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REVIEW ARTICLE

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Fowl adenovirus-induced diseases and strategies for their control – a review on the current global situation

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ABSTRACT

The stand-alone pathogenicity of fowl adenoviruses (FAdVs) had long been disputed, given the ubiquity of the viruses versus sporadic outbreaks, and variation between experimental studies. However, a globally emerging trend of FAdV-associated diseases has marked the past two decades, with hepatitis-hydropericardium syndrome mainly in Asia besides Arabian and Latin American countries, and geographically more disseminated outbreaks of inclusion body hepatitis. Finally, the appearance of FAdV-induced gizzard erosion (AGE) in Asia and Europe completed the range of diseases. Epidemiological studies confirmed serotype FAdV-4 as agent of hepatitis-hydropericardium syndrome, whereas inclusion body hepatitis is related to FAdV-2, -8a, -8b and -11. Members of the biologically more distant serotype FAdV-1 induce AGE. Urged by increasing problems in the field, numerous pathogenicity studies with FAdVs from outbreaks substantiated the primary aetiologic role of particular strains for distinct clinical conditions.

Developments in the poultry industry towards highly specialized genetic breeds and rigorous biosecurity additionally contribute to the growing incidence of FAdV-related diseases. Confirming field observations, recent studies connected a higher susceptibility of broilers with their distinct physiology, implying the choice of bird type as a factor to be considered in infection studies. Furthermore, elevated biosecurity standards have generated immunologically naïve breeding stocks, putting broilers at risk in face of vertical FAdV transmission. Therefore, future prevention strategies should include adequate antibodies in breeders prior to production and – if necessary – vaccination, in order to protect progenies. This review aims to deliver a detailed overview on the current global situation about FAdV-induced diseases, their reproduction *in vivo* and vaccination strategies.

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Introduction

In the middle of the last century, embryonated eggs gained popularity to isolate filterable agents from varied origin but also for vaccine production. In the course of such procedures it was occasionally noticed that a virus could be isolated which was unrelated to the original material but resembled the quail bronchitis virus isolated earlier on (Olson, 1950; Yates & Fry, 1957). As a consequence, vertical transmission was recognized as one of the first important biological features of fowl adenoviruses (FAdVs). Later on, experimental infections and epidemiological studies were performed in order to determine the role of FAdVs in a newly described disease condition, inclusion body hepatitis (IBH) (Helmboldt & Frazier, 1963). The sporadic occurrence of IBH in context with the wide spread of FAdVs in chicken flocks and the importance of immunosuppression to induce IBH initially questioned the primary pathogenicity of FAdVs (Hess, 2017).

In later years, the appearance of hepatitis-hydropericardium syndrome (HHS) and adenoviral gizzard erosion (AGE) led towards an increased awareness of FAdVs as primary aetiologic agents, emphasizing the importance of FAdV infections particularly in young chickens, primarily broilers (Hess, 2017). This was further supported by more frequent reports of IBH outbreaks in different parts of the world during the last 15 years.

The actual review aims to provide a comprehensive overview about the existing knowledge on field outbreaks and experimental studies on FAdVs on a global scale, in order to underline the changes noticed in recent years. As a consequence of increased mortality and production losses, more efforts are needed in the future to monitor and control FAdV infections, which will be addressed in the final section.

Inclusion body hepatitis

IBH is a disease caused by FAdVs belonging mainly to serotypes FAdV-2, FAdV-11 (species *Fowl aviadenovirus D*) and FAdV-8a and FAdV-8b (species *Fowl aviadenovirus E*). FAdV species were established recently to combine closely related serotypes (Harrach

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et al., 2012). Historically, IBH was first reported in chickens by Helmboldt and Frazier (1963), who described an "acute hepatic catastrophe" due to the extent of liver damage in affected birds. In the following years, IBH was perceived as the result from concurrent infections by FAdVs and immunosuppressive agents, such as infectious bursal disease virus (IBDV) and chicken anaemia virus (CAV), in which FAdVs were considered opportunistic agents (Hoffmann *et al.*, 1975; Rosenberger *et al.*, 1975; Fadly *et al.*, 1976). Other reports established an association between IBH and aflatoxins present in the feed (Singh *et al.*, 1996). However, reports from Australia, New Zealand, Canada and Japan documented IBH outbreaks in the absence of predisposing factors, strengthening the role of FAdVs as primary pathogens (Reece *et al.*, 1986; Christensen & Saifuddin, 1989; Gomis *et al.*, 2006; Nakamura *et al.*, 2011; Steer *et al.*, 2011). Moreover, in a recent study, a statistically significant association between flocks being exposed to FAdV and co-infected with CAV or IBDV was not found (Eregae *et al.*, 2014). Nonetheless, the importance of FAdVs as primary pathogens is still a matter of debate as strains from the same serotype can vary in their pathogenicity (Cook, 1983; Erny *et al.*, 1991; Slaine *et al.*, 2016; Absalón *et al.*, 2017). Furthermore, FAdVs have been isolated from both healthy and sick chickens, a finding also noticed in recent studies (Kaján *et al.*, 2013; Niczyporuk, 2016).

Field reports

In the last two decades, an increasing number of IBH outbreaks has been reported in different geographic locations stressing the worldwide spread of the disease (Figure 1; Supplementary table 1). In the field, IBH principally affects broilers up to five weeks of age, but has also been reported sporadically in layers and broiler breeders. Mortality during IBH outbreaks peaks within 3–4 days and can reach 10% and occasionally be as high as 30% (Hess, 2013; Schachner *et al.*, 2016). Additional clinical signs which may be recorded on affected chickens include poor growth, apathy, prostration, ruffled feathers and huddling behaviour. Clinically, IBH resembles very much HHS, although being less severe. Furthermore, concurrent infections are frequently observed in flocks suffering from IBH, which might explain why certain features of field outbreaks are not experimentally reproducible.

Experimental studies

In vivo studies have shown that the outcome of experimentally induced IBH is highly dependent on the route of inoculation, viral dose and the age of birds (Supplementary table 2). From early on, the age-related resistance is a marked characteristic of aviadenoviral infections (Clemmer, 1972; Cook, 1974; Nakamura *et al.*, 2000; Lim *et al.*, 2011). Typically, when chickens are over one week of age, an invasive route of infection is needed to induce a clinical manifestation of IBH (Hess, 2017). However, the mechanisms behind this are not fully understood and, so far, no study has unequivocally clarified this phenomenon. The type of chickens affected by IBH is also a crucial element which influences the outcome of the disease. By using different chicken breeds of specific pathogen-free (SPF) and non-SPF origin, Cook (1974) studied the influence of host, age and route of inoculation on the outcome of an FAdV infection. In that study, SPF Light Sussex chickens were highly susceptible to the infection in comparison to SPF Rhode Island Red chickens, with mortalities of 67% and 33% being recorded, respectively, following intraperitoneal inoculation at day-old. More recently, a mortality rate of 100% was recorded when SPF broilers were orally infected at day-old with an FAdV-8b strain, while in SPF layers inoculated under the same conditions the mortality was 20% (Matos *et al.*, 2016a), corroborating the situation reported from the field and a higher susceptibility of broilers.

Following inoculation of chickens by the oral route, it was demonstrated that the virus colonizes the intestinal epithelium at 12 hours post infection and it can be detected in the blood as early as 24 hours post infection (Saifuddin & Wilks, 1991a). From 2 and 3 days post infection, the virus is present in its target organs, liver and pancreas. This phase corresponds to the incubation period, in which neither clinical signs nor gross lesions are recorded (Steer *et al.*, 2015). The incubation period is succeeded by virus multiplication and a fast viraemia, producing pathological lesions in its target organs, in coincidence with clinical manifestation of the disease (Saifuddin & Wilks, 1991a; Steer *et al.*, 2015; Matos *et al.*, 2016b). Recovery of the birds occurs from 7 to 9 days post infection onwards and is manifested by a reduction in severity of clinical signs, together with cellular regeneration and a decrease of viral load in the target organs (Steer *et al.*, 2015; Matos *et al.*, 2016b). However, the virus remains latent in the caecal tonsils and it is shed in faeces for long periods. After oral infection at day-old with an FAdV-1 strain, the virus could be recovered from the gut of SPF chickens at 12 weeks post infection (Jones & Georgiou, 1984). Moreover, quantity and duration of virus shedding in the faeces do not correlate with the pathogenicity of an individual strain, but rather with the administered viral dose (Cook, 1983; Matos *et al.*, 2016b; Oliver-Ferrando *et al.*, 2017).

Gross pathology

During post-mortem examination, a severe hepatitis in which the liver is swollen, friable, with a marble-like

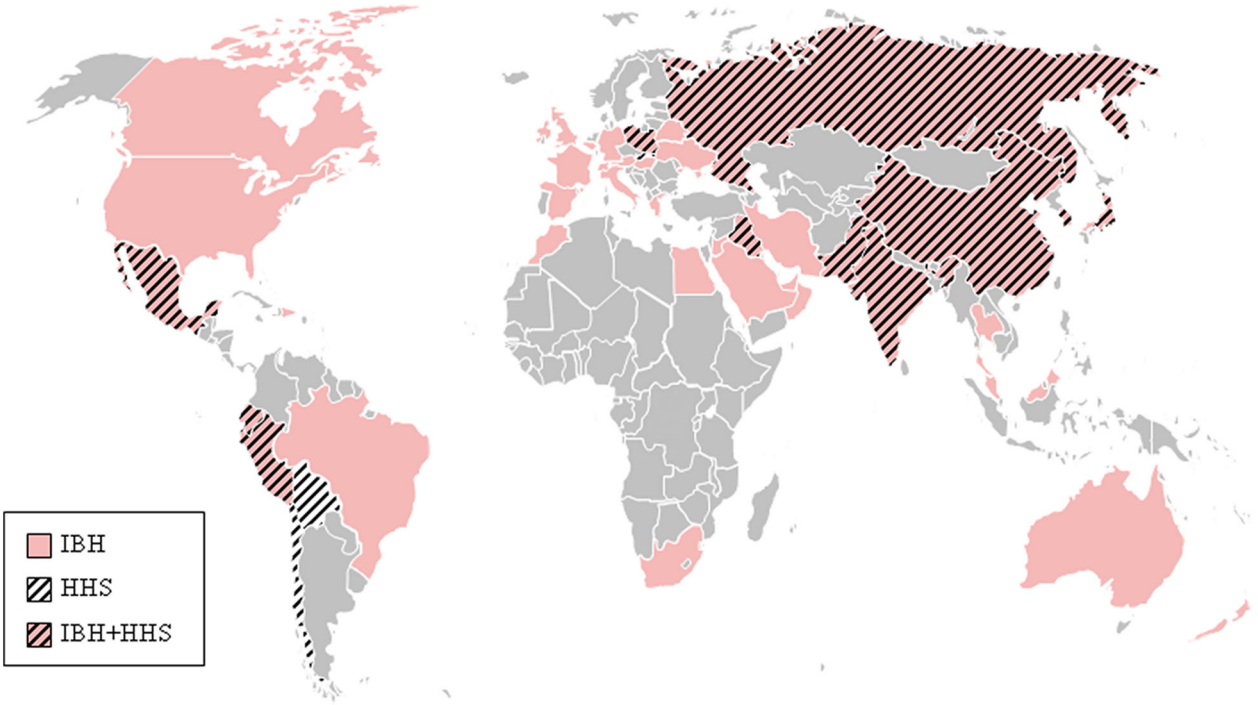

Figure 1. Global distribution map of IBH and HHS according to outbreaks reported in published literature and based on information from the field made available through personal communication, supported by diagnostic investigations. Countries with prevalence of IBH are marked in red, hachures indicate countries from which HHS has been reported.

pattern and necrotic foci can be noticed. Additionally, some studies reported necrosis, atrophy, colour change and petechiae in the pancreas of birds suffering from IBH (Winterfield *et al.*, 1973; Grimes *et al.*, 1978). Moreover, in both experimental and field cases of IBH, swollen and haemorrhagic kidneys were observed (Howell *et al.*, 1970; Pettit & Carlson, 1972; Young *et al.*, 1972; Macpherson *et al.*, 1974; Antillón & Lucio, 1975; Saifuddin & Wilks, 1990; Erny *et al.*, 1991; Steer *et al.*, 2015; Matos *et al.*, 2016b). A detailed histomorphometric evaluation, regarding the glomerular size and cellularity of swollen, pale or mottled kidneys recorded in broilers during an IBH outbreak demonstrated the presence of a glomerulonephritis (Wilson *et al.*, 2010). Earlier reports suggested the haemopoietic system as an important target for FAdVs (Pettit & Carlson, 1972; Fadly & Winterfield, 1973; Rosenberger *et al.*, 1974; Hoffmann *et al.*, 1975). However, some of the findings described in those studies such as aplastic anaemia were most likley due to co-infections with CAV.

Histology

Histologically, large areas of cellular degeneration and necrosis, lymphoid infiltration and inclusion bodies are typical features noticed in the liver of chickens suffering from IBH. In addition to the hepatitis, aviadenoviral pancreatitis has been described from both field cases and experimental studies, in which necrosis of pancreatic acinar cells, lymphoid infiltration and inclusion bodies were observed (Gallina *et al.*, 1973; Grimes *et al.*, 1978; Tanimura *et al.*, 1993; Goodwin *et al.*, 1996; Matos *et al.*, 2016a, b). Recent studies demonstrated a correlation between the extension of lesions in target organs and the clinical manifestation of IBH (Steer *et al.*, 2015; Matos *et al.*, 2016b). Additional lesions in the primary and secondary lymphoid tissues may be observed, such as atrophy of bursa and thymus, and lymphoid depletion in bursa and spleen (Itakura *et al.*, 1974; Macpherson *et al.*, 1974; Steer *et al.*, 2015; Matos *et al.*, 2016b). Moreover, focal necrosis, lymphocytic infiltration, nephrosis and, more rarely, inclusion bodies may be found in the kidney (Howell *et al.*, 1970; Pettit & Carlson, 1972; Itakura *et al.*, 1974; Macpherson *et al.*, 1974; Antillón & Lucio, 1975; Steer *et al.*, 2015).

Earlier detailed histological studies on IBH in chickens reported the presence of basophilic and eosinophilic inclusion bodies of variable appearance in the liver, following H&E staining (Itakura *et al.*, 1974). Ultrastructurally, the basophilic inclusions consist of oval/hexagonal virus particles, which are around 70 nm in diameter, granular material and sometimes also of lamellae concentrically enclosing the virus core, which are probably related to the process of virus formation. On the other hand, the eosinophilic inclusions contain either moderately electrondense fibrillar-granular material or crystals composed of narrowly spaced thin filaments and may represent degenerated material in cells dying from the effects of the viral infection (Itakura *et al.*, 1977). It has been proposed that these

inclusions are analogous to human intranuclear aggregates (Strnad *et al.*, 2013). Nonetheless, the exact composition and origin of these inclusions still remain to be determined, which may help in elucidating the pathogenesis of IBH.

Metabolic disturbances

Selected clinical chemistry analytes related to the cellular integrity and physiological function of liver and pancreas were recently used as biomarkers for strain pathogenicity and IBH pathogenesis (Matos *et al.*, 2016b). As an outcome, disturbances in different enzymatic systems and metabolite concentrations were noticed. Additionally, acute changes in the plasmatic lipase together with severe histopathological lesions indicated the pancreas as an important target organ in IBH pathogenesis. In subsequent experimentally induced IBH, day-old orally infected SPF broiler presented severe clinical signs as a manifestation of hypoglycaemia and severe hepatitis and pancreatitis (Matos *et al.*, 2016a). Earlier on, Goodwin *et al.* (1993) described a flock with spiking mortality, in which broilers suffering from hypoglycaemia had adenoviral inclusion bodies in liver, pancreas and small intestine. Such findings may explain why most IBH outbreaks are reported in broilers, which are physiologically very different from layers (Supplementary table 1). Interestingly, broilers which suffered from hypoglycaemia, metabolic acidosis and hypocalcaemia during an IBH outbreak were effectively treated with glucose together with sodium bicarbonate and calcium, supporting the metabolic component of IBH pathogenesis (Venne & Chorfi, 2012).

Hepatitis-hydropericardium syndrome

HHS, also named hydropericardium syndrome (HPS), emerged in Pakistan in the late 1980s, subsequently spreading to other Asian countries, where it became endemic, but also some Arabian countries and parts of Latin America.

Historically, the aetiology of HHS was explained by feed disorders or intoxications (Jaffery, 1988; Qureshi, 1989), while a viral aetiology of the syndrome was proposed, based upon the observation of basophilic nuclear inclusion bodies in hepatocytes and adenovirus particles in liver homogenates (Cheema *et al.*, 1989). In the years following the first emergence of the disease, a gradual recognition of the infectious nature of HHS took place, for which *in vivo* transmission experiments have played a key role.

Field reports

The first reported cases of the syndrome near Karachi, Pakistan, in 1987 (Anjum *et al.*, 1989) were rapidly followed by massive outbreaks across the region, including a further spread to India, where it severely affected the intensive poultry husbandry during the early 1990s (Gowda & Satyanarayana, 1994; Kumar *et al.*, 1997). In the following two decades, natural outbreaks were documented from various regions, including reports from Middle East (Abdul-Aziz & Al-Attar, 1991; Hess *et al.*, 1999), Russia (Borisov *et al.*, 1997), Slovakia (Jantosovic *et al.*, 1991), Central and South America (Mazaheri *et al.*, 1998; Toro *et al.*, 1999; Rodriguez *et al.*, 2014; Vera-Hernández *et al.*, 2016), Japan (Abe *et al.*, 1998; Mase *et al.*, 2010) and Korea (Kim *et al.*, 2008; Lim *et al.*, 2011; Choi *et al.*, 2012).

A substantial amount of epidemiological data collected during this period has strengthened the outstanding role of a single serotype, FAdV-4 of species FAdV-C, in the primary aetiology of HHS (Supplementary table 3).

Particularly during the last decade, a trend towards more epidemic, rather than sporadic, occurrence of outbreaks has been observed in many countries. At present, accumulating reports of severe HHS outbreaks in China provide the latest documentation for the emerging potential of the disease (Zhao *et al.*, 2015; Changjing *et al.*, 2016; Li *et al.*, 2016a, b; Liu *et al.*, 2016; Niu *et al.*, 2016; Ye *et al.*, 2016; Pan *et al.*, 2017).

Experimental studies

Prior to the first attempts of disease induction with the isolated agent (Naeem *et al.*, 1995), basic transmission experiments were carried out using homogenized tissue samples (Cheema *et al.*, 1989). However, conduct of infection experiments in commercial birds, as performed in this and various other studies, requires cautious interpretation, considering the widespread of FAdVs and their respective antibodies.

Concurrent factors and/or agents were still considered mandatory for development of the disease throughout a longer period of time (Afzal *et al.*, 1991; Toro *et al.*, 1999). This was supported by inconsistent field observations, together with varying results obtained from different infection studies. This notion chiefly prevailed until experimental reproduction of HHS in SPF chickens with plaque purified FAdVs marked a critical milestone to demonstrate the standalone virulence of specific virus strains (Mazaheri *et al.*, 1998). Parallel to that, experimental evidence led further to the recognition that the outcome of an infection may be primarily determined by the virulence of a particular FAdV strain, rather than additive effects of co-agents (Toro *et al.*, 2001).

This is supported by longitudinal comparison of numerous available infection studies (Supplementary table 4), performed with FAdVs belonging to the same serotype, although considerable variances in virulence between strains was noticed (Mazaheri *et al.*,

1998; Ahmad, 1999; Toro *et al.*, 1999). This observation also correlates with the field scenario of FAdV-4 isolation from non-HHS-related specimen (Ojkić *et al.*, 2008; Marek *et al.*, 2010a; Griffin & Nagy, 2011; Niczyporuk, 2016).

In the light of contemporary efforts to study virulence markers on a molecular level (Griffin & Nagy, 2011; Zhao *et al.*, 2015; Vera-Hernández *et al.*, 2016), precise assessment of individual differences in clinicopathological properties of FAdV-4 strains is desirable, yet difficult to establish because of apparent variations attributed to host-related susceptibility and efficiency of the infection. Although they may not optimally reflect the natural infection via the oral route, parenteral routes were shown to induce a more severe pathogenicity in various experimental settings (Mazaheri *et al.*, 1998; Naeem *et al.*, 2001; Ahmad *et al.*, 2011; Lim *et al.*, 2011; Li *et al.*, 2016b). This effect is particularly apparent to induce infection in increasingly older birds; however, potential distortions of the picture may result from the use of commercial chickens with a possible level of maternally derived antibodies, and the use of native vs. cell culture propagated inoculum in various studies.

Altogether, such effects on pathogenicity of a strain are well documented by a plethora of infection studies comparing inoculum dose, infection route, age and genetic background of chickens, whereby the lack of standardization has, at the same time, been a continuous critical remark throughout the relevant literature.

Clinicopathological aspects

The main type of birds affected are broilers, aged 3–6 weeks (Cheema *et al.*, 1989; Mittal *et al.*, 2014a), with exceptional reports on layers and broiler breeders (Asrani *et al.*, 1997), corroborating particular host-related factors, such as age and genetic type of birds, for susceptibility. Besides sporadic reports in other domestic bird species, including pigeons (Naeem & Akram, 1995; Hess *et al.*, 1998), quails (Karunamoorthy & Manickam, 1998), ducks (Chen *et al.*, 2015) and ostriches (Changjing *et al.*, 2016), a possible carry-over of the disease into wild birds has also been described (Kumar *et al.*, 2010).

The course of disease and the clinicopathological signs exhibit certain parallels to IBH (as described in the section "Inclusion body hepatitis"), although being typically more pronounced. Losses are reported within a range of one- to ample two-digit percentages, in which case mortality may be the principal clinical manifestation due to the acute course of the disease. Fluid accumulation in the pericardial sac constitutes the most prominent gross pathological finding which is generally perceived as a pathognomonic feature of HHS. However, there are also reports of the absence of hydropericardium in certain outbreaks (Rodriguez *et al.*, 2014). The accompanying hepatic involvement, characterized by swollen, friable, discoloured livers with focal necroses and petechial haemorrhages, bears resemblance to classical IBH; therefore the condition is sometimes also termed IBH-HPS. Histopathological changes, similar to IBH, are principally found in the liver, while inflammatory as well as degenerative processes are also common in other organs, mainly in the heart, kidneys, lungs and intestine (Anjum *et al.*, 1989; Cheema *et al.*, 1989). Importantly, tropism for lymphoid tissue constitutes an important aspect of the pathogenesis of HHS strains, resulting in degeneration of lymphoid organs alongside with lymphocyte depletion, altogether highlighting the immunosuppressive potential of virulent FAdV-4 strains (Naeem *et al.*, 1995a; Shivachandra *et al.*, 2003; Schonewille *et al.*, 2008).

Adenoviral gizzard erosion

The literature on gizzard erosions in poultry is very limited, although it goes back to the early 1930s when the condition was first reported by nutritionists. Several non-infectious, alimentary factors as well as some infectious causes have been investigated and described to induce macroscopic lesions in the gizzard with FAdV to be considered as one of such (Gjevre *et al.*, 2013).

Field reports

Although gizzard erosions have been described already in the context of FAdV infections during IBH and/or HHS outbreaks (Grimes *et al.*, 1977; Nakamura *et al.*, 2002), detailed investigations in the course of a field outbreak of AGE were conducted by Tanimura *et al.* (1993). These authors supplied a comprehensive description of AGE concurrent with necrotizing pancreatitis in association with an aviadenovirus infection from a natural outbreak in 60–70 days old pullets with increased mortality using immuno-histochemical and electron microscopic methods. Applying similar methods, adenoviral gizzard lesions were further reported in a retrospective study from pullets and broiler flocks in the USA (Goodwin *et al.*, 1993) and from an outbreak with increased mortality in Japanese broilers (Abe *et al.*, 2001). However, it was Ono *et al.* (2001) who, for the first time, characterized the adenovirus as FAdV serotype-1 (FAdV-1) by polymerase chain reaction-restriction fragment length polymorphism as aetiological agent from condemned gizzards in the slaughter house. Although FAdV-8a or -8b were sporadically isolated from affected gizzards (Okuda *et al.*, 2004; Mase & Nakamura, 2014), the majority of subsequent outbreaks of the disease could be traced back to FAdV-1 strains. Geographically, the disease is mainly described in broilers from Europe and Asia

(Supplementary table 5). From such outbreaks various molecular biological approaches have been used in order to differentiate between pathogenic and apathogenic FAdV-1 focusing on the fibre gene (Okuda *et al.*, 2006; Marek *et al.*, 2010b; Matczuk *et al.*, 2017). On the host side, an initial study demonstrated that FAdV-1 interacts with a protein of approximately 200 kDa in the gizzard (Taharaguchi *et al.*, 2007). Both, vertical as well as horizontal transmission of FAdV-1, and the subsequent clinical and pathological manifestation of AGE have been described in literature (Ono *et al.*, 2007; Grafl *et al.*, 2012). In affected broiler flocks, considerable economic losses due to AGE have been documented due to growth retardation, higher mortality rates and/or condemnations of affected gizzards in the slaughterhouse (Supplementary table 5). Several recent reports of AGE outbreaks in layers which coincide with increased mortality altogether indicate an impact of the disease on health and production also in layer-type birds (Lim *et al.*, 2012; Totsuka *et al.*, 2015; Matczuk *et al.*, 2017). Independent of the production type, gross pathology and histology in the course of the disease are alike. Macroscopically, affected birds show gizzard lesions characterized by multiple brown or black areas of erosion of the keratinoid layer as well as inflammation and/or ulceration of the gizzard mucosa underneath (Tanimura *et al.*, 1993; Abe *et al.*, 2001; Ono *et al.*, 2001; Grafl *et al.*, 2012; Lim *et al.*, 2012; Schade *et al.*, 2013; Matczuk *et al.*, 2017). In dead birds, sanguineous fluid in the gizzard as well as the proventricular and/or intestinal lumen and gizzard perforation can be observed. In general, no other macroscopic pathological changes are observed in affected birds. Histologically, infiltration with inflammatory cells such as macrophages and lymphocytes are observed in gizzard mucosa, submucosa and/or muscle layer in the affected gizzards (Tanimura *et al.*, 1993; Abe *et al.*, 2001; Ono *et al.*, 2001; Grafl *et al.*, 2012; Schade *et al.*, 2013; Matczuk *et al.*, 2017). Concurrently, erosion and loss of the keratinoid layer as well as degeneration and necrosis of glandular epithelial cells with/without basophilic intranuclear inclusion bodies can be detected.

Experimental studies

Successful experimental reproduction of AGE after infection with FAdV-1 strains isolated from affected gizzards derived from field outbreaks have been reported in SPF layers and broilers as well as in commercial broilers (Supplementary table 6). In one study the development of mild gizzard lesions was reported following infection with FAdV-8 isolated from gizzard lesions of slaughtered broiler chickens (Okuda *et al.*, 2004). Characteristic pathomorphological changes of AGE were reproduced by Okuda *et al.* (2001b) in 5 and 53 days old SPF layers via oral and ocular inoculation. Independent of the type of birds, age and inoculation route, the majority of experimental studies reported no or only mild clinical signs after inoculation with FAdV-1, while characteristic gross lesions were commonly observed in gizzards of infected birds for up to four weeks post infection. Okuda *et al.* (2001a) documented a slightly delayed onset of pathological changes when using a lower infection dose of FAdV-1. In general, typical histological changes including degeneration and necrosis of the glandular epithelial cells, intranuclear inclusion bodies and lymphatic cell infiltration in the lamina propria and muscle layer were described simultaneous to the detection of gross lesions in the gizzards (Okuda *et al.*, 2001b; Ono *et al.*, 2003; Grafl *et al.*, 2013). However, in these studies the detection of adenoviral intranuclear inclusion bodies in the gizzard mucosa of inoculated birds was only documented up to two weeks post infection. Additionally, birds inoculated parenterally with FAdV-1 showed pathohistological changes also in the pancreas and/or liver (Ono *et al.*, 2004; Lim *et al.*, 2012). A quite atypical clinical and pathological development of the disease was described by Domanska-Blicharz *et al.* (2011); while in one-day-old SPF layers infected with FAdV-1 ocular-nasally, mortality of up to 100% and severe gizzard erosions were noticed, 21 days old infected birds did not develop any clinical or pathomorphological signs of AGE. Overall, experimental studies together with field reports indicate that birds hardly develop an age resistance which differentiates AGE from IBH and HHS.

Horizontal transmission of AGE was confirmed in experimental studies reported by Ono *et al.* (2007) following successful reproduction of AGE not only in orally FAdV-1-infected SPF layers but also in in-contact birds. Furthermore, immunological mechanisms in the context of AGE have been investigated with various experimental models (Okuda *et al.*, 2001b; Ono *et al.*, 2004; Grafl *et al.*, 2013; Grafl *et al.*, 2014; for more information see section "Protection and vaccination strategies against FAdV infections").

Finally, a dietary influence on the outcome of AGE has been excluded for vertically infected broilers, as all SPF broilers experimentally infected with virulent FAdV-1 prior to administration of varying feeding regimes, intended to support gizzard stimulation, developed characteristic gizzard lesions (Grafl *et al.*, 2015).

Protection and vaccination strategies against FAdV infections

To this end, understanding of immune responses against adenoviruses derives mainly from investigations in mammals, particularly humans. Although considerable differences in the immune response mechanisms of mammalian and avian species are

well acknowledged, similarities in some fundamental structural and biological features between adenovirus genera can help explain certain parallels in the FAdV-directed host response. Adenoviruses are generally known to elicit a strong humoral response, directed mainly against the most abundant capsid protein hexon, constituting the dominant, serotype-specific neutralization epitope (Toogood *et al.*, 1992). Antibodies are also commonly generated in response to FAdVs (Calnek *et al.*, 1982), although quantity and kinetics of response can vary according to the age of chickens and route of exposure (Maiti & Sarkar, 1997; Ojkić & Nagy, 2003). The latter may also explain the absence of a neutralizing antibody response, as observed in particular strains, possibly resulting from the failure to establish a systemic infection upon oral infection (Schonewille *et al.*, 2010).

Notably, however, neutralizing antibodies seem to be dispensable for clinical protection against FAdVs, as challenge protection studies have independently shown (Schonewille *et al.*, 2010; Schachner *et al.*, 2014), strengthening the contribution of cell-mediated immunity for combating FAdV infections. The role of cellular immune mechanisms during FAdV infections is also supported by investigations of cytokine expression patterns, indicating a polarization towards the T_h1-pathway upon infection with non-pathogenic FAdV-4 and -8b strains (Grgić *et al.*, 2013a, b).

In particular with regard to HHS, a situation of high infection pressure has prioritized the development of commercial vaccines for control and prevention of FAdVs, accounting for the topicality of the research conducted in this area, as summarized in Table 1. In addition, in certain regions, the practice of immunizing chickens with inactivated vaccines prepared from liver suspensions of diseased flocks has been reported (Chishti *et al.*, 1989; Afzal & Ahmad, 1990; Anjum, 1990; Afzal *et al.*, 1991; Kumar *et al.*, 1997). Such vaccines have been extensively investigated and are, under the prevailing conditions, perceived as an easy and cheap method to control HHS.

However, various concerns related to safety, efficacy and applicability of this practice limits its use. Incomplete inactivation can lead to a further spread of HHS and other pathogens. Besides this, the respective formulations are poorly characterized, containing undefined amounts of antigen. Varying formaldehyde concentrations and uncertainties as to how individual virus strains differ in their resistance to inactivation further aggravated this lack of standardization, which is also reflected by contradictory findings between studies comparing the efficacy of different formulations (Chishti *et al.*, 1989; Hussain *et al.*, 1996; Zia *et al.*, 2001). Additionally, the need for parenteral application requires extensive handling procedures, and repeated administration might be needed to elicit sufficient protection (Hassan *et al.*, 1994; Hussain *et al.*, 1999).

Based on the demand for both safer and more efficacious vaccines, alternative systems have been developed. Virus propagation in embryonated eggs or cell culture prior to inactivation enabled a standardized production of antigen (Naeem *et al.*, 1995b). Such vaccines are commercially available in some countries for prevention of HHS and IBH, retaining, however, the impediments of relatively cost-intensive production and individual administration. Adaptation of FAdVs to susceptible but atypical culturing systems was shown to attenuate their virulence (Schonewille *et al.*, 2010; Mansoor *et al.*, 2011), providing the basis for live virus vaccines. These would offer the advantage of application via the oral route, and have in some cases been shown to elicit a stronger antibody response than vaccines based on inactivated antigens (Kaur *et al.*, 1997; Mansoor *et al.*, 2011).

More recently, efforts towards improved immunoprophylactic strategies are seen in the development of subunit vaccines, generated from recombinant capsid components of the virus. Protection of domestic poultry by recombinant adenoviral proteins has already been demonstrated for certain non-FAdVs, such as egg drop syndrome virus (EDS-V) (Fingerut *et al.*, 2003) and haemorrhagic enteritis virus (HEV) (Pitcovski *et al.*, 2005), with the EDS-V fiber protein implemented as a commercial vaccine product. For FAdVs the concept of subunit vaccination has been examined using both structural and non-structural proteins of the virus. The structural antigens penton base (Shah *et al.*, 2012) and fiber (Schachner *et al.*, 2014), derived from FAdV-4, conferred high levels of protection in the face of severe challenge with HHS. The observed level of protection correlated with vaccination-induced antibody levels, although antibodies raised against the fiber did not exhibit any neutralization activity *in vitro*, while this information is so far unknown for penton base directed antisera. Neutralizing antibodies against recombinant fiber from an FAdV-8b isolate were detected in breeders and progenies following 2× vaccination of breeders (Gupta *et al.*, 2017).

On the other hand, hexon-based subunit formulations, derived from FAdV-4 as well as FAdV-8b, were independently reported to elicit weak responses (Schachner *et al.*, 2014; Dar *et al.*, 2015), the same applying for recombinantly expressed non-structural 100K which conferred no protection against challenge with homologous FAdV-4 (Shah *et al.*, 2016).

With regard to the susceptibility of young chickens to clinically manifest FAdV infections, vertical transmission of the virus and antibodies from parental to progeny birds gains high priority to control FAdVs. Both transmission of antigen and a virus-directed response depend on a critical timespan from infection to seroconversion of parental birds, with a more pronounced effect on either virus transmission, or transfer

Table 1. Vaccination studies for the control of FAdV-induced disease complexes.

Vaccine type	Preparation/ formulation	FAdV strain	Assessment of vaccine response	Protection (% survival rate)	Reference
Inactivated vaccine	Formalinized (0.5%) liver homogenate extract	FAdV from an HHS field outbreak, n.c.[a]	Challenge test: homologous virus	80% (vs. 0% in challenge control group)	Chishti *et al.* (1989)
Inactivated vaccine	Formalinized (0.1%) liver homogenates	FAdV field strains, n.c.	Field testing	Prophylactic administration: 98.92% (vs. 89.73% in unvaccinated birds); administration during an outbreak: 97.67% (vs. 89.32% in unvaccinated birds)	Afzal and Ahmad (1990)
Inactivated vaccine	Formalinized (0.1%, 0.5%) liver homogenates	K31/89 (FAdV-4 isolated from an HHS field outbreak)	Challenge test: homologous virus	≥85% (vs. 25–60% in challenge control groups)[b]	Anjum (1990)
Inactivated vaccine	Cell cultured and egg-passaged formalinized virus	PARC-1 (FAdV-4 isolated from an HHS field outbreak)	Serological response: AGPT; challenge test: homologous virus	100% (vs. 30% in challenge control groups)	Naeem *et al.* (1995b)
Inactivated vaccine	Cell cultured formalinized (0.01%) virus	PL-1 (FAdV isolated from an IBH field outbreak)	Serological response: neutralization test in embryonated eggs; challenge test: homologous virus	n.i.[c,d]	Kaur *et al.* (1997)
Live vaccine	Cell culture propagated virus, orally administered				
Inactivated vaccine	Formalinized, oil-emulsified virus	FAdV isolated from an HHS field outbreak, n.c.	Serological response: IHA; challenge test: homologous virus	100% (vs. 0% in challenge control group)	Zia *et al.* (2001)
Commercial inactivated vaccine	Cell cultured inactivated, oil-emulsified virus	FAdV-4	Serological response in vaccinated breeders: SNT; challenge test in progenies: FAdV-4 field isolate	86.7% (vs. 73.3% in challenge control group)	Toro *et al.* (2002)
Commercial inactivated dual-serotype vaccine	Inactivated virus	1047 (FAdV-11) + 8565 (FAdV-8a) isolated from IBH field outbreaks	Serological response: maternal antibody measurement by ELISA based on strain 8565; challenge test in progenies: homologous strains and FAdV-8b	≥98% (vs. 0% in challenge control groups) for challenge with FAdV-8b[d]; ≥92% for challenge with homologous strains[d,e]	Alvarado *et al.* (2007)
Live vaccine	Chicken embryo-adapted vaccine, orally administered	FAdV-4 isolated from an HHS field outbreak	Serological response: whole-virus-based ELISA with the homologous strain; challenge test: homologous virus	94.74% (vs. 30% in challenge control group)	Mansoor *et al.* (2011)
Live vaccine	*In vitro* attenuated vaccine, produced on QT35 cells, orally administered	INT4 (FAdV-4)	Challenge test: virulent progenitor virus AG234	100% (vs. 34.5% and 46.2% in challenge control groups)[d]	Schonewille *et al.* (2010)
Passive immunization	Passive immunization by IgY from egg yolk	FAdV-4 isolated from an HHS field outbreak	Challenge test: homologous virus	86.67% (vs. 33.34% in challenge control group)	Rani *et al.* (2012)
Subunit vaccine	Recombinant penton base protein, expressed in *E. coli*	FAdV-4 isolated from an HHS outbreak (HE653773)	Serological response: recombinant penton base ELISA; challenge test: homologous virus	90% (vs. 10% in challenge control group)	Shah *et al.* (2012)
Inactivated vaccine	Formalinized (0.2%), oil-adjuvanted virus	FAdV-4 isolated from an HHS field outbreak (HQ697593)	Serological response: AGPT, commercial ELISA; challenge test in vaccinated and progeny chickens: homologous and serotype-heterologous viruses	Significant differences in survival rates in homologously and heterologously challenged vaccinated, as well as progeny chickens in comparison to challenge control groups	Kim *et al.* (2014)
Subunit vaccine	Recombinant fiber-1, fiber-2 and hexon loop-1 proteins, expressed in a baculovirus system	FAdV-4 reference strain KR5	Serological response: recombinant fiber-based ELISA, SNT; challenge test: virulent FAdV-4 field isolate	Fiber-1: 62% Fiber-2: 96% Hexon loop-1: 27% (vs. 22% in challenge control group)	Schachner *et al.* (2014)
Inactivated vaccine	Heat- and formalin (0.1%) treated virus	IBHV(SK) (FAdV-8b isolated from an IBH outbreak) (JN112373)	Serological response: ELISA based on inactivated homologous whole virus	n.d.[f]	Dar *et al.* (2015)
Subunit vaccine	PCEP adjuvanted recombinant hexon protein expressed in *E. coli*				

Inactivated vaccine	Binary ethyleneimine (BEI)-inactivated, oil-adjuvanted virus	FAdV-2 isolated from an IBH outbreak	Serological response: recombinant hexon-based ELISA, SNT; challenge test in embryonic eggs and progeny: homologous virus	90% (embryonic eggs), 100% (progeny of vaccinated broilers)[e]	Junnu *et al.* (2015)
Subunit vaccine	Recombinant 100K, expressed in *E. coli*	FAdV-4 isolated from an HHS outbreak	Serological response: recombinant 100K ELISA challenge test: homologous virus	40% (vs. 10% in challenge control group)	Shah *et al.* (2016)
Inactivated vaccine	Heat- and formalin (0.1%) treated virus, PCEP adjuvanted, *in ovo* administered	IBHV(SK) (FAdV-8b isolated from an IBH outbreak) (JN112373)	Serological response: ELISA based on inactivated homologous whole virus; cytokine expression analysis from spleen cells	n.d.	Sarfraz *et al.* (2017)
Virus-like particles (VLPs) subunit vaccine	2× vaccination with: empty viral capsids, separated by CsCl gradient centrifugation or recombinant fiber and fiber knob proteins expressed in *E. coli*	IBHV(SK) (FAdV-8b isolated from an IBH outbreak) (JN112373)	Serological response: SNT; cellular immune response: flow cytometry; challenge test in progeny: homologous virus	100% in VLPs-vaccinated, 82.7% in fiber-vaccinated, ~55% in fiber-knob-vaccinated birds (vs. ~50% in challenge control group)	Gupta *et al.* (2017)

[a]n.c., not characterized.
[b]Results summarized if more than one experiment was conducted.
[c]n.i., not indicated.
[d]Post-challenge sequential killing of birds was additionally performed.
[e]No values reported for challenge control group.
[f]n.d., not done.

of maternal antibodies to progenies. Based on the presence of FAdVs in eggs of breeders with neutralizing antibodies, earlier works suggest a possible co-existence of viral antigen with neutralizing antibodies (Saifuddin & Wilks, 1991b), whereby egg-derived Abs have been incriminated in limiting both duration of virus transmission (Dawson *et al.*, 1980) and pathological effects of vertically transmitted FAdVs, resulting in a latent infection (Grgić *et al.*, 2006).

Field studies proposing that neutralizing Abs in breeder flocks account for the absence of vertically transmitted FAdVs (Philippe *et al.*, 2007) are to some degree contradicted by experimental evidence of vertical transmission despite neutralizing antibodies in breeders (Toro *et al.*, 2001; Mazaheri *et al.*, 2003). This complies with the finding that neutralizing Abs, elicited by inactivated FAdV-4 vaccine of layer breeders, do not completely protect the respective progenies against intramuscular challenge with HHS (Toro *et al.*, 2002), altogether disputing the stand-alone role of a neutralizing humoral response for protection against FAdVs in such settings. In contrast, another study by Kim *et al.* (2014) reported significant reduction of mortality as well as tissue lesions in progenies derived from FAdV-4 immunized broiler breeders, conferring protection not only against the homologous serotype, but also against challenge with IBH strains of the heterologous serotypes FAdV-8b and -11 (belonging to FAdV-E and FAdV-D, respectively).

This finding is somewhat unanticipated given the phylogenetic and serological distance between immunogenic determinants of heterologous FAdV species, additionally contradicting the frequent observation that chickens are susceptible to co-infections with different FAdV serotypes under field conditions (Gomis *et al.*, 2006; Ojkić *et al.*, 2008; Kaján *et al.*, 2013; Mittal *et al.*, 2014b; Li *et al.*, 2016b). On the other hand, it cannot be outruled that formaldehyde treatment alters structural components of the virion (Akhtar *et al.*, 2000), which might explain the broader antigenicity of such a formulation.

In Australia, where IBH is controlled by a commercial live vaccine based on FAdV-8b, disease outbreaks related to FAdV-8b and FAdV-11 were reported (Steer *et al.*, 2011). This not only demonstrates limited efficacy of this method since various breeder flocks had failed to generate antibodies in response to vaccination, it also underlines a poor cross-protectivity between the relevant serotypes which is also reported from Canada with autogenous vaccines (Venne, 2013). The heterogeneity of IBH-causing FAdV types, belonging to two different FAdV species, argues for the use of dual-serotype vaccines against this disease, such as implemented by an inactivated, autogenous product combining serotypes from FAdV-D and FAdV-E, which has been shown to elicit adequate progeny protection against various challenge strains (Alvarado

et al., 2007). With updated FAdV nomenclature in place, it is particularly interesting to note that the respective vaccine apparently contains serotype FAdV-8a (El-Attrache & Villegas, 2001; Alvarado *et al.*, 2007; Schachner *et al.*, 2016), while at the same time providing adequate protection against challenge with the phylogenetically and serologically distinct serotype FAdV-8b (hitherto designated as FAdV-9). Efficacy of potential new approaches to killed IBH vaccines, using *in ovo* administered formulations containing inactivated serotype FAdV-8b together with next-generation adjuvants (Sarfraz *et al.*, 2017), has been proposed on basis of immune response evaluation, without providing challenge protection studies.

In contrast to HHS and IBH, which share similarities in pathogenesis and protective mechanisms, marked differences are observed in the protection against AGE. Both SPF and commercial broilers with homologous maternal antibodies developed characteristic clinical signs as well as pathomorphological gizzard lesions post ocular and/or oral infection with a virulent FAdV-1, indicating that vertically transmitted humoral immunity does not play a role in protection against AGE (Okuda *et al.*, 2001b; Grafl *et al.*, 2013). However, a resistance to re-infection with the same pathogenic FAdV-1 has been described previously (Ono *et al.*, 2004) and after live vaccination of day-old birds with the non-pathogenic FAdV-1 reference strain CELO, complete protection against AGE could be demonstrated (Grafl *et al.*, 2014). This indicates that the development of a local immunity seems to be critical in the development of the disease. Independent of this, experimental suppression of the immune system due to IBDV infection or cyclophosphamide treatment prior to inoculation with FAdV-1 resulted in higher gizzard lesion scores compared to those in non-immunosuppressed control birds (Muroga *et al.*, 2006).

Outlook and perspectives

On a global scale, an increase of FAdV-induced disease outbreaks has been recorded, particularly within the last 10 to 15 years. To date, at least one, but more often a combination of more than one FAdV-associated condition, has been reported from every continent with the limitation that documented outbreaks still remain underrepresented in face of the actual epidemiologic situation (Figure 1). The lack of documentation may partly be explained by a certain reluctance to publish singular cases, particularly from regions with already existing reports available. On the other hand, the metabolic component of FAdV infections, often resulting in reduced performance without obvious signs and mortalities, may easily conceal outbreaks. In this context, it remains to be clarified how recently developed parameters such as clinical chemistry analytes can be applied to assess subclinical FAdV manifestations.

The increasing incidence of FAdV-related diseases is substantially linked to the contemporary trends in poultry production, husbandry and rearing, following rigorously elevated standards in biosecurity and environmental conditions. Importantly, this development has not only led to the desired prevention of pathogen introduction into breeder stocks, but has also deprived parental birds of the possibility to generate a natural immune response against FAdVs prior to production, failing to transfer maternal antibodies to the progeny. The interference of an FAdV infection with birds' metabolism seems to be a key factor in the development of natural IBH and HHS outbreaks, as increasingly observed in very young birds. Furthermore, it can be hypothesized that the lack of immune competency at an early stage of life, at which age resistance mechanism against FAdV infection are not effective, contributes to the development of FAdV-induced diseases.

Future strategies to control IBH and HHS should aim to address the harmonization of protection strategies alongside with monitoring of the status of flocks, which are ideally realized through combined serological monitoring and vaccination. On both ends, such systems are to date still not fully commercially established and/or need to be adapted to the requirements in the field. For serological monitoring, detection methods for rapid and large-scale application, covering the relevant clinical types and their respective vaccine products, would be highly desirable. Given the variety of FAdV serotypes, often co-existing in the field and inducing varying degrees of serological cross-reactions, the use of existing assays such as enzyme-linked immunosorbent assays (ELISAs) based on whole virus particles is currently a compromise at the expense of specificity and sensitivity of the test system, whereas the adequately type-specific and sensitive serum neutralization test imposes severe limitations on large-scale sample processing. Addressing these criteria, recently developed ELISAs based on recombinant proteins hold promise for a next-generation test system which allows for differentiation of FAdVs along with applicability for mass screening. Additionally, this approach may pave the way towards a strategy for differentiating between infected and vaccinated animals, possibly in context with certain viral subunits that have been shown as protective immunogens.

Considering the significance of both vertical transmission and an early horizontal infection with FAdVs for induction of IBH and HHS, there is an increasing need for immunization strategies targeting maternal antibody production with transfer to progenies. The use of recombinant FAdV proteins, so far at an experimental stage, holds promise for the development of respective vaccination strategies, being both efficacious and safe without the risk of pathogen dissemination,

while potential use of such vaccines in context of the discussed settings remains to be evaluated.

Paradoxically, with the extensive use of adenoviruses as vectors mainly in human medicine, and recognition of FAdVs as an alternative to mastadenovirus vectors, FAdVs are no longer confined to their role as pathogen, but have also emerged in the context of serving as backbone for the construction of analogous vaccines. However, it remains to be investigated how this approach fits into an attainable vaccination strategy, given a possible interference with maternally derived Abs in a scenario where young chickens are immunized, and, in the case of breeder vaccination, concerns about insufficient antibody induction, together with the previously reported inefficacy of live virus vaccination to protect progenies. While important principles of pathogenesis and protective mechanisms are shared between IBH and HHS, implicating that many of the above-discussed aspects for control apply to both diseases alike, AGE takes a quite unique position among the FAdV-induced conditions, which will require the development of somewhat different approaches for its control.

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