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REVIEW ARTICLE

Hepatitis-Hydropericardium Syndrome (Angara Disease) in Poultry: A Comprehensive Review

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Abstract

Hepatitis-Hydropericardium Syndrome (HHS), also known as Angara disease, is an acute, highly contagious viral disease primarily affecting broiler chickens aged 3–6 weeks, posing a significant threat to global poultry production. First reported in Pakistan in 1987, HHS has since spread across Asia, the Middle East, the Americas, and Europe, driven by fowl adenovirus serotype 4 (FAdV-4) of species C. This non-enveloped, double-stranded DNA virus causes sudden mortality rates of 10–80%, characterized by hepatic inflammation, hydropericardium, and systemic lesions including hepatomegaly, pericardial effusion, renal pallor, and pulmonary edema. Transmission occurs via vertical (egg contamination) and horizontal (fecal-oral) routes, with FAdV-4 replicating in intestinal epithelia before viremic dissemination to target organs such as the liver, heart, and kidneys. Pathogenesis involves hepatocellular necrosis, basophilic intranuclear inclusions, and immunosuppression, exacerbated by hypervirulent strains emerging since 2015, featuring genomic deletions in fiber-2 and hexon genes. Clinical signs include lethargy, ruffled feathers, anorexia, and discolored droppings, with post-mortem hallmarks of friable livers and watery to gelatinous transudate straw-colored pericardial fluid. Diagnosis combines epidemiological patterns, gross pathology, histopathology, and molecular tools such as PCR for FAdV-4 detection, differentiating HHS from Inclusion Body Hepatitis caused by other serotypes. Prevention relies on biosecurity (hygiene and pest control as a mechanical carrier), and vaccination of breeder flocks using inactivated or recombinant vaccines is important for transferring maternal antibodies. No specific antivirals exist; supportive antibiotics mitigate secondary infections. HHS inflicts substantial economic losses through mortality, impaired growth, poor feed conversion, and control costs. Enhanced surveillance, strain-specific vaccines, and host resistance research are crucial for sustainable mitigation, underscoring HHS's ongoing challenge to poultry health and industry viability.

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Introduction

Defining Hepatitis-Hydropericardium Syndrome (HHS) and Angara Disease

Hepatitis-Hydropericardium Syndrome (HHS) is an acute, highly infectious disease of broiler chickens that represents a major threat to global poultry production (1). The condition is characterized by hepatic inflammation (hepatitis) and the accumulation of serous fluid within the pericardial sac (hydropericardium) (2). The etiological agent is fowl adenovirus serotype 4 (FAdV-4), a member of Group I adenoviruses, which induces sudden mortality in affected flocks, with reported rates ranging from 65% to 80% in severe outbreaks (3). The syndrome has been described under different names across regions: "Angara disease" in Pakistan, "Leachy" in India, and "Infectious Hydropericardium" in some contexts. In scientific literature, it is also referred to as "Inclusion Body Hepatitis-Hydropericardium Syndrome" (IBH-HPS). This diversity in terminology reflects regional recognition and the association with Inclusion Body Hepatitis (IBH), although a clear distinction between HHS and IBH remains essential for accurate diagnosis and effective control (4).

Historical Background

HHS was first reported in 1987 in broiler chickens in the Angara Goth area near Karachi, Pakistan, from which the term "Angara disease" originated. The syndrome rapidly disseminated across Pakistan and subsequently to neighboring countries, including India, Iraq, and Kuwait, before extending its presence to the Americas, where it was documented in Mexico, Ecuador, Peru, and Chile (4, 5). Affected flocks typically comprised broilers aged 3–5 weeks and were characterized by sudden high mortality accompanied by pericardial effusion and hepatic discoloration. For several years, the causative agent remained unidentified, which hindered the development of control measures (6). The definitive recognition of FAdV-4 as the primary etiological agent in the late 1990s was a pivotal advance, facilitating research on pathogenesis and enabling the development of vaccination-based prevention strategies (7).

Current Understanding and Significance

Despite clarification of its etiology, HHS continues to impose significant economic losses worldwide due to high mortality, reduced productivity, and costs associated with prevention and control (8). Outbreaks typically occur in broilers between 3 and 6 weeks of age, a critical stage in intensive production systems. Characteristic lesions include hepatomegaly, hepatic discoloration, and watery to gelatinous transudate straw-colored pericardial fluid, reflecting the severe systemic effects of infection. Moreover, FAdV-4 exhibits immunosuppressive properties that predispose affected birds to secondary infections, thereby exacerbating flock losses. The continued emergence of hypervirulent strains, regional variability in biosecurity practices, and inconsistent implementation of vaccination strategies sustain the importance of HHS as a global poultry health concern (1). A comprehensive approach integrating epidemiological surveillance, biosecurity enhancement, and vaccination remains essential for mitigating its impact and safeguarding the sustainability of commercial poultry production (4).

Etiology

Causative Agent: Fowl Adenovirus (FAdV)

Hepatitis-Hydropericardium Syndrome (HHS) is caused by fowl adenovirus (FAdV), a member of the family Adenoviridae. FAdVs are non-enveloped, double-stranded DNA viruses classified within the genus *Aviadenovirus*, which includes adenoviruses pathogenic to avian species. The genus is divided into five species (A–E) comprising at least 12 recognized serotypes (FAdV-1 to FAdV-11, with subtypes FAdV-8a and FAdV-8b). These viruses are widely distributed in poultry populations and vary in pathogenic potential across serotypes (9) (Table 1).

Role of FAdV Serotype 4

Among the known serotypes, FAdV-4 (species C, commonly referred to as FAdV-C) has been established as the principal etiological agent of HHS worldwide. Its role was conclusively demonstrated in the late 1990s, resolving long-standing uncertainty about the disease's origin. Since 2015, hypervirulent strains of FAdV-4 have emerged, particularly in China, where they have been associated with markedly higher morbidity and mortality compared to earlier strains. This evolution underscores the continuing importance of monitoring viral variation and its impact on disease outbreaks (10).

Characteristics and Genetic Makeup of FAdV-4

The FAdV-4 virion is a non-enveloped, icosahedral particle measuring 70–90 nm in diameter. Its genome is a linear, double-stranded DNA molecule of approximately 45 kilobases, with a guanine–cytosine (G+C) content of 53–59%. The viral genome encodes multiple structural proteins

(e.g., hexon, penton base, fiber-1, fiber-2, and minor capsid proteins VI, VII, VIII, III, μ) and non-structural proteins (e.g., E1A, E1B, E3, E4, DNA-binding protein, terminal protein, 100K, 52/55K, and pIVaII), which are essential for replication and assembly (11, 12).

A distinctive feature of FAdV-4 is the presence of two fiber proteins (fiber-1 and fiber-2), which differ in length and function. Fiber-1 mediates attachment to host cell receptors, while fiber-2 has been implicated in virulence. Genomic analyses of hypervirulent FAdV-4 strains have identified deletions in specific open reading frames (ORFs 19, 27, and 48) and mutations in major structural genes, particularly fiber-2 and hexon. These alterations are strongly associated with enhanced pathogenicity, suggesting a molecular basis for the increased virulence observed in recent outbreaks (13, 14).

Table 1. Classification of adenoviruses affecting poultry (8).

Family	Genus	Species	Serotype	Host range	Disease
Adenoviridae	*Aviadenovirus*	Fowl adenovirus	A	Chicken, quail, guinea fowl, ostrich	CELO, AGE, QB
			B	Chicken, pigeon	
			C	Chicken, psittacine	HHS
			D	Chicken, pigeon, ostrich	IBH
			E	Chicken, ostrich, pigeon	
		Duck adenovirus	B	Muscovy duck	
		Turkey adenovirus	B	Turkey	HE, MSD, AAS
			C	Turkey	
			D	Turkey	
		Goose adenovirus	A	Goose	
		Falcon adenovirus	A	Aplomado/orange-breasted/teita falcon, kestrel	
		Pigeon adenovirus	A	Pigeon	
			B	Pigeon	
	Siadenovirus	Pheasant adenovirus	A	Pheasant, Turkey	HE, MSD, AAS
		Raptor adenovirus	A	Raptor	
	Atadenovirus	Duck adenovirus	A	Duck, Chicken	EDS76

CELO, Chicken Embryo Lethal Orphan; QB, Quail Bronchitis; IBH, Inclusion Body Hepatitis; HHS, Hepatitis-Hydropericardium Syndrome; AGE, Adenoviral Gizzard Erosion; AAS, Avian Adenoviral Splenomegaly; EDS, Egg Drop Syndrome; MSD, Marble Spleen Disease; HE, Hemorrhagic Enteritis.

Pathogenesis

Mechanisms of Infection

The transmission of Hydropericardium Hepatitis Syndrome (HHS) occurs through both vertical and horizontal routes (15). The primary method of transmission from one generation of intensively raised poultry to the next occurs vertically through the embryonated egg. Viral antigens can be identified in both the yolk and the albumen of the egg (16). In contrast, horizontal transmission is facilitated by direct contact between birds or indirectly through contaminated environments, most commonly via the fecal–oral route (4, 8). This mode of spread is supported by the persistence of the virus in infected feces and by contamination of egg trays, transport boxes, vehicles, and other fomites within poultry facilities (17).

Once ingested by a susceptible bird, fowl adenovirus serotype 4 (FAdV-4) initially establishes replication within the epithelial cells of the small and large intestines. Following this primary replication phase, the virus gains entry into the bloodstream, producing a viremic stage that enables systemic dissemination to a variety of organs (7, 18). Target tissues commonly affected include the liver, heart, kidneys, lungs, bone marrow, and bursa of Fabricius (19). The incubation period of HHS is remarkably short, generally ranging from 24 to 48 hours, a feature that accounts for the acute onset and rapid progression of outbreaks. Virus shedding occurs through feces, ocular and nasal discharges, as well as from the bursa of Fabricius, facilitating both direct bird-to-bird transmission and extensive environmental contamination (4, 20).

Target Organs

The liver is recognized as the principal site of FAdV-4 replication and pathology. Extensive viral replication in hepatic tissue induces hepatocellular necrosis and inflammation, leading to hepatitis as a defining lesion of the disease. The heart is another critical target organ; infection produces hydropericardium, manifested by the accumulation of a clear to straw-colored, watery to gelatinous transudate in the pericardial sac. This exudate imposes mechanical pressure on the myocardium,

disrupting cardiac function and contributing significantly to mortality (21, 22).

Additional organs may also exhibit marked pathological alterations. The kidneys often present with pallor, enlargement, and a mottled appearance characterized by alternating pale and hemorrhagic foci. Pulmonary involvement, including congestion and edema, can contribute to respiratory distress. Enlargement of the spleen is frequently observed, reflecting an immune response, while thymic atrophy has also been reported, suggesting an immunosuppressive effect of infection. Collectively, these lesions demonstrate the systemic nature of FAdV-4 infection and its capacity to compromise multiple organ systems (19, 23) (Figure 1).

Cellular Damage

Histopathological assessment of the liver in affected birds reveals multifocal areas of hepatocellular necrosis accompanied by infiltration of mononuclear cells, indicating an active inflammatory response (24). A distinctive diagnostic hallmark of FAdV infection is the presence of basophilic intranuclear inclusion bodies within hepatocytes, representing viral replication complexes within the nucleus. These inclusions are critical for confirming the diagnosis of HHS in histological examinations (25).

In cardiac tissue, infection may induce myocardial edema and necrosis of cardiomyocytes, changes that underlie functional impairment of the heart and the development of hydropericardium. Renal pathology often includes congestion, hemorrhage, and parenchymal damage, reflecting the kidney's role as a secondary target organ (21).

Recent studies have expanded the understanding of cellular pathogenesis in FAdV-4 infection. Evidence suggests that viral exploitation of autophagy pathways within kidney cells may promote replication efficiency (28). In addition, viral structural proteins such as the hexon protein have been shown to interact with host chaperone proteins, notably CCT7, thereby enhancing viral propagation (27). FAdV-4 infection is also associated with endoplasmic reticulum stress and a robust inflammatory response, both of which exacerbate tissue injury and contribute to disease progression. These cellular-level mechanisms highlight the complex interplay between viral replication strategies and host defense systems in determining the outcome of infection (28, 29) (Table 2).

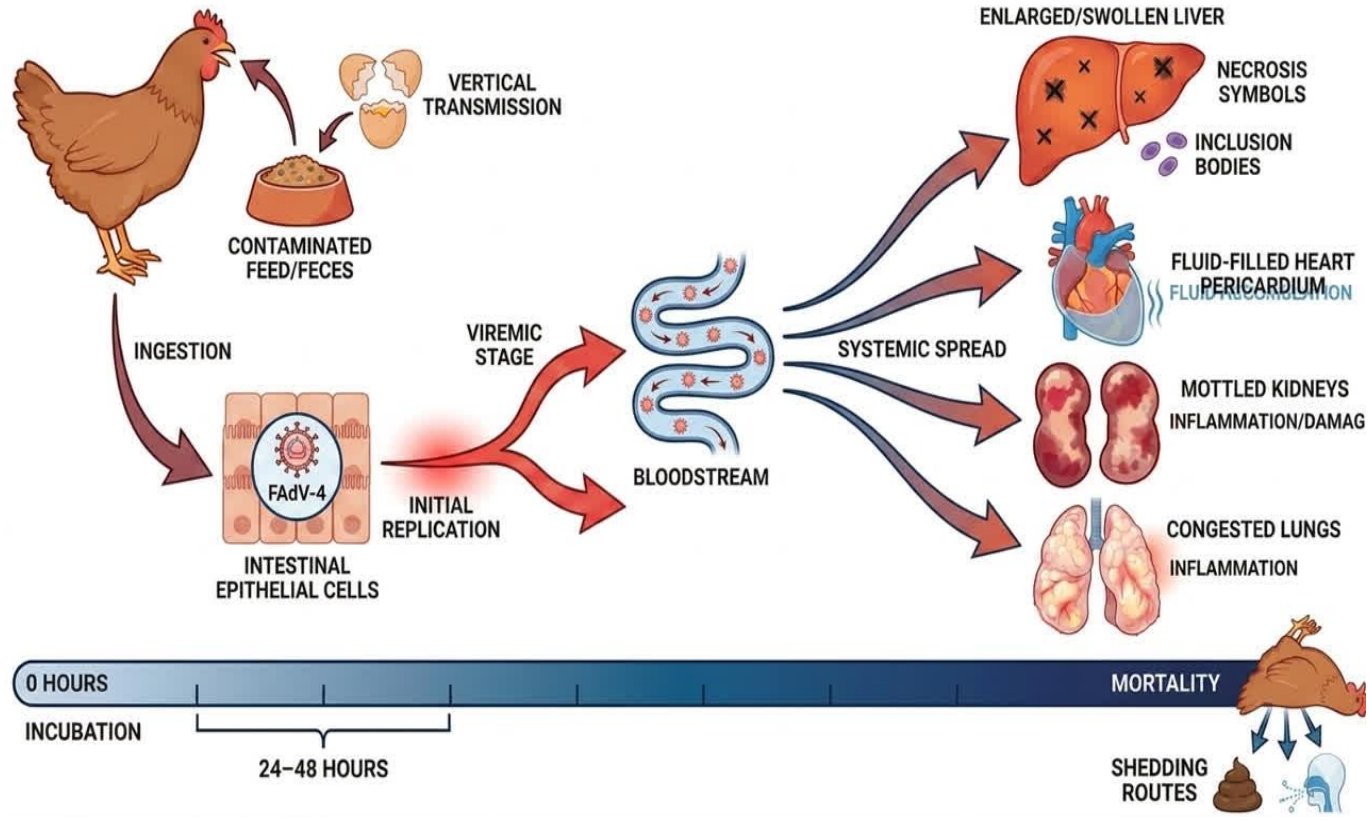


Figure 1. Pathogenesis pathway of FAdV-4 in HHS

Table 2. Pathogenesis of FAdV-4 in Hepatitis-Hydropericardium Syndrome (HHS): Transmission, Target Organs, and Cellular Pathology

Aspect	Description	Key Features/Mechanisms
Transmission Routes	Vertical: From infected breeder hens to progeny via contaminated eggs.	Early infection in newly hatched chicks; perpetuates virus across generations.
	Horizontal: Direct bird-to-bird contact or indirect via contaminated environments (fecal-oral route).	Supported by virus persistence in feces; fomites include egg trays, transport boxes, vehicles.
Initial Infection	Ingestion by susceptible bird; replication in epithelial cells of small and large intestines.	Primary replication phase leads to viremia and systemic dissemination to organs.
Incubation Period	24–48 hours.	Accounts for acute onset and rapid outbreak progression.
Virus Shedding	Through feces, ocular/nasal discharges, and bursa of Fabricius.	Facilitates direct transmission and environmental contamination.
Target Organs	Liver (primary); heart, kidneys, lungs, bone marrow, bursa of Fabricius, spleen, thymus.	Systemic involvement; spleen enlargement (immune response); thymic atrophy (immunosuppression).
Lesions in Organs	Liver: Hepatocellular necrosis and inflammation (hepatitis).	Hepatomegaly, friable tissue.
	Heart: Hydropericardium (clear/straw-colored transudate in pericardial sac).	Mechanical pressure on myocardium; disrupts cardiac function, contributes to mortality.
	Kidneys: Pallor, enlargement, mottled (pale/hemorrhagic foci).	Congestion, hemorrhage, parenchymal damage.
	Lungs: Congestion and edema.	Contributes to respiratory distress.
Cellular Damage	Liver: Multifocal hepatocellular necrosis, mononuclear cell infiltration, basophilic intranuclear inclusion bodies.	Diagnostic hallmark; viral replication complexes in nucleus.
	Heart: Myocardial edema, cardiomyocyte necrosis.	Underlies functional impairment and hydropericardium.
	Kidneys: Congestion, hemorrhage, parenchymal damage; exploitation of autophagy pathways.	Enhances viral replication efficiency.
Molecular Interactions	Hexon protein interacts with host chaperone (CCT7); endoplasmic reticulum stress; robust inflammatory response.	Exacerbates tissue injury; highlights virus-host interplay in disease progression.

Epidemiology

Geographical Distribution

Hepatitis-Hydropericardium Syndrome (HHS) was first reported in Pakistan in 1987 and has since developed a significant global presence (2, 30). The disease is well-documented across Asia, affecting major poultry-producing countries such as India, Iraq, Iran, Kuwait, Korea, Japan, and more recently Bangladesh, where its prevalence appears to be increasing (32, 41). In India, it is also referred to as Leachy disease, highlighting its regional impact. The Middle East has similarly experienced outbreaks, confirming the virus's ability to spread across diverse poultry systems (4).

Beyond Asia, HHS has been reported in North America (Canada and the United States) and throughout Central and South America, including Mexico, Ecuador, Peru, and Chile (4). Its distribution across both industrial and small-scale production systems in the Americas underscores the adaptability of the virus. In Europe, outbreaks have been recorded in countries such as Russia, Slovakia, Hungary, and Poland, demonstrating its spread beyond its original regions. The continuing identification of cases in new geographic areas emphasizes the need for sustained global surveillance and control strategies (32, 33) (Figure 2).

Prevalence in Different Poultry Populations

HHS primarily affects broiler chickens, with the highest susceptibility observed between 3 and 6 weeks of age, a critical phase for growth in commercial production. Broiler parents during the rearing period can also be affected, raising concerns about vertical transmission and long-term impacts on breeder stock (34). In contrast, laying flocks and breeder pullets generally show lower susceptibility, likely due to age-related resistance and differences in housing or management (35).

Although chickens remain the principal host, sporadic cases in other avian species, such as pigeons and quail, indicate a broader host range under certain conditions. A recent study in Bangladesh reported an overall prevalence of 10.55% in broiler populations, with the highest rate (15.31%) occurring in birds between two and three weeks

of age. These findings suggest an early peak of vulnerability in young broilers (31).

Factors Influencing Spread

The spread of HHS is shaped by several interrelated factors. Host age is critical, as younger broilers (3–6 weeks) are far more susceptible and experience higher mortality. Susceptibility may also vary among poultry species and chicken breeds (36).

Farm management practices significantly influence outbreak dynamics. High stocking densities, multi-age rearing systems, and inadequate biosecurity facilitate rapid horizontal transmission through contaminated feces, feed, water, and environmental surfaces. In contrast, strict biosecurity can markedly reduce viral spread (37).

Co-infections with immunosuppressive agents such as chicken anemia virus (CAV) and infectious bursal disease virus (IBDV) exacerbate disease severity by weakening immune defenses, thereby heightening mortality. The protective role of maternal antibodies transferred from vaccinated breeder hens is particularly important in early life, while vertical transmission via eggs remains a critical pathway for perpetuating the virus across generations (31, 38).

Environmental conditions also contribute. Seasonal patterns, such as higher incidence during summer and rainy months in Bangladesh, point to the role of temperature and humidity. Additional stressors—heat, poor ventilation, overcrowding, and nutritional deficiencies—further compromise immunity and increase susceptibility to infection (4, 11) (Table 3).

Table 3. Global Epidemiology and Spread of Hepatitis–Hydropericardium Syndrome (HHS)

Category	Summary of Key Points	References
Initial Emergence	First identified in Pakistan in 1987; rapid subsequent international spread.	(2, 30)
Geographical Distribution – Asia	Widely reported in India (also called *Leachy disease*), Iraq, Kuwait, Korea, Japan, and Bangladesh (increasing prevalence).	(4, 31)
Geographical Distribution – Americas	Documented in Canada, USA, Mexico, Ecuador, Peru, and Chile; occurs in both industrial and small-scale farms.	(4)
Geographical Distribution – Europe	Outbreaks in Russia, Slovakia, Hungary, and Poland.	(32, 33)
Primary Affected Population	Broilers aged **3–6 weeks** most susceptible; broiler parents during rearing may also be affected.	(34)
Lower Susceptibility Groups	Layers and breeder pullets generally less affected due to increased age-related resistance.	(35)
Other Avian Hosts	Occasional infections in pigeons and quail.	—
Reported Prevalence	Bangladesh: overall 10.55% in broilers; highest prevalence (15.31%) in birds aged 2–3 weeks.	(31)
Host Factors Influencing Spread	Younger age increases susceptibility; possible breed differences; immunosuppressive co-infections (CAV, IBDV) increase severity.	(36, 38)
Farm Management Factors	High density, multi-age systems, poor sanitation, weak biosecurity increase spread; strong biosecurity reduces outbreaks.	(37)
Environmental & Seasonal Factors	Higher incidence during hot and rainy seasons; heat stress, humidity, poor ventilation, overcrowding, and poor nutrition enhance susceptibility.	(4, 11)
Transmission Dynamics	Horizontal spread via feces, feed, water, contaminated surfaces; vertical transmission through infected eggs perpetuates outbreaks.	(31, 38)

Clinical Signs and Symptoms

Observed Signs in Affected Poultry

Hepatitis-Hydropericardium Syndrome (HHS) in poultry is most commonly recognized by a sudden and sharp rise in flock mortality, often serving as the first warning sign for producers. Affected birds typically present with lethargy, ruffled feathers, and reduced responsiveness, often huddling in corners of the poultry house (39). Yellow to green and watery to mucoid droppings are frequently reported, reflecting liver dysfunction and excess bile secretion (40).

Other clinical manifestations include depression, reduced activity, and discolored droppings ranging from yellowish to greenish, suggestive of hepatobiliary involvement. Infected birds may also develop fever, anorexia or inappetence, and, in advanced cases, prostration with inability to rise. Loss of appetite (asitia) is frequently reported, while flock uniformity is often compromised, with some birds showing stunting, poor growth, or general debilitation compared to their healthy counterparts (1, 9, 15) (Figure 3).

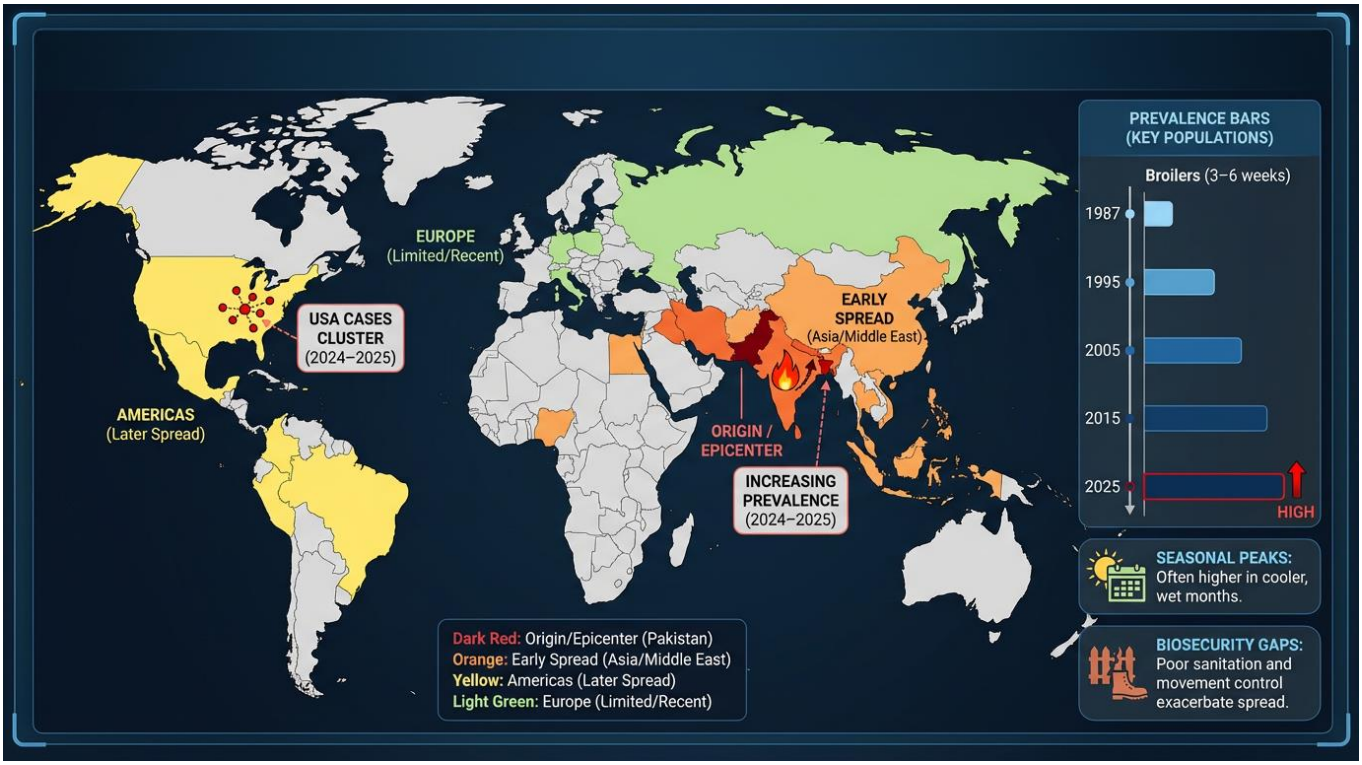


Figure 2. HHS geographical distribution and outbreak history (1987-2025)

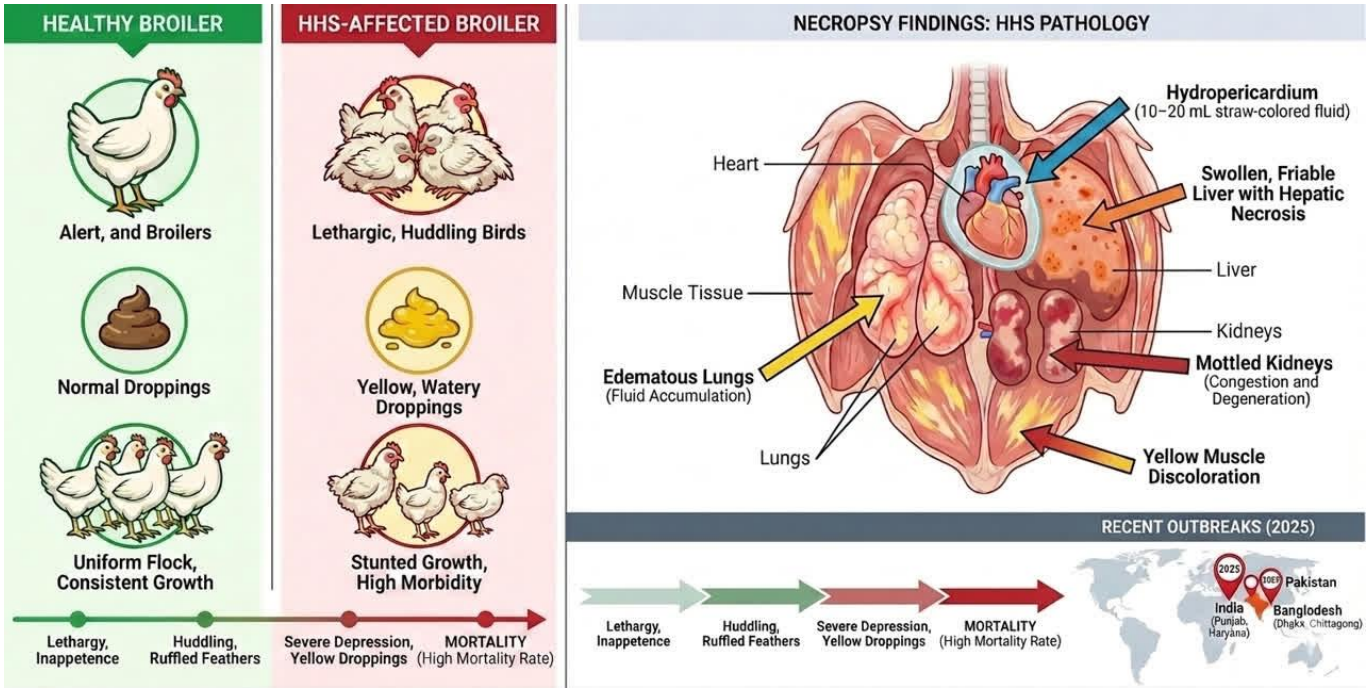


Figure 3. Comparison of healthy vs. HHS-affected poultry

Post-Mortem Lesions

The hallmark lesion of HHS is hydropericardium, characterized by the accumulation of clear to straw-colored fluid (often 10–20 mL) in the pericardial sac. This pathognomonic finding is usually accompanied by severe hepatic changes: enlarged, pale, and friable livers with focal to coalescing necrotic areas (40).

Other systemic changes are frequently observed. Carcasses may exhibit generalized congestion, and the lungs typically appear edematous. The kidneys often show swelling with alternating pale and hemorrhagic areas (41). Lymphoid organs are variably affected: the bursa of

Fabricius may be enlarged and edematous (42), the spleen may be swollen with mottled pale and hemorrhagic regions, and the thymus may appear atrophied. The heart often appears flabby due to pericardial distension (43).

Additional characteristic findings include a turmeric-yellow discoloration of the dividing lines between breast muscles and the abdominal cavity, sometimes accompanied by jaundice of the skin and body fat. Ascites and pancreatic necrosis may occur in severe cases (22). Petechial hemorrhages can appear in the leg muscles and the proventricular mucosa, while congestion and ecchymotic hemorrhages may be present in the intestines. Occasional hemorrhages are also noted on the pericardium and liver capsule (8) (Table 4).

Table 4. Clinical Signs and Post-Mortem Lesions of Hepatitis-Hydropericardium Syndrome (HHS) in Poultry

Category	Subcategory/Aspect	Description/Key Features
Clinical Signs	Sudden Mortality	Sharp rise in flock mortality; first warning sign for producers.
	Behavioral Changes	Lethargy, ruffled feathers, reduced responsiveness, huddling in corners; depression, reduced activity.
	Gastrointestinal/Droppings	Yellow to mucoid droppings (reflecting liver dysfunction and excess bile); yellowish-green discoloration.
	Systemic Signs	Fever, anorexia/inappetence, prostration (inability to rise), asitia (loss of appetite); stunting, poor growth, compromised flock uniformity.
Post-Mortem Lesions	Hydropericardium (Hallmark)	Accumulation of clear/straw-colored fluid (10–20 mL) in pericardial sac; flabby heart due to distension.
	Hepatic Changes	Enlarged, pale, friable livers with focal/coalescing necrotic areas.
	Renal Changes	Swelling with alternating pale/hemorrhagic areas; congestion, hemorrhage.
	Pulmonary/Systemic	Edematous lungs; generalized carcass congestion; ascites in severe cases.
	Lymphoid Organs	Enlarged/edematous bursa of Fabricius; swollen spleen with mottled pale/hemorrhagic regions; thymic atrophy.
	Other Characteristic Lesions	Turmeric-yellow discoloration of breast muscle/abdominal lines; jaundice of skin/fat; pancreatic necrosis; petechial hemorrhages in leg muscles/proventriculus; intestinal congestion/ecchymotic hemorrhages; occasional pericardial/liver capsule hemorrhages.

Diagnosis

Tentative Diagnosis

A tentative diagnosis of Hepatitis-Hydropericardium Syndrome (HHS), or Angara disease, can often be made on the basis of flock mortality patterns. A sudden and unexplained increase in daily mortality, particularly in broilers between 3 and 6 weeks of age, is highly suggestive. This spiking mortality, especially in an otherwise healthy flock, is often the first indicator of HHS (15, 24, 31).

Post-mortem findings strengthen the presumptive diagnosis. The accumulation of clear to straw-colored fluid in the pericardial sac (hydropericardium), together with hepatic enlargement, pallor, and friability, are regarded as highly characteristic (2, 44). The combination of epidemiological evidence and gross lesions usually leads to a provisional diagnosis, which then requires confirmation through laboratory testing (15, 45).

Definitive Diagnosis

A definitive diagnosis relies on laboratory confirmation of the causative agent and its associated pathological changes. Histopathological examination is important, as affected liver and heart tissues typically show acute hepatocellular degeneration, necrosis, mononuclear cell infiltration, and basophilic intranuclear inclusion bodies within hepatocytes—findings considered hallmarks of adenovirus infection (45, 46, 47).

Molecular methods, particularly Polymerase Chain Reaction (PCR), provide highly sensitive and specific confirmation by detecting the DNA of fowl adenovirus serotype 4 (FAdV-4) in affected tissues. PCR is widely regarded as the gold standard due to its accuracy and ability to differentiate HHS from other adenovirus-associated diseases (48, 49, 50).

Laboratory Tests

Several complementary laboratory tests support the diagnosis and characterization of HHS. Virus isolation, though less commonly used today, can be achieved by inoculating embryonated chicken eggs or primary cell cultures (liver and kidney) with homogenates of infected tissues. Successful propagation confirms the presence of the virus (51).

Serological assays are important for flock monitoring and epidemiological investigations. Methods include agar gel immunodiffusion (AGID), counterimmunoelectrophoresis, indirect haemagglutination (IHA), fluorescent antibody technique (FAT), enzyme-linked immunosorbent assay (ELISA), and virus neutralization (VN) (52). Among these, ELISA is most commonly applied for routine antibody surveillance due to its sensitivity and scalability (8, 15). The VN test is particularly valuable in identifying specific FAdV serotypes, providing greater diagnostic precision (7).

Differential Diagnosis

Accurate diagnosis requires differentiation of HHS from other conditions with overlapping features. The most important is Inclusion Body Hepatitis (IBH), also caused by fowl adenoviruses (notably serotypes 2, 8a, 8b, and 11) (53). While both diseases present with hepatitis in young broilers, hydropericardium is more pronounced and consistent in HHS. Careful evaluation of pericardial fluid accumulation therefore provides an important diagnostic clue. Molecular confirmation through PCR allows precise serotyping, distinguishing HHS (FAdV-4) from IBH caused by other serotypes (54).

Flock history, bird age, and the specific distribution of lesions should also be considered in differential diagnosis to ensure accurate identification and appropriate intervention (55).

Prevention and Control Strategies

Biosecurity Measures

Stringent biosecurity practices remain the cornerstone of preventing the horizontal transmission of FAdV-4 between and within poultry flocks (56). Essential measures include strict hygiene and sanitation protocols, with routine cleaning and disinfection of poultry houses and equipment to minimize viral load (57). Effective control of immunosuppressive diseases, notably Infectious Bursal Disease (IBD) and chicken anemia virus (CAV), is equally critical, as co-infections substantially increase both susceptibility and disease severity (58).

Water sanitation, such as the use of disinfectants like iodophor solutions, can reduce the risk of transmission via contaminated water sources. Reducing environmental stressors, by maintaining optimal stocking densities, ensuring proper ventilation, and providing nutritionally balanced diets, improves flock resilience to infection. Thorough disinfection between production cycles is essential to break the infection chain (59).

Vertical transmission can be prevented by sourcing chicks and fertile eggs exclusively from breeder flocks verified as free of FAdV-4. Additionally, rodent and pest control programs should be implemented to limit the risk of mechanical transmission (60).

Vaccination Programs

Vaccination represents the most effective strategy for the prevention and control of Hepatitis-Hydropericardium Syndrome (HHS) (61). In endemic regions, formalin-inactivated oil-adjuvant vaccines are widely employed and have been shown to significantly reduce mortality and morbidity. These vaccines may be prepared from liver homogenates of infected birds or from virus propagated in cell cultures. Live attenuated vaccines are also available in some countries, offering an alternative immunization approach (30).

A key preventive measure is the vaccination of breeder flocks, which ensures the transfer of maternal antibodies to offspring via the egg, conferring passive immunity during the highly susceptible early weeks of life (62). Vaccination of broiler flocks with inactivated vaccines has been reported in various countries (8). In Iran, vaccination of broiler flocks is also carried out in high-risk areas, although precise information on the efficacy and success rate of the vaccination is not available. In circumstances where commercial vaccines are either ineffective against local strains or unavailable, autogenous vaccines developed from region-specific FAdV-4 isolates are used to provide homologous protection (63).

Recent advancements have introduced novel vaccine platforms, including recombinant newcastle disease virus (NDV) vectors expressing FAdV-4 antigens and chimeric fiber protein-based vaccines. These approaches show promise in enhancing efficacy and potentially broadening protection (64) (Figure 4).

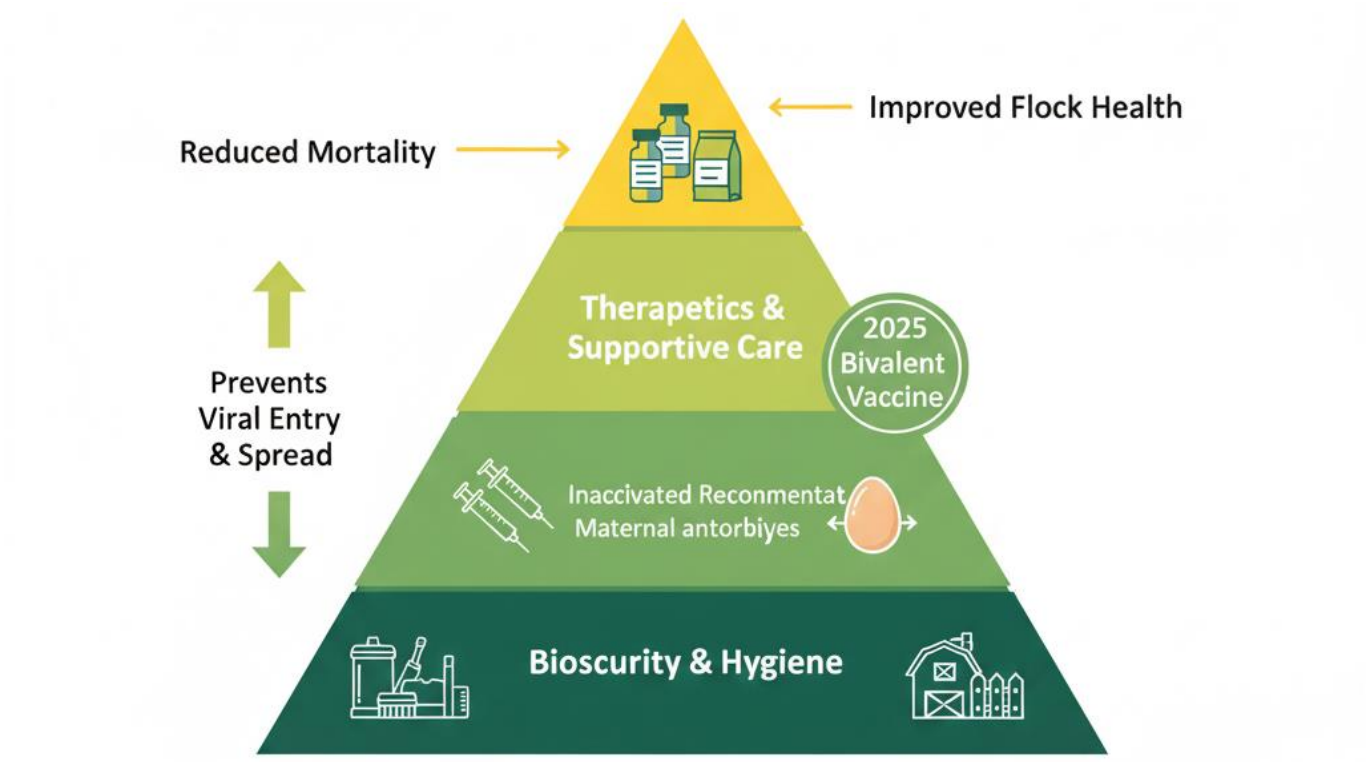


Figure 4. FAdV-4 HHS prevention pyramid

Table 5. Prevention and Control Strategies for Hepatitis-Hydropericardium Syndrome (HHS) in Poultry

Category	Subcategory/Aspect	Description/Key Features
Biosecurity Measures	Hygiene and Sanitation	Strict protocols: routine cleaning/disinfection of houses/equipment to minimize viral load; thorough disinfection between production cycles to break infection chain.
	Water and Environmental Management	Disinfectants (e.g., iodophor solutions) for water sources; optimal stocking densities, ventilation, balanced nutrition to reduce stressors and improve resilience.
	Vertical Transmission Prevention	Source chicks/eggs from FAdV-4-free breeders; rodent/pest control to limit mechanical spread.
Vaccination Programs	Inactivated Vaccines	Formalin-inactivated oil-adjuvant vaccines (from liver homogenates or cell cultures); reduce mortality/morbidity in endemic areas.
	Live Attenuated and Breeder Vaccination	Live attenuated vaccines available; vaccinate breeders for maternal antibody transfer via eggs (passive immunity in early weeks).
	Autogenous and Novel Platforms	Region-specific autogenous vaccines for local strains; recombinant NDV vectors expressing FAdV-4 antigens; chimeric fiber-2 protein vaccines.
Therapeutic Interventions	Supportive Care and Antibiotics	No specific antivirals; focus on preventing secondary bacterial infections via antibiotics; water sanitation with disinfectants to reduce viral load.
	Nutritional Adjuncts	Experimental: arginine supplementation to boost humoral/cell-mediated immunity against immunosuppression; requires further validation.

Economic Impact

Mortality Rates

Hepatitis-Hydropericardium Syndrome (HHS) is associated with high mortality in susceptible poultry populations, particularly broilers, and represents a major source of economic loss. Mortality rates in broilers during severe outbreaks can reach 60–80%, while typical ranges are reported between 20-80%, depending on viral virulence, host factors, and environmental conditions. In extreme cases, especially among unvaccinated flocks or those exposed to highly virulent FAdV-4 strains, mortality may approach 100%. In contrast, mortality in laying hens is generally much lower, often below 10% (1, 15, 43).

Epidemiological studies support this variability. For instance, a study in Bangladesh over one year and across different farms reported a mortality rate of 58.77% in affected broiler chickens in one case and an average mortality of 6.20% across farms during the study period (31). Mortality levels are influenced by multiple factors, including bird age, breed susceptibility, viral dose, and infection route, underscoring the complex interplay between host and pathogen determinants (22).

Production Losses

In addition to direct mortality, HHS imposes substantial production losses on poultry enterprises. Affected flocks exhibit impaired growth, weight loss, and reduced weight gain, resulting in an unfavorable feed conversion ratio (FCR). Since FCR is a critical determinant of economic efficiency, worsening ratios translate directly into increased feed costs per unit of weight gain (67).

The disease also contributes to reduced overall productivity due to immunosuppression in surviving birds (68). Such immunodepression not only hampers long-term performance but also increases vulnerability to secondary infections, compounding production losses. Reduced feed intake, poor flock uniformity, and stunted growth are further consequences that diminish economic returns (69).

Control Costs

The economic burden of HHS extends beyond mortality and production losses to the significant costs of control measures. Vaccination programs, particularly those requiring autogenous vaccines tailored to local FAdV-4 strains, demand substantial investment. Similarly, the maintenance of stringent biosecurity measures incurs ongoing costs for infrastructure, personnel training, and sanitation supplies (4, 8).

In the event of an outbreak, additional expenses arise from flock depopulation, carcass disposal, and comprehensive disinfection of facilities, all of which contribute to the cumulative economic impact of HHS. Thus, the disease exerts a multifaceted financial strain on the poultry industry, encompassing mortality, reduced productivity, and high control expenditures (30, 70).

Conclusion

Hepatitis-Hydropericardium Syndrome (HHS), caused by fowl adenovirus serotype 4, remains a significant threat to poultry production due to its rapid onset, high mortality, and substantial economic impact. Although much progress has been made in understanding the virus's pathology, epidemiology, and genetic evolution—particularly the emergence of hypervirulent strains—HHS continues to challenge global poultry health systems. Advances in molecular diagnostics and genomic characterization have enhanced our ability to detect and monitor circulating strains, while innovations in vaccine development, including recombinant and chimeric platforms, offer promising avenues for broader and more durable protection.

Effective control of HHS, however, requires more than scientific insight. The integration of strengthened biosecurity, targeted vaccination strategies, and region-specific surveillance remains essential for mitigating disease spread and reducing losses. Future research should focus on unraveling host–virus interactions, identifying genetic determinants of resistance, and optimizing next-generation vaccines tailored to evolving viral profiles. By combining sustained scientific investment with practical field-level implementation, the poultry industry will be better equipped to manage HHS and safeguard both animal health and production efficiency.

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Authors' Contributions

Mohammadjavad Jahedi and Hemad Shafiei: data curation, investigation, writing – original draft, writing-review and editing.

Data Availability

Not applicable.

Ethical Approval

Not applicable.

Conflict of Interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent for Publication

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