involved with immunosuppressive infections such as infectious bursal disease and Mark's disease, which helps reduce the side effects of cytokines (tissue damage) (60). Of course, the difference between the pathogenicity of adenovirus alone and with other infections should be further investigated and researched.

3.4 The host

Most of the recent studies in China show that chickens are more sensitive to this virus than ducks, and at the same doses, chickens, unlike ducks, show distinct clinical signs and necropsy lesions (55). This could be because ducks have retinoic acid-inducible gene I (RIG-I)-like receptors, which chickens lack. In infection with FAdV-4, two virus-associated RNAs called VA I and VA-II are produced, which can cause antiviral immune responses by binding to RIG-I (61, 62). The pathogenicity of adenoviruses and the symptoms of Angara disease have been reported in broiler chickens more than in mother and egg-laying chickens. However, the leading cause of this issue has not yet been thoroughly studied (42).

We can also refer to the study of Matos et al. (2016), which investigated the effect of FAdVs on broilers and layers. A substantial variation in the degree of susceptibility was observed with high mortalities in the FAdV-E and D infected SPF broiler groups (96-100%), whereas in the groups of infected SPF layers, fewer mortalities (only 8-20%) were noticed (37).

3.5 Age factor

FAdV-4 usually causes infection at the age of 3 to 5 weeks and is more pathogenic for younger chickens (63). In a study in which geese were inoculated subcutaneously with FAdV-4, younger geese were more susceptible to infection. For example, ten-day-old geese showed clinical signs such as pericardial effusion, while twenty-day-old and thirty-day-old geese did not (64). High susceptibility to adenoviruses at young ages can be due to lack of immunity.

3.6 Maternal Antibody

One of the ways of adenovirus transmission and Angara disease in chickens is vertical transmission. If the breeder Birds are not adequately vaccinated against this virus, there is a possibility of transmission to the offspring and an increase in the spread of the disease (65). Chickens that hatch from infected eggs do not shed the virus until 14 to 28 days later, but they may shed the virus from birth.

The decrease of maternal antibodies with age can cause the emergence of latent viruses, and for this reason, most of the time, 3 to 5-week-old children get Angara disease. Moreover, chickens younger than 21 days are infected due to the lack of maternal antibodies (66).

4 Epidemiology

HHS was detected in Pakistan (67), Iraq (68), India (69), Ecuador, Mexico, Chile, Peru (70), central and south America (11), Canada (71), Hungary (72), Poland (73), Korea (74), Russia (75), Japan (75) and China (76). Due to sudden mortality and weight loss, Angara is a crucial economic disease leading to enormous loss in poultry industries around the world (5, 77, 78).

FAdV is found in healthy and ill chickens (73), and some risk factors induce disease. Angara disease is contagious and spreads from farm to farm (9), causing outbreaks in breeders and layer farms. In China, the HLJFAd15 strain (hypervirulent strain) of FAdV was isolated from layers and caused a mortality rate from 30% to 90% (79). Although the disease mortality rate depends on the age of the chicken, type of chicken, dose of virus, and route of infection (75), some reports mentioned that the FAdV-4 mortality rate is approximately 10% to 80% in broilers and 0% to 10% in layers (4, 69). In unvaccinated birds, it causes 100% mortality (4, 80). While in field observation, the mortality rate is a prominent clinical feature of the disease. Also, in Korean flocks, the mortality rate ranges between 1.3% to 11.1%, although in Pakistan, Iraq, and India, it ranges from 60% to 70%, 10% to 30%, and 10% to 60%, respectively (16). Chicken is the primary host for FAdV, although some rare outbreak of HHS was seen in quail and pigeon (81, 82). Growing broiler farms were affected more (12).

In recent years, the morbidity of disease in some countries has risen. In Korean poultry farms, broiler and native chickens are more susceptible (74) and the KR5 strain was seen (83), although the chine HLJFAd15 strain was seen. Deletion of ORF19 and ORF27 is suspect of a chine outbreak circulating in this region (79). Before 2015 there were some sporadic cases in China, but after 2015, some outbreak was seen in some part of China (76). Indian strain was responsible for the new outbreak in China (32).

Due to the higher titers found in feces, FAdVs are transmitted horizontally by oral-fecal route, although vertical transmission is one essential characteristic of adenovirus (84, 85). FAdV transmits via eggs and from parents to progeny (86). However, the researcher mentions mechanical transmission, intramuscular inoculation, and oral route (21, 85). Mechanical transmission by vaccinator to another farm was mentioned by Akhtar et. all (19). Guan et.al discovered that intramuscular injection is the most susceptible way of inducing HHS, and nasal inoculation was experimentally done, which implies creating an effective and

safe vaccine (87). wild birds are important in spreading FAdV from farm to farm (9). Anjum et.all experimented on the subcutaneous route by infected homogenate liver, which initiates disease after 2 to 5 days of inoculation (88). The virus was transmitted via an infected kidney in an experimental study (89). The virus can be detected in the liver and pancreas as early as two to three days after infection. Clinical symptoms and apparent abnormalities do not appear during incubation (90). The median incubation period of FAdV in experimental studies was ten days (19).

Immunosuppression disease and co-infection with other diseases like Chicken infectious anemia or bursal disease predispose factors to induce HHS (2). Nutritional disorders predispose factors for initiation of HHS; vitamin and mineral imbalance, fishmeal, and rancid fat are inconsistent with nutritional disorders (91, 92). Age, host species, status of vaccination, level of biosecurity, co-infection with another viral disease, immunosuppressive disease, nutritional disorder, and strain of virus are risk factors of the HHS.

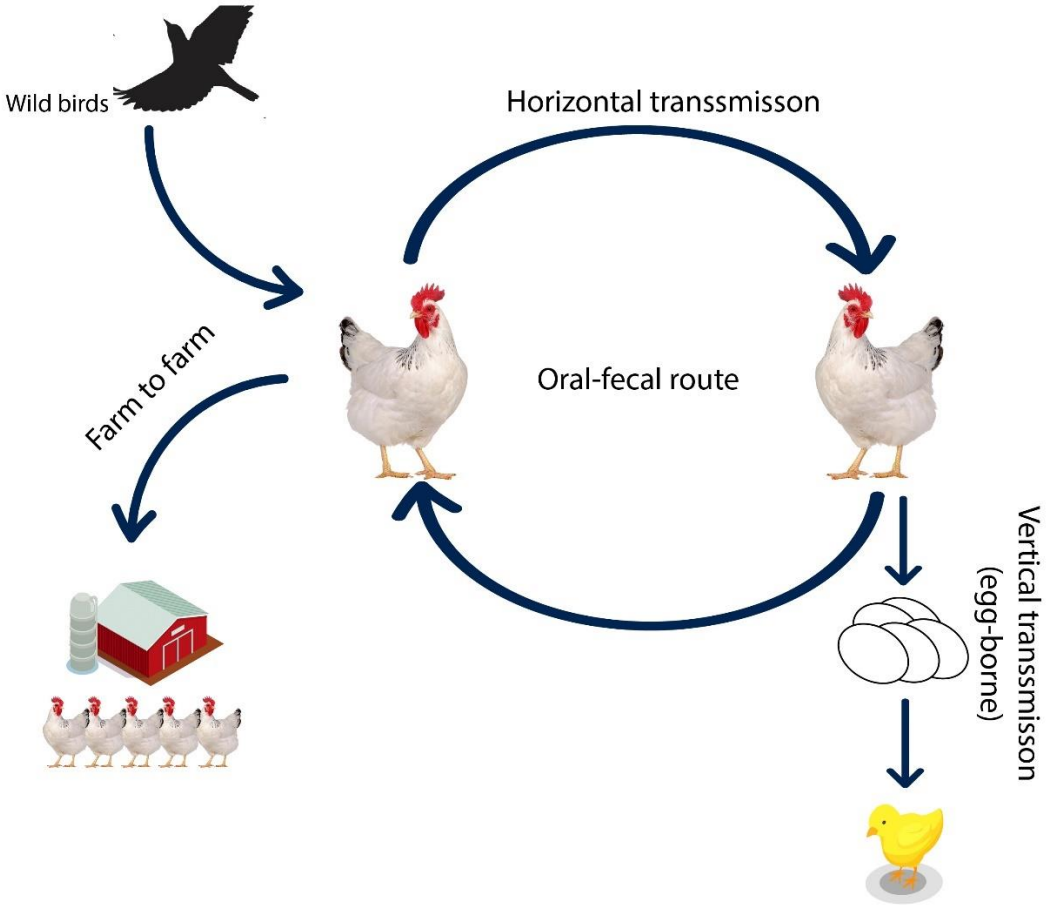

Figure 2. Transmission of Angara

5 Clinical signs and gross pathology

Birds suffering from this disease show different symptoms, such as lethargy, loss of appetite, ruffled feathers, and unwillingness to move (76). Following the decrease in appetite and food intake, weight gain and food conversion rate also decrease (93). Generally, poultry naturally infected with HHS have no typical clinical symptoms. The disease is usually detected by sudden death in young broilers in good growth conditions (42).

Macroscopic lesions are seen in vital and essential organs such as the liver, kidney, heart, and lungs (94). One of the most prominent macroscopic lesions of Angara's disease is the accumulation of jelly-like and straw-colored liquid in the heart pericardium (up to 20 ml volume). In this case, the heart is floating in the pericardial sac (95). The liver is swollen, pale, fragile, and sometimes with necrotic foci. Petechial and ecchymosis hemorrhages are seen in the heart muscles and other organs (96), And the lungs have edema and congestion (97). Furthermore, kidneys are pale, yellow, and swollen. Fragile kidneys with ureters containing urates

are visible lesions in this disease (98). In addition, some researchers have reported thymus atrophy and spleen enlargement in dead poultry following HHS (99). Some affected birds show congestion of the intestinal blood vessels and enlargement of the bursa of Fabricius (100).

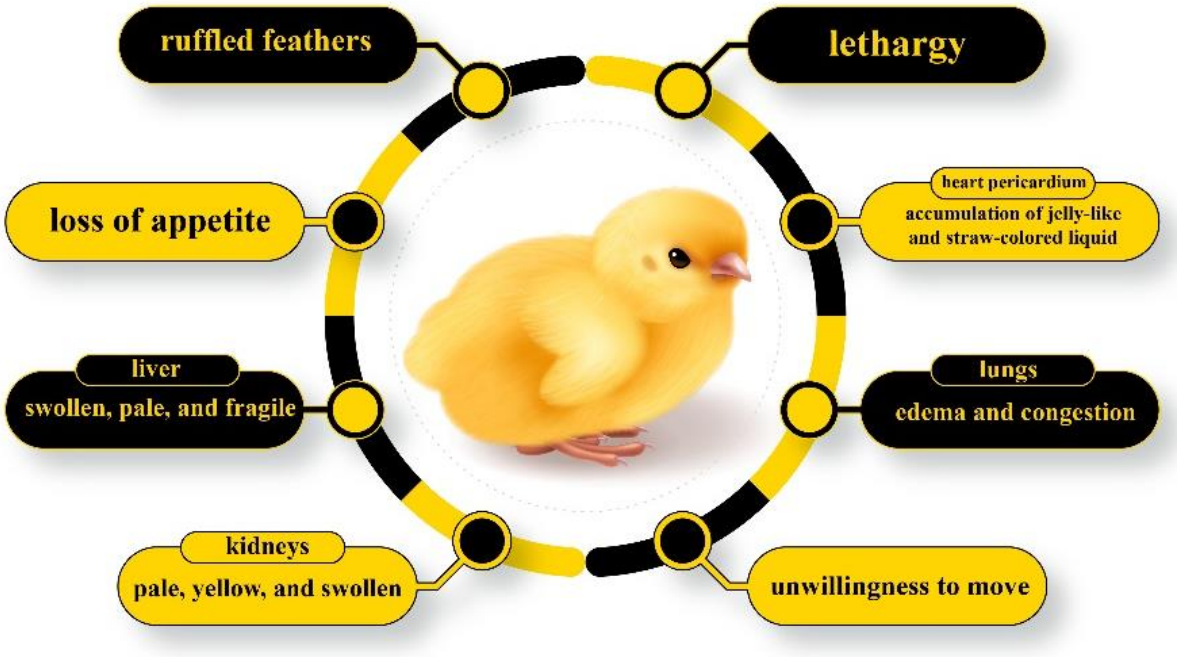

Figure 3. The schematic clinical sign and gross pathology of Angara in poultry

6 Treatment

Medications included in regular medication regimens may effectively treat infectious diseases by enhancing humoral and cell-mediated immune (CMI) responses. The host bird could produce antibodies by positive immune manipulation, respond to CMI, inhibit tumor growth, function as macrophages efficiently and optimally, and express protective cytokines. These claims are supported by several clinical pieces of evidence, including improved growth performance, mortality decreases, immune responses to antigens delivered by vaccines, and increased resistance to field infections (101). The literature has reported that various substances, vitamins, and medications can affect chicken humoral and CMI responses for prophylactic, therapeutic, or growth purposes. These medications may positively or negatively impact vaccine effectiveness. Using immunosuppressive drugs may have adverse clinical effects on chickens and result in financial losses for farmers. The effectiveness of vaccines may be increased by combining immunostimulant medications and vaccines (102).

Studies have suggested that salinomycin enhances broilers' protection against HHS virus and NDV virus (NDV) antibodies. Several studies have shown that salinomycin and monensin strengthen the immune responses of broilers against ADV and NDV, supporting their use in poultry production. Both ADV and NDV were significantly increased in birds treated with salinomycin. However, monensin did not significantly increase protection against either virus. Thus, immune-stimulating drugs and vaccines can be combined to make vaccines more effective. Salinomycin in poultry feed can act as a coccidiostat and an immunomodulator by stimulating the humoral response and CMI of chickens to antigens in vaccination programs. This can enhance protection against pathogens (103, 104).

In terms of immune function, dietary arginine is beneficial to both animals and humans. Through increased nitric oxide production and thymus weight and function in animals, arginine improves macrophage nitric oxide production and promotes lymphocyte responses to mitogens such as concanavalin A and phytohemagglutinin. In addition to improving immune system function, it stimulates cytokines and other immune cells to produce or function. Arginine is essential for diffusing and releasing B lymphocytes from the bone marrow, but chickens cannot synthesize it because of a defective urea cycle. According to two recent studies, arginine significantly improves chickens' ability to overcome immune suppression caused by

infectious bursa disease virus vaccine strains. This study compared arginine's effects on broilers' humoral and cell-mediated immune responses with two reference drugs (cyclophosphamide and cyclosporine). Chicks supplemented with arginine displayed significant lymphoproliferation and cutaneous basophilic hypersensitivity reactions compared to untreated control chicks (105). In addition, chicks supplemented with arginine had significantly higher body weights and lymphoid organs than those not treated with arginine. After virulent challenges to HHSV, chicks vaccinated with HHS supplemented with arginine had the highest survival rate compared with immunocompromised chicks (chicks treated with cyclophosphamide and cyclosporine and vaccinated with HHS) and untreated control chicks unvaccinated. After HHS vaccination with arginine supplementation, the post-exposure tissues of HHS-vaccinated chicks were not found to be infected with HHSV, either by cell culture or PCR. It has been shown that dietary arginine supplementation improves humoral and cell-mediated immune responses to HHSV in broiler chickens (101). A study looked into the effectiveness of passive immunization using immunoglobulins derived from egg yolk to protect broiler chickens from HHS. In experimentally infected broiler chickens, IgY treatment provided 86.66% protection against HHS virus infection. These results indicate that egg yolk technology enabled the production of immunoglobulins against the HHS virus. The IgY of hens could offer a new treatment for broiler hydropericardium syndrome immunized against the HHS virus (106).

7 Prevention and Control

The condition frequently occurs where multi-age operation is commonplace and high poultry densities exist. Since it is unclear what epidemiological factors contribute to the emergence and spread of HHS (107), it is essential to thoroughly clean all surfaces and equipment, restrict access for visitors and vaccination teams, and provide adequate ventilation and lighting in poultry houses. These measures also play an essential role in disease prevention. It has been discovered that adding iodophor solution (2.5%) to drinking water at a rate of 0.07_0.1% significantly reduces the course and mortality of HHS in broilers and can be helpful to disease control (68). The sensitivity of the HHS agent to pH varies from 3 to 10. In contrast to other adenoviruses, the HHS virus in the liver preparations withstood heating at 60°C for 30 minutes and at 50°C for an hour. However, the agent was inactive by heating at 60°C for an hour, 80°C for ten minutes, and 100°C for five minutes. The HHS virus's ability to spread was destroyed by treatment with the normally inactivating chemicals chloroform (5%) or ether (10%) (4, 108). The control of underlying immunosuppressive diseases may aid in limiting losses. (109).

The primary strategy to control HHS is adequate immunization against the HHS virus using inactivated vaccines made from chicken-infected liver homogenates (110). However, under field circumstances, HHS vaccines frequently fail to offer the desired level of protection. Field observations imply that the simultaneous presence of noninfectious factors like stress and aflatoxins, as well as infectious immunosuppressive agents like infectious bursal disease and chicken infectious anemia, may negatively affect the desired outcome of HHS vaccination (5). Several reports have shown the coexistence of IBD and CIA viruses in areas where HHS is prevalent (111). The immunosuppressive effects of IBD and CIA are well documented (112), and fowl adenoviruses (FAdVs) require impairment of the immune response to produce their pathogenic potential (113). So, in addition to using effective vaccines, immune-competent chickens, and better management techniques, the success of a vaccination program against an infectious disease also depends on the use of immune stimulants that can boost the targeted immune responses (114). The birds' IBD vaccination unaffected the disease outcome, as all birds were equally susceptible to the HHS agent (5). FAdV-4 vaccines are vital and the most efficient tool for preventing and managing HHS. Several vaccines were developed and evaluated against FAdV-4, including inactivated, live-attenuated, subunit, and combination. In addition to contributing significantly to the control of HHS, further studies are required to determine whether FAdVs offer cross-protection and whether vaccines are immunogenic (115).

In two field tests involving 570000 birds across 128 farms, the overall mortality ranged from 0.77% to 3.8% for birds receiving vaccinations and 11.11% to 30% for birds not (116). In a different experiment, the mortality rate for vaccinated birds was 0.52% versus 5.34% for unvaccinated birds kept on the same premises. When used in response to an outbreak, vaccination was also successful when used in response to an outbreak, with mortality in vaccinated infected birds being 2.33% compared to 10.27% in unvaccinated infected birds (110).

It may be possible to develop safe vaccines that will provide broiler chicks with robust and active immunity to protect them throughout their growing period. In addition, recombinant DNA technology may have advantages over other approaches (5).

The development of vaccines against FAdV-4, especially the newly emerged genotype, is of extreme importance for preventing and controlling the disease.

7.1 Inactivated Monovalent Vaccines

FAdV-4 has emerged as a hypervirulent new genotype, so inactivated vaccines are the primary prevention method since they are safe, cost-effective, and have a high degree of immunity (115). The study showed that the vaccine could produce high levels of antibodies, preferential T helper 2 (Th2) responses, and complete immunity against a lethal dose of the new hypervirulent FAdV-4 virus. The novel genotype SDJN0105 strain (59), HN strain (117), and CH/GZXF/1602 strain (118) all developed inactivated vaccines that produced high levels of antibodies. It provided sufficient protection against HHS in chickens . Vaccinated chickens and the progeny of vaccine-vaccinated breeders may benefit from the inactivated FAdV-4 vaccine since it provides cross-protection against different FAdV serotypes. Xia et al. prepared an FAdV-4 vaccine that protected chickens against the virulent strains of FAdV-4 and FAdV-8b (118). In India, FAdV-4 grown in cell culture was used to create a killed, oil-emulsified vaccine. A 0.5-ml dose of the vaccine (105.5 TCID50/0.1 ml) administered to 3-week-old chicks completely protected them from the HHS virus challenge at 1, 2, 3, 4, or 6 weeks after vaccination (119). In addition to strict biosecurity and high standards of hygiene and management, developing a suitable vaccine in Specific Pathogen Free (SPF) chickens and cell culture systems appears to be the best solution given the contagious nature of the illness. When administered subcutaneously at 103.5 LD50/dose/bird, an inactivated vaccine produced in chicken liver cell culture and embryonated eggs provided defense against a challenge with 1 ml of a 20% liver homogenate at a biological titer of 2×105 LD50/0.5 ml (120).

An autogenous formalin-inactivated vaccine from an infected liver homogenate suspension has been used to control HHS. Results were satisfactory at 10–15 days of age after a dose of 0.25 ml/bird (116, 121). A vaccination between 15 and 18 days prevented relapses between 35 and 40 days of age (116). In an experimental challenge study, protection was 90_100% in the double-vaccinated group compared to 80_100% in the single-vaccinated group, and 70_100% of the birds in the unvaccinated control group perished (122).

An oil-emulsified inactivated cell culture vaccine or a formalin-inactivated vaccine that was created from a 20% (w/v) suspension of infected liver homogenates in PBS (pH 7.4) and inactivated with 0.1% formalin for 24 hours have both been used to control the disease (123).

On numerous farms in India experiencing severe HHS outbreaks, birds were immunized. At 10 to 12 days of age, a single 0.25 ml/bird dose of the vaccine provided 100% protection. It was found that using the vaccine inactivated with 0.1% formalin alone was superior to using it inactivated with either 0.5% formalin or 0.1% β-propiolactone for 72 hours or heat treatment at 56 C for one hour, followed by overnight inactivation with 0.1% formalin (88, 121).

A vaccine made from freeze-dried, inactivated liver homogenate resuspended in saline was more effective than a vaccine made from an ultracentrifugation pellet resuspended in saline (124). A Formalinized vaccine produced lower antibody titers than an oil-emulsified vaccine did. 90% to 100% protection was achieved when an oil-emulsion vaccine was administered to 30 DPV. In chickens aged 4, 5, and 7 weeks, an inactivated vaccine made from chloroform-extracted liver homogenate, inactivated with formalin, and adjuvanted with liquid paraffin was highly effective against challenges with infected liver homogenate (67, 125).

Table 1. Different types of inactivated vaccines

Strain	Origin	Adjuvant
HLJFAd15	CEL[1]	oil
CH/GZXF/1602	CEK[2]	oil
SDJN0105	CEF[3]	oil
HN	LMH[4]	oil
HN	CE[5]	oil
K531/07	CEL	Seppic ISA 70
rHN20	LMH	oil

1- Chicken embryo liver cells. 2- Chicken embryo kidney cells. 3- Chicken embryo fibroblast cells. 4- Leghorn male hepatocellular cells. 5- Chicken embryo.

7.2 Live-Attenuated Monovalent Vaccines

As a result of the modification of virulent FAdV-4 isolates to the QT-35 fibroblast cell line, a live HHS vaccine was found to reduce the immunopathology caused by significant challenges (54, 126). A brand-new FAdV serotype four vaccine that was recently developed was serially passed through 12 times to achieve complete

attenuation, effectively protecting chickens from IBH-HHS. Dual vaccination with FAdV-4 and CAV can effectively protect chicken offspring against IBH-HHS. At 14 days old, groups of broiler chickens that had no maternal antibodies to the HHS virus were given either the 16th-passage attenuated HHS virus vaccine or the commercially available liver organ vaccine. The liver organ vaccine demonstrated significantly low ($p<0.05$; 55%) protection based on clinical signs, gross liver, and heart lesions, histopathological lesions, and mortality. In contrast, vaccination with the 16th-passage attenuated HHS virus provided 94.73% protection. Only 10% of birds in the unvaccinated control group were protected from morbidity, mortality, and gross and histopathological lesions. It has been shown that the HHS virus vaccine is immunogenic, so chickens may not contract it (127, 128).

Schonewille and his colleague developed an attenuated FAdV-4 vaccine. Birds challenged with the attenuated virus did not show clinical signs or die. According to serology and neutralization tests, the live vaccine resulted in a weak antibody response in some birds. Zhang and his collaborators identified two recombinant chimeric viruses by exchanging the hexon and fiber-2 genes of nonpathogenic FAdV-4. According to serology tests and neutralization tests, the live vaccine resulted in a weak antibody response in some birds. Zhang and his collaborators identified two recombinant chimeric viruses by exchanging the hexon and fiber-2 genes of nonpathogenic FAdV-4. FAdV-4's virulence is determined by its hexon, not fiber-2, as demonstrated by no clinical signs or mortality in chickens inoculated with rHN20. Zhang et al demonstrated that rR188I strains are not pathogenic to SPF chickens. Therefore, the strain is considered for HHS as a live attenuated vaccine candidate (35, 126).

For FAdV-4, Schonewille et al. developed an adipose FAdV-4 vaccine and observed no clinical signs or deaths in birds infected with the attenuated virus (129). Several birds could produce two recombinant chimeric viruses, such as rHN20 and rFB2, by transferring FAdV-4-negative hexagons or fiber-2 genes, and in response to live vaccination, Zhang et al. found weak antibody reactions in some birds. Chickens inoculated with rHN20 did not cause clinical signs or mortality, demonstrating that hexane determines the virulence of FAdV-4., not fiber-2. In addition, Zhang et al. showed that rR188I strains were pathogenic in SPF chickens. Later, rR188I was considered a potential candidate for a live attenuated vaccine for HHS vaccines (130).

In order to rescue FAdV4-RFP_F1 from fiber-1's N-terminus, Yaru Mu et al. used CRISPR/Cas9 technology. The recombinant virus FAdV4-RFP_F1 is a promising live-attenuated vaccine candidate for FAdV-4, and the fiber-1 N-terminus can be a site for expressing foreign genes to build a vaccine based on FAdV-4. By using the N-terminus of fiber-1 as an insertion site for FAdV-4-based vaccines, FAdV4-RFP_F1 could be developed as an effective live-attenuated vaccine for FAdV-4 (131). Additionally, Xie et al. used CRISPR/Cas9 to create the EGFP-fiber-2 fusion protein-expressing recombinant virus FA4-EGFP in chickens. FA4-EGFP did not cause any clinical signs or deaths in chickens, suggesting the virus had attenuated significantly (132).

Table 2. Different types of live-attenuated monovalent vaccines

Strain	Origin
FAdV-4/QT35	QT35
rR188I	LMH[1]
rHN20	LMH
FAdV4-RFP_F1	LMH
FA4-EGFP	LMH
FAdV4-EGFP- rF2	LMH

[1]Leghorn male hepatocellular cells

7.3 Subunit Monovalent Vaccines

There has been considerable progress in developing subunit vaccines, which are safer than vaccines containing the whole virus. In a study conducted by Wang et al., the immune effects of expressed capsid proteins of fowl adenovirus serotype 4, including fiber-1, fiber-2, penton base, and hexon (loop-1 region), were compared in chickens. In the study, fibers-2 and fibers-1 were able to induce complete protection, whereas L1-hexon and penton bases could induce excellent protection, but not wholly (129).

Yin et al. prepared a subunit vaccine candidate derived from the bacterially expressed recombinant Fiber2 protein of the FAdV-4 GZ-QL strain and a recombinant plasmid pVAX1-Fiber2 as a DNA vaccine candidate. Results showed that the rFiber2 subunit and Fiber2 DNA vaccine candidate induced meaningful humoral and cellular immune responses, while the rFiber2 subunit vaccine candidate had better potential in the fight against FAdV-4 infection (133).

Subunit vaccines are safer in the production and treatment process than vaccines based on the whole virus, and researchers have made considerable efforts to develop subunit vaccines for FAdV- 4. Different subunit antigens, expression systems, and anti-inflammatory substances have

been evaluated to develop the FAdV-4 subunit vaccine. Before the new FAdV-4 genotype, several studies tried to develop a traditional subunit vaccine for FAdV-4.

Shah and colleagues developed a subunit vaccine that demonstrated 90% protection for chickens using a procaryotic expression protein penton base and Freund's complete adjuvant (FCA) (134). Aziz et al. evaluated both full-length prokaryotic and epitope-centered 1-225 aa peptides with Montanide ISA 71VG adjuvants, and both vaccines showed a 50% protection rate (135). Schachner et al. compared the immunogenicity of FAdV-4 capsid proteins, including fiber-1,fiber-2, and L1 hexon (L1 hexons) (136). Fiber-1,fiber-2, and L1-hexon are simultaneously expressed in the Baculovirus system, and the GERBU adjuvant LQ no. 3000,fiber-2 (27/28) is more likely to protect from the adverse reactions than fiber-1 (16/26) and L1-hexon (7/26), demonstrating that fiber-2 may be an ideal antigen component for the development of subunit vaccines. Shah et al. first tried a nonstructural protein expressed by the prokaryotic FAdV-4 with 100K of FCA; unfortunately, it showed only a protection rate of 40% (115).

HHS is associated with developing a new type of FAdV-4 gene, but progress has been made in developing subunit vaccines. Wang et al. evaluated the efficacy of the FAdV-4 surface proteins fiber-1,fiber-2, L1-hexon, and penton bases expressed in Escherichia coli in formulas formulated with FCA (129). The results show that fiber-2 (50 g/bird) and fiber-1 (100 g/bird) can induce complete protection but that L1 hexagon and penton base protection can induce considerable protection at high doses but not wholly. If fiber-2 is combined with different adjuvants, such as FCA (130), Montanide ISA 71VG (137), Sigma (138), the immunogenicity of prokaryotic expressions of fiber-2 is even greater.

Table 3. Different Types of Subunit Monovalent Vaccines

Antigen	Strain	Expression system
penton	PR-06	E. coli[1]
penton	NIAB/NIBGE 01	E. coli
Penton (1-225aa[a])	NIAB/NIBGE 01	E. coli
L1-hexon	KR5	Baculovirus
100K	NIAB/NIBGE 01	E. coli
fiber-1	KR5	Baculovirus
fiber-1	SXD15	E. coli

[1]Escherichia coli.

[2]Lactococcus lactis.

7.4 Combined Vaccines

Several combined vaccines were analyzed and showed sound effects. Some studies showed that chimeric fiber protein (crecFib-4/11) combination vaccines protected chickens against HHS and IBH (95). Tian and colleagues studied a recombinant NDV LaSota vaccine strain expressing the full-length fiber-2 gene of FAdV-4 (rLaSota-fiber2) generated using reverse genetics. Results indicated that both vaccines are hopeful bivalent vaccine candidates to control both HHS and ND (139). Because of the high pathogenicity of the new FAdV-4 genotype, weakening vibration is critical for vector development. Zhang et al. first identified the critical gene and key aa for the virality of the new FAdV-4 (140). Then, they obtained the non-pathogenic strain rHN20, which became the basis for development and application. Subsequently, the immune genetic VP2 gene of the highly virulent infectious bursa disease virus (vvIBDV) was inserted into the 1966Del natural site of elimination and induced total protection in chickens against the new challenge FAdV-4 and vvIBDV when used as an inactivated vaccine (141) or live vector vaccine (142). Lu et al. inserted an FAdV-8b fiber into the fiber-2 position of the FAdV-4, which simultaneously protected chickens from new FAdV-4-induced HHS and FAdV-8b-induced IBH (143). In addition to the FAdV-4 vector vaccines above, several other combined vaccines have been evaluated and shown promising effects. Luca et al. constructed a chimeric fiber protein (crecFib-4/11), which could simultaneously protect chickens from HHS and IBH (95), highlighting a new concept: chimeric fiber vaccines can be extended to a variety of viruses. Tian et al. developed a recombinant Newcastle disease virus (NDV) LaSota vaccine strain, which expresses fiber-2 of FAdV-4 (rLaSota-fiber2) and live and inactivated vaccines from rLaSota-fiber2 (139). Both vaccines provided complete protection against viral NDV. However, the live rLaSota-fiber2 vaccine provides better protection against the challenge of FAdV-4 than the inactive vaccine, indicating that the NDV-treated FAdV-4 vaccine is a promising candidate for double vaccines to control HHS and ND.

8 Conclusion

Angara disease is an emerging disease that must be combated via vaccination and effective biosecurity due to sudden death and high morbidity rate as the most significant clinical signs; treatment against it is impossible. The severity of HHS in farms associated with age, sex, host, farm management, level of biosecurity, co-infection with viral

disease, and serotype of FadV. Consider further action for active monitoring and better surveillance systems improving diagnostic tests and rapid action action. Also, new technology in making an effective vaccine considers prevention against HHS in poultry farms.

Conflict of Interest

The authors declared no conflicts of interest.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

References

1. Abd El-Ghany WA. A Comprehensive Review on Adenoviruses Infections in Fowl: Epidemiology, Forms, Diagnosis, and Control. Journal of World's Poultry Research. 2021;11(2):151-67.
2. Kataria J, Dhama K, Dey S, Rahul S, Gupta S. Hydropericardium syndrome: An emerging disease of poultry. Monograph published from Division of Avian Diseases, Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India. 2006.
3. Abdul-Aziz T, Hasan S. Hydropericardium syndrome in broiler chickens: its contagious nature and pathology. Research in Veterinary Science. 1995;59(3):219-21.
4. Asthana M, Chandra R, Kumar R. Hydropericardium syndrome: current state and future developments. Archives of virology. 2013;158(5):921-31.
5. Balamurugan V, Kataria J. The hydropericardium syndrome in poultry–a current scenario. Veterinary research communications. 2004;28(2):127-48.
6. Alemnesh W, Hair-Bejo M, Aini I, Omar A. Pathogenicity of fowl adenovirus in specific pathogen free chicken embryos. Journal of comparative pathology. 2012;146(2-3):223-9.
7. Gowda RS, Satyanarayana M. Hydropericardium syndrome in poultry. Indian Journal of Veterinary Pathology. 1994;18(2):159-61.
8. Ahmad I. Disease pattern and etiology of hydropericardium syndrome (Angara disease) in broiler chickens in Pakistan. Pak J Agr Res. 1989;10:195-9.
9. Cowen BS. Inclusion body hepatitis–anaemia and hydropericardium syndromes: aetiology and control. World's Poultry Science Journal. 1992;48(3):247-54.
10. Jadhao SJ, Deepak J, Kataria J, Kataria R, Tiwari A, Somvanshi R, et al. Characterisation of fowl adenoviruses from chickens affected with infectious hydropericardium during 1994-1998 in India. 2003.
11. Shane S. Hydropericardium-Hepatitis Syndrome the current world situation. Zootecnica International. 1996;19:20-7.
12. Asrani R, Gupta V, Sharma S, Singh S, Katoch R. Hydropericardium-hepatopathy syndrome in Asian poultry. The Veterinary Record. 1997;141(11):271-3.
13. Toro H, Prusas C, Raue R, Cerda L, Geisse C, Gonzalez C, Hess M. Characterization of fowl adenoviruses from outbreaks of inclusion body hepatitis/hydropericardium syndrome in Chile. Avian Diseases. 1999:262-70.
14. Borisov V, Borisov A, Gusev A. Hydropericardium syndrome in chickens in Russia. Proc 10th Int Cong World Vet Poult Assoc (Budapest, Hungary). 1997;258.
15. Abe T, Nakamura K, Tojo H, Mase M, Shibahara T, Yamaguchi S, Yuasa N. Histology, immunohistochemistry, and ultrastructure of hydropericardium syndrome in adult broiler breeders and broiler chicks. Avian diseases. 1998:606-12.
16. Kim JN, Byun SH, Kim MJ, Kim JJ, Sung HW, Mo IP. Outbreaks of hydropericardium syndrome and molecular characterization of Korean fowl adenoviral isolates. Avian diseases. 2008;52(3):526-30.
17. Hess M, Raue R, Prusas C. Epidemiological studies on fowl adenoviruses isolated from cases of infectious hydropericardium. Avian Pathology. 1999;28(5):433-9.
18. Kaján GL, Affranio I, Bistyák AT, Kecskeméti S, Benkő M. An emerging new fowl adenovirus genotype. Heliyon. 2019;5(5):e01732.
19. Akhtar S. Hydropericardium syndrome in broiler chickens in Pakistan. World's Poultry Science Journal. 1994;50(2):177-82.
20. Rabbani M, Naeem K, editors. In vitro and in vivo evaluation of avian adenovirus isolates from outbreaks of hydropericardium syndrome. Proceedings of the International Symposium on Adenovirus and Reovirus Infections in Poultry, Rauischholzhausen, Germany; 1996.
21. Mazaheri A, Prusas C, Voss M, Hess M. Some strains of serotype 4 fowl adenoviruses cause inclusion body hepatitis and hydropericardium syndrome in chickens. Avian Pathology. 1998;27(3):269-76.
22. Hess M. Detection and differentiation of avian adenoviruses: a review. Avian Pathology. 2000;29(3):195-206.
23. Benkő M, Aoki K, Arnberg N, Davison AJ, Echavarría M, Hess M, et al. ICTV virus taxonomy profile: Adenoviridae 2022. Journal of General Virology. 2022;103(3):001721.
24. Steer PA, Kirkpatrick NC, O'Rourke D, Noormohammadi AH. Classification of fowl adenovirus serotypes by use of high-resolution melting-curve analysis of the hexon gene region. Journal of clinical microbiology. 2009;47(2):311-21.
25. Hess M, Prusas C, Bergmann V, Mazaheri A, Raue R. Epizootiology of fowls adenoviruses. Berliner und Munchener Tierarztliche Wochenschrift. 2000;113(5):202-8.
26. McMullin PF. Diseases of poultry 14th edition: David E. Swayne, Martine Boulianne, Catherine M. Logue, Larry R. McDougald, Venugopal Nair, David L. Suarez, Sjaak de Wit, Tom Grimes, Deirdre Johnson, Michelle Kromm, Teguh Yodiantara Prajitno, Ian Rubinoff & Guillermo Zavala (Eds.), Hoboken, NJ, John Wiley & Sons, 2020, 1451 pp.,£ 190 (hardcover)/£ 171.99 (e-book), ISBN 9781119371168. Taylor & Francis; 2020.

27. Redondo H, Fragoso JS, Tahala MA, Bensassi Y, Gil I, Elbachir E, et al. Characterization of strain of fowl adenoviruses circulating in Morocco. Poultry science. 2018;97(11):4057-62.
28. Louis N, Fender P, Barge A, Kitts P, Chroboczek J. Cell-binding domain of adenovirus serotype 2 fiber. Journal of virology. 1994;68(6):4104-6.
29. Pallister J, Wright PJ, Sheppard M. A single gene encoding the fiber is responsible for variations in virulence in the fowl adenoviruses. Journal of Virology. 1996;70(8):5115-22.
30. Cheema A. An adenovirus infection of poultry in Pakistan. Rev Sci Tech l'Offce Inter Epizootics. 1989;8:789-98.
31. viralzone. Aviadenovirus [Available from: https://viralzone.expasy.org/184.
32. Shah M, Ashraf A, Khan M, Rahman M, Habib M, Chughtai M, Qureshi J. Fowl adenovirus: history, emergence, biology and development of a vaccine against hydropericardium syndrome. Archives of virology. 2017;162(7):1833-43.
33. Wang Z, Zhao J. Pathogenesis of hypervirulent fowl adenovirus serotype 4: the contributions of viral and host factors. Viruses 11: 741. 2019.
34. Sohaimi NM, Hair-Bejo M. A recent perspective on fiber and hexon genes proteins analyses of fowl adenovirus toward virus infectivity—A review. Open Veterinary Journal. 2021;11(4):569–80-–80.
35. Zhang Y, Liu A, Wang Y, Cui H, Gao Y, Qi X, et al. A single amino acid at residue 188 of the hexon protein is responsible for the pathogenicity of the emerging novel virus fowl adenovirus 4. Journal of Virology. 2021;95(17):e00603-21.
36. Sohaimi NM, Bejo MH, Omar AR, Ideris A, Isa NM. Hexon and fiber gene changes in an attenuated fowl adenovirus isolate from Malaysia in embryonated chicken eggs and its infectivity in chickens. Journal of veterinary science. 2018;19(6):759-70.
37. Matos M, Grafl B, Liebhart D, Hess M. The outcome of experimentally induced inclusion body hepatitis (IBH) by fowl aviadenoviruses (FAdVs) is crucially influenced by the genetic background of the host. Veterinary Research. 2016;47(1):1-10.
38. Li L, Wang J, Chen P, Zhang S, Sun J, Yuan W. Pathogenicity and molecular characterization of a fowl adenovirus 4 isolated from chicken associated with IBH and HPS in China. BMC veterinary research. 2018;14(1):1-8.
39. Zhang Y, Liu R, Tian K, Wang Z, Yang X, Gao D, et al. Fiber2 and hexon genes are closely associated with the virulence of the emerging and highly pathogenic fowl adenovirus 4. Emerging microbes & infections. 2018;7(1):1-10.
40. Liu R, Zhang Y, Guo H, Li N, Wang B, Tian K, et al. The increased virulence of hypervirulent fowl adenovirus 4 is independent of fiber-1 and penton. Research in veterinary science. 2020;131:31-7.
41. Fender P, Boussaid A, Mezin P, Chroboczek J. Synthesis, cellular localization, and quantification of penton-dodecahedron in serotype 3 adenovirus-infected cells. Virology. 2005;340(2):167-73.
42. Liu Y, Wan W, Gao D, Li Y, Yang X, Liu H, et al. Genetic characterization of novel fowl aviadenovirus 4 isolates from outbreaks of hepatitis-hydropericardium syndrome in broiler chickens in China. Emerging Microbes & Infections. 2016;5(1):1-8.
43. Pan Q, Wang J, Gao Y, Cui H, Liu C, Qi X, et al. The natural large genomic deletion is unrelated to the increased virulence of the novel genotype fowl adenovirus 4 recently emerged in China. Viruses. 2018;10(9):494.
44. Tan PK, Michou A-I, Bergelson JM, Cotten M. Defining CAR as a cellular receptor for the avian adenovirus CELO using a genetic analysis of the two viral fibre proteins. Journal of General Virology. 2001;82(6):1465-72.
45. Henry LJ, Xia D, Wilke ME, Deisenhofer J, Gerard RD. Characterization of the knob domain of the adenovirus type 5 fiber protein expressed in Escherichia coli. Journal of virology. 1994;68(8):5239-46.
46. Gao J, Zhao M, Duan X, Wang Y, Cao H, Li X, Zheng SJ. Requirement of cellular protein CCT7 for the replication of fowl adenovirus serotype 4 (FAdV-4) in leghorn male hepatocellular cells via interaction with the viral hexon protein. Viruses. 2019;11(2):107.
47. Khare R, Reddy VS, Nemerow GR, Barry MA. Identification of adenovirus serotype 5 hexon regions that interact with scavenger receptors. Journal of virology. 2012;86(4):2293-301.
48. Gout E, Gutkowska M, Takayama S, Reed J, Chroboczek J. Co-chaperone BAG3 and adenovirus penton base protein partnership. Journal of cellular biochemistry. 2010;111(3):699-708.
49. Yan J, Dong J, Wu J, Zhu R, Wang Z, Wang B, et al. Interaction between hexon and L4-100K determines virus rescue and growth of hexon-chimeric recombinant Ad5 vectors. Scientific reports. 2016;6(1):22464.
50. Xi Q, Cuesta R, Schneider RJ. Tethering of eIF4G to adenoviral mRNAs by viral 100k protein drives ribosome shunting. Genes & development. 2004;18(16):1997.
51. Toro H, Gonzalez O, Escobar C, Cerda L, Morales M, Gonzalez C. Vertical induction of the inclusion body hepatitis/hydropericardium syndrome with fowl adenovirus and chicken anemia virus. Avian diseases. 2001:215-22.
52. Su Q, Li Y, Meng F, Cui Z, Chang S, Zhao P. Newcastle disease virus-attenuated vaccine co-contaminated with fowl adenovirus and chicken infectious anemia virus results in inclusion body hepatitis-hydropericardium syndrome in poultry. Veterinary microbiology. 2018;218:52-9.
53. Naseem MN, Saleemi MK, Khan A, Khatoon A, Gul ST, Rizvi F, et al. Pathological effects of concurrent administration of aflatoxin B1 and fowl adenovirus-4 in broiler chicks. Microbial pathogenesis. 2018;121:147-54.
54. Schonewille E, Singh A, Göbel TW, Gerner W, Saalmüller A, Hess M. Fowl adenovirus (FAdV) serotype 4 causes depletion of B and T cells in lymphoid organs in specific pathogen-free chickens following experimental infection. Veterinary Immunology and Immunopathology. 2008;121(1-2):130-9.
55. Li R, Li G, Lin J, Han S, Hou X, Weng H, et al. Fowl adenovirus serotype 4 SD0828 infections causes high mortality rate and cytokine levels in specific pathogen-free chickens compared to ducks. Frontiers in Immunology. 2018;9:49.
56. Niu Y, Sun Q, Zhang G, Liu X, Shang Y, Xiao Y, Liu S. Fowl adenovirus serotype 4-induced apoptosis, autophagy, and a severe inflammatory response in liver. Veterinary microbiology. 2018;223:34-41.
57. Chi G, Feng X-X, Ru Y-X, Xiong T, Gao Y, Wang H, et al. TLR2/4 ligand-amplified liver inflammation promotes initiation of autoimmune hepatitis due to sustained IL-6/IL-12/IL-4/IL-25 expression. Molecular immunology. 2018;99:171-81.
58. Niu Y, Sun Q, Liu X, Liu S. Mechanism of fowl adenovirus serotype 4-induced heart damage and formation of pericardial effusion. Poultry science. 2019;98(3):1134-45.

59. Meng K, Yuan X, Yu J, Zhang Y, Ai W, Wang Y. Identification, pathogenicity of novel fowl adenovirus serotype 4 SDJN0105 in Shandong, China and immunoprotective evaluation of the newly developed inactivated oil-emulsion FAdV-4 vaccine. Viruses. 2019;11(7):627.
60. Gimeno I, Cortes A, Reddy S, López de Juan Abad B, Käser T, Limsatanun A. Highly virulent Marek's disease virus strains affect T lymphocyte function and viability of splenocytes in commercial meat-type chickens. Avian Pathology. 2019;48(6):564-72.
61. Minamitani T, Iwakiri D, Takada K. Adenovirus virus-associated RNAs induce type I interferon expression through a RIG-I-mediated pathway. Journal of virology. 2011;85(8):4035-40.
62. Barber MR, Aldridge Jr JR, Webster RG, Magor KE. Association of RIG-I with innate immunity of ducks to influenza. Proceedings of the National Academy of Sciences. 2010;107(13):5913-8.
63. Li H, Wang J, Qiu L, Han Z, Liu S. Fowl adenovirus species C serotype 4 is attributed to the emergence of hepatitis-hydropericardium syndrome in chickens in China. Infection, Genetics and Evolution. 2016;45:230-41.
64. Wei Z, Liu H, Diao Y, Li X, Zhang S, Gao B, et al. Pathogenicity of fowl adenovirus (FAdV) serotype 4 strain SDJN in Taizhou geese. Avian Pathology. 2019;48(5):477-85.
65. Schachner A, Matos M, Grafl B, Hess M. Fowl adenovirus-induced diseases and strategies for their control–a review on the current global situation. Avian Pathology. 2018;47(2):111-26.
66. McFerran J, Smyth J. Avian adenoviruses. Revue scientifique et technique (International Office of Epizootics). 2000;19(2):589-601.
67. Khan A, Sabri A, Mansoor M, Hussain I. Hydropericardium syndrome in Pakistan: a review. World's poultry science journal. 2005;61(4):647-54.
68. Abdul-Aziz T, Al-Attar M. New syndrome in Iraqi chicks. Veterinary Record. 1991;129(12).
69. Mittal D, Jindal N, Tiwari AK, Khokhar RS. Characterization of fowl adenoviruses associated with hydropericardium syndrome and inclusion body hepatitis in broiler chickens. Virusdisease. 2014;25(1):114-9.
70. Cowen B, Lu H, Weinstock D, Castro A, editors. Pathogenicity studies of fowl adenoviruses isolated in several regions of the world. International symposium on adenovirus infections in poultry, Rauischholzhausen, Germany; 1996.
71. Grgić H, Yang D-H, Nagy É. Pathogenicity and complete genome sequence of a fowl adenovirus serotype 8 isolate. Virus research. 2011;156(1-2):91-7.
72. Kaján GL, Kecskeméti S, Harrach B, Benkő M. Molecular typing of fowl adenoviruses, isolated in Hungary recently, reveals high diversity. Veterinary Microbiology. 2013;167(3-4):357-63.
73. Niczyporuk JS. Phylogenetic and geographic analysis of fowl adenovirus field strains isolated from poultry in Poland. Archives of virology. 2016;161(1):33-42.
74. Lim T-H, Lee H-J, Lee D-H, Lee Y-N, Park J-K, Youn H-N, et al. Identification and virulence characterization of fowl adenoviruses in Korea. Avian diseases. 2011;55(4):554-60.
75. Nakamura K, Mase M, Yamaguchi S, Shibahara T, Yuasa N. Pathologic study of specific-pathogen-free chicks and hens inoculated with adenovirus isolated from hydropericardium syndrome. Avian Diseases. 1999:414-23.
76. Zhao J, Zhong Q, Zhao Y, Hu Y-x, Zhang G-z. Pathogenicity and complete genome characterization of fowl adenoviruses isolated from chickens associated with inclusion body hepatitis and hydropericardium syndrome in China. Plos one. 2015;10(7):e0133073.
77. Ye J, Liang G, Zhang J, Wang W, Song N, Wang P, et al. Outbreaks of serotype 4 fowl adenovirus with novel genotype, China. Emerging Microbes & Infections. 2016;5(1):1-12.
78. Choi KS, Kye SJ, Kim JY, Jeon WJ, Lee EK, Park KY, Sung HW. Epidemiological investigation of outbreaks of fowl adenovirus infection in commercial chickens in Korea. Poult Sci. 2012;91(10):2502-6.
79. Pan Q, Liu L, Gao Y, Liu C, Qi X, Zhang Y, et al. Characterization of a hypervirulent fowl adenovirus 4 with the novel genotype newly prevalent in China and establishment of reproduction infection model of hydropericardium syndrome in chickens. Poultry Science. 2017;96(6):1581-8.
80. Vera-Hernández PF, Morales-Garzón A, Cortés-Espinosa DV, Galiote-Flores A, García-Barrera LJ, Rodríguez-Galindo ET, et al. Clinicopathological characterization and genomic sequence differences observed in a highly virulent fowl Aviadenovirus serotype 4. Avian Pathology. 2016;45(1):73-81.
81. Karunamoorthy G, Manickam R. Hydropericardium syndrome in quails. Poultry Times of India. 1998;2:1-31.
82. Naeem K, Akram HS. Hydropericardium syndrome outbreak in a pigeon flock. The Veterinary Record. 1995;136(12):296-7.
83. Choi K, Kye S, Kim J, Jeon W, Lee E, Park K, Sung H. Epidemiological investigation of outbreaks of fowl adenovirus infection in commercial chickens in Korea. Poultry science. 2012;91(10):2502-6.
84. Morshed R, Hosseini H, Langeroudi AG, Fard MHB, Charkhkar S. Fowl adenoviruses D and E cause inclusion body hepatitis outbreaks in broiler and broiler breeder pullet flocks. Avian diseases. 2017;61(2):205-10.
85. El-Shall NA, El-Hamid HSA, Elkady MF, Ellakany HF, Elbestawy AR, Gado AR, et al. Epidemiology, pathology, prevention, and control strategies of inclusion body hepatitis and hepatitis-hydropericardium syndrome in poultry: A comprehensive review. 2022.
86. Hafez HM. Avian adenoviruses infections with special attention to inclusion body hepatitis/hydropericardium syndrome and egg drop syndrome. 2011.
87. Guan R, Tian Y, Han X, Yang X, Wang H. Complete genome sequence and pathogenicity of fowl adenovirus serotype 4 involved in hydropericardium syndrome in Southwest China. Microbial pathogenesis. 2018;117:290-8.
88. Anjum A. Experimental transmission of hydropericardium syndrome and protection against it in commercial broiler chickens. Avian Pathology. 1990;19(4):655-60.
89. Anjum A, Sabri M, Iqbal Z. Hydropericarditis syndrome in broiler chickens in Pakistan. The Veterinary Record. 1989;124(10):247-8.
90. Steer PA, Sandy JR, O'Rourke D, Scott PC, Browning GF, Noormohammadi AH. Chronological analysis of gross and histological lesions induced by field strains of fowl adenovirus serotypes 1, 8b and 11 in one-day-old chickens. Avian pathology. 2015;44(2):106-13.
91. Jaffery M. A treatise on Angara disease (hydropericardium-pulmonary oedema-hepatonephritis syndrome). J Pak Vet Med Assoc. 1988;34(1):1-33.

92. Qureshi A. Hydropericardium and ascites. Poultry International. 1989;28(6):44-8.
93. Niu Y-j, Sun W, Zhang G-h, Qu Y-j, Wang P-f, Sun H-l, et al. Hydropericardium syndrome outbreak caused by fowl adenovirus serotype 4 in China in 2015. Journal of General Virology. 2016;97(10):2684-90.
94. Cui J, Xu Y, Zhou Z, Xu Q, Wang J, Xiao Y, et al. Pathogenicity and molecular typing of fowl adenovirus-associated with hepatitis/hydropericardium syndrome in central China (2015–2018). Frontiers in Veterinary Science. 2020;7:190.
95. De Luca C, Schachner A, Heidl S, Hess M. Vaccination with a fowl adenovirus chimeric fiber protein (crecFib-4/11) simultaneously protects chickens against hepatitis-hydropericardium syndrome (HHS) and inclusion body hepatitis (IBH). Vaccine. 2022;40(12):1837-45.
96. Nahed A, Abd El-Hamid HS, Elkady MF, Ellakany HF, Elbestawy AR, Gado AR, et al. Epidemiology, pathology, prevention, and control strategies of inclusion body hepatitis and hepatitis-hydropericardium syndrome in poultry: A comprehensive review. Frontiers in Veterinary Science. 2022;9.
97. Das T, Panda S, Panda H, Acharya A, Das N. Pathology of inclusion body hepatitis and hydropericardium syndrome in broiler chicken in natural outbreaks in Odisha. 2015.
98. Toroghi R, Sodavari S, Tabatabaeizadeh S-E, Sharghi A, Irankhah N, Fakhraee M, et al. The First Occurrence of Hepatitis-Hydropericardium Syndrome in Iran and Effective Applied Control Measures in the Affected Commercial Broiler Flock. Avian Diseases. 2022;66(2):213-9.
99. Ren G, Wang H, Yan Y, Liu F, Huang M, Chen R. Pathogenicity of a fowl adenovirus serotype 4 isolated from chickens associated with hydropericardium-hepatitis syndrome in China. Poultry science. 2019;98(7):2765-71.
100. Singh R, Bassessar V, Rani P, Mehra M, Azmi S. Pathomorphological diagnosis of Hepatitis-hydropericardium syndrome in poultry: A case report. Journal of Entomology and Zoology Studies. 2019;7:621-3.
101. Munir K, Muneer M, Tiwari A, Masaoud E, Chaudhry R. Effects of salinomycin on cell-mediated immunity of broiler chickens against hydropericardium syndrome and Newcastle disease viruses. Poultry science. 2009;88(1):86-91.
102. Tayade C, Jaiswal T, Mishra S, Koti M. L-Arginine stimulates immune response in chickens immunized with intermediate plus strain of infectious bursal disease vaccine. Vaccine. 2006;24(5):552-60.
103. Munir K, Muneer M, Tiwari A, Chaudhry R, Muruganandan S. Effects of polyether ionophores on the protective immune responses of broiler chickens against Angara disease and Newcastle disease viruses. Veterinary research communications. 2007;31(7):909-29.
104. Yin J, Jin H, Yang F, Ding Z, Huang C, Zhu Q, Wang B. Synergistic effects of adjuvants interferon-γ and levamisole on DNA vaccination against infection with Newcastle disease virus. Viral Immunology. 2007;20(2):288-99.
105. de Jonge WJ, Kwikkers KL, te Velde AA, van Deventer SJ, Nolte MA, Mebius RE, et al. Arginine deficiency affects early B cell maturation and lymphoid organ development in transgenic mice. The Journal of clinical investigation. 2002;110(10):1539-48.
106. Rani V, Kumar R, Upadhyay A, Kumar M. Therapeutic efficacy of chicken egg yolk immunoglobulins against hydropericardium syndrome in broiler chickens. Indian Journal of Animal Sciences. 2012;82(6):552-6.
107. Akhtar S. Studies on the rate of lateral spread of hydropericardium syndrome agent (s). Etiology, pathogenesis and control of hydropericardium syndrome in poultry Board on Science and Technology for International Development (BOSTID), Washington, DC. 1992.
108. Afzal M, Muneer R, Stein G. Studies on the aetiology of hydropericardium syndrome (Angara disease) in broilers. The Veterinary Record. 1991;128(25):591-3.
109. Ganesh K, Raghavan R. Hydropericardium hepatitis syndrome of broiler poultry: current status of research. Research in Veterinary Science. 2000;68(3):201-6.
110. Afzal M, Ahmad I. Efficacy of an inactivated vaccine against hydropericardium syndrome in broilers. The Veterinary Record. 1990;126(3):59-60.
111. Shafique M, Khan M, Javeed M, Khan A. Lesions of hydropericardium syndrome in embryonating eggs and in broiler chicks under immunosuppression. Singapore Veterinary Journal. 1993;16(17):58-64.
112. Shivachandra S, Sah R, Singh S, Kataria J, Manimaran K. Immunosuppression in broiler chicks fed aflatoxin and inoculated with fowl adenovirus serotype-4 (FAV-4) associated with hydropericardium syndrome. Veterinary research communications. 2003;27(1):39-51.
113. Monreal L, Cesarini C. Coagulopathies in horses with colic. The Veterinary Clinics of North America Equine Practice. 2009;25(2):247-58.
114. Akhtar S, Zahid S, Khan M. Risk factors associated with hydropericardium syndrome in broiler flocks. The Veterinary Record. 1992;131(21):481-4.
115. Liu A, Zhang Y, Cui H, Wang X, Gao Y, Pan Q. Advances in vaccine development of the emerging novel genotype fowl adenovirus 4. Frontiers in Immunology. 2022;13:916290.
116. Ahmad I, Malik M, Iqbal K, Ahmed K, Naz S. Efficacy of formalinized liver-organ-vaccine against Angara disease in broilers. Veterinarski Arhiv. 1990;60(3):131-8.
117. Du D, Zhang P, Li X, Tian H, Cheng Y, Sheng D, et al. Cell-culture derived fowl adenovirus serotype 4 inactivated vaccine provides complete protection for virus infection on SPF chickens. Virusdisease. 2017;28(2):182-8.
118. Xia J, Yao K-C, Liu Y-Y, You G-J, Li S-Y, Liu P, et al. Isolation and molecular characterization of prevalent Fowl adenovirus strains in southwestern China during 2015–2016 for the development of a control strategy. Emerging microbes & infections. 2017;6(1):1-9.
119. Kataria J, Verma K, Jadhao S, Deepak J, Sah R. Efficacy of an inactivated oil emulsified vaccine against inclusion body hepatitis-hydropericardium syndrome (Litchi disease) in chicken prepared from cell culture propagated fowl adenovirus. INDIAN JOURNAL OF COMPARATIVE MICROBIOLOGY IMMUNOLOGY AND INFECTIOUS DISEASES. 1997;18:38-42.
120. Naeem K, Rabbani M, Hussain M, Cheema A. Development of cell culture vaccine against hydropericardium syndrome in poultry. Pakistan Veterinary Journal. 1995;15:150-.
121. Kumar R, Chandra R, Shukla S, Agrawal D, Kumar M. Hydropericardium syndrome (HPS) in India: a preliminary study on the causative agent and control of the disease by inactivated autogenous vaccine. Tropical Animal Health and Production. 1997;29(3):158-64.
122. Afzal M, Hameed A, Khan A. Immune response to inactivated hydropericardium syndrome vaccine in broilers. Pakistan Veterinary Journal. 1994;14:5-.
123. Shane S, Jaffery M. Hydropericardium-hepatitis syndrome (Angara disease). Diseases of poultry. 1997;10:1019-22.

124. Mashkoor S, Hameed A, Ahmad H, Qureshi M. Improved Angara disease vaccine for broiler chicks. Veterinarski Arkhiv. 1994;64:27-33.
125. Roy P, Koteeswaran A, Manickam R. Efficacy of an inactivated oil emulsion vaccine against hydropericardium syndrome in broilers. Veterinary record. 1999;145(16):458-9.
126. Schonewille E, Jaspers R, Paul G, Hess M. Specific-pathogen-free chickens vaccinated with a live FAdV-4 vaccine are fully protected against a severe challenge even in the absence of neutralizing antibodies. Avian Diseases. 2010;54(2):905-10.
127. Mansoor MK, Hussain I, Arshad M, Muhammad G. Preparation and evaluation of chicken embryo-adapted fowl adenovirus serotype 4 vaccine in broiler chickens. Tropical animal health and production. 2011;43(2):331-8.
128. Toro H, Gonzalez C, Cerda L, Morales M, Dooner P, Salamero M. Prevention of inclusion body hepatitis/hydropericardium syndrome in progeny chickens by vaccination of breeders with fowl adenovirus and chicken anemia virus. Avian diseases. 2002;46(3):547-54.
129. Wang X, Tang Q, Chu Z, Wang P, Luo C, Zhang Y, et al. Immune protection efficacy of FAdV-4 surface proteins fiber-1, fiber-2, hexon and penton base. Virus research. 2018;245:1-6.
130. Ruan S, Zhao J, Yin X, He Z, Zhang G. A subunit vaccine based on fiber-2 protein provides full protection against fowl adenovirus serotype 4 and induces quicker and stronger immune responses than an inactivated oil-emulsion vaccine. Infection, Genetics and Evolution. 2018;61:145-50.
131. Mu Y, Xie Q, Wang W, Lu H, Lian M, Gao W, et al. A Novel Fiber-1-Edited and Highly Attenuated Recombinant Serotype 4 Fowl Adenovirus Confers Efficient Protection Against Lethal Challenge. Frontiers in Veterinary Science. 2021;8.
132. Xie Q, Cao S, Zhang W, Wang W, Li L, Kan Q, et al. A novel fiber-2-edited live attenuated vaccine candidate against the highly pathogenic serotype 4 fowl adenovirus. Veterinary research. 2021;52(1):1-10.
133. Yin D, He L, Zhu E, Fang T, Yue J, Wen M, et al. A fowl adenovirus serotype 4 (FAdV-4) Fiber2 subunit vaccine candidate provides complete protection against challenge with virulent FAdV-4 strain in chickens. Veterinary Microbiology. 2021;263:109250.
134. Shah M, Ashraf A, Rahman M, Khan M, Qureshi J. A subunit vaccine against hydropericardium syndrome using adenovirus penton capsid protein. Vaccine. 2012;30(50):7153-6.
135. MacDonald NE. Vaccine hesitancy: Definition, scope and determinants. Vaccine. 2015;33(34):4161-4.
136. Pulcini C, Massin S, Launay O, Verger P. Factors associated with vaccination for hepatitis B, pertussis, seasonal and pandemic influenza among French general practitioners: a 2010 survey. Vaccine. 2013;31(37):3943-9.
137. Chen L, Yin L, Zhou Q, Li Q, Luo Y, Xu Z, et al. Immunogenicity and protective efficacy of recombinant fiber-2 protein in protecting SPF chickens against fowl adenovirus 4. Vaccine. 2018;36(9):1203-8.
138. Vickers NJ. Animal communication: when i'm calling you, will you answer too? Current biology. 2017;27(14):R713-R5.
139. Tian K-y, Guo H-F, Li N, Zhang Y-h, Wang Z, Wang B, et al. Protection of chickens against hepatitis-hydropericardium syndrome and Newcastle disease with a recombinant Newcastle disease virus vaccine expressing the fowl adenovirus serotype 4 fiber-2 protein. Vaccine. 2020;38(8):1989-97.
140. Zhang Y, Liu A, Wang Y, Cui H, Gao Y, Qi X, et al. A single amino acid at residue 188 of the hexon protein is responsible for the pathogenicity of the emerging novel virus fowl adenovirus 4. Journal of Virology. 2021;95(17):10.1128/jvi. 00603-21.
141. Zhang Y, Liu A, Jiang N, Qi X, Gao Y, Cui H, et al. A novel inactivated bivalent vaccine for chickens against emerging hepatitis-hydropericardium syndrome and infectious bursal disease. Veterinary Microbiology. 2022;266:109375.
142. Pan Q, Zhang Y, Liu A, Cui H, Gao Y, Qi X, et al. Development of a novel avian vaccine vector derived from the emerging fowl adenovirus 4. Frontiers in Microbiology. 2021;12:780978.
143. Lu H, Xie Q, Zhang W, Zhang J, Wang W, Lian M, et al. A novel recombinant FAdV-4 virus with fiber of FAdV-8b provides efficient protection against both FAdV-4 and FAdV-8b. Viruses. 2022;14(2):376.