



**UNIVERSITI PUTRA MALAYSIA**

**GLOBAL DISTRIBUTION OF FOWL ADENOVIRUS INFECTIONS IN 2011-  
2021: A SYSTEMATIC REVIEW**

**NG YOONG CHIN**

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FPV 2021 11**

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IN 2011-2021: A SYSTEMATIC REVIEW**



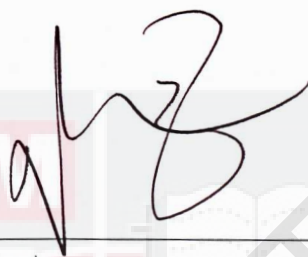
**NG YOONG CHIN**

A project paper submitted to the  
Faculty of Veterinary Medicine, Universiti Putra Malaysia  
In partial fulfilment of the requirement for the  
DEGREE OF DOCTOR OF VETERINARY MEDICINE  
Universiti Putra Malaysia  
Serdang, Selangor Darul Ehsan.

**December 2021**

**CERTIFICATION**

It is hereby certified that we have read this project paper entitled “Global distribution of fowl adenovirus infections in 2011-2021: A systematic review” by Ng Yoong Chin and in our opinion, it is satisfactory in terms of scope, quality and presentation as partial fulfilment of the requirement for the course VPD4999 – Final Year Project.



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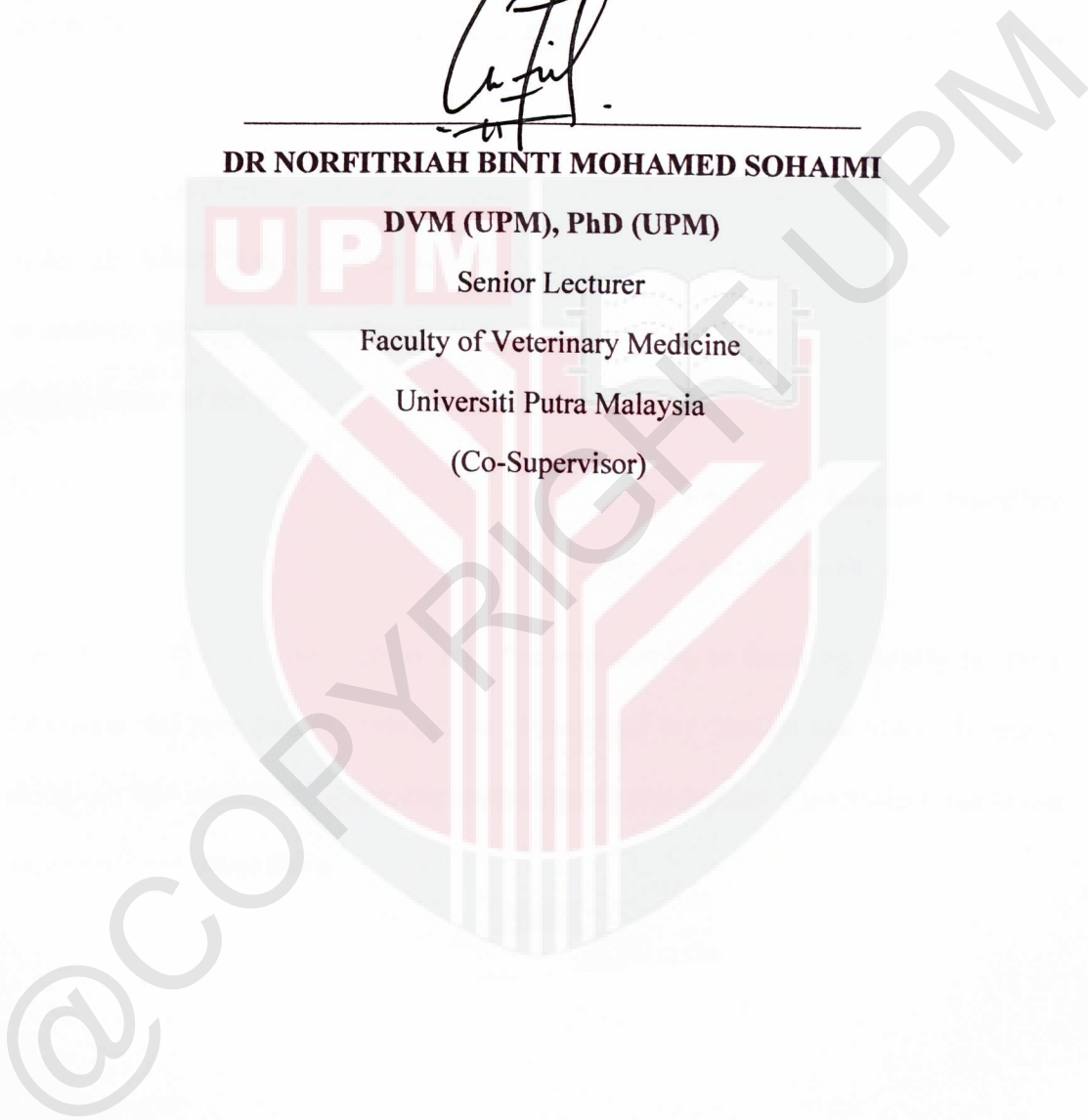
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## ABBREVIATIONS

FAdV	Fowl adenovirus
IBH	Inclusion Body Hepatitis
HHS	Hepatitis-Hydropericardium Syndrome
GE	Gizzard Erosion
QB	Quail Bronchitis
PRISMA	Preferred Reporting Items for Systematic review and Meta-Analysis
SPF	Specific Pathogen Free
PCR	Polymerase Chain Reaction
ELISA	Enzyme-Linked Immunosorbent Assay
AGID	Agar Gel Immunodiffusion Assay
VNT	Virus Neutralisation Test
CIAV	Chicken Infectious Anemia Virus
IBDV	Infectious Bursal Disease Virus

## ABSTRAK

Abstrak daripada kertas projek yang dikemukakan kepada Fakulti Perubatan Veterinar untuk memenuhi sebahagian daripada keperluan kursus VPD 4999 – Projek Ilmiah Tahun Akhir

### **TABURAN GLOBAL JANGKITAN ADENOVIRUS UNGGAS PADA 2011-2021: KAJIAN SISTEMATIK**

Oleh

**Ng Yoong Chin**

2022

**Penyelia: Dr Nik Mohd Faiz Nik Mohd Azmi**

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Dr Norfitriah binti Mohamed Sohaimi**

Adenovirus unggas (FAdV) adalah agen berjangkit biasa dalam ayam dan burung liar, yang menyebabkan hepatitis badan inklusi, sindrom hepatitis hydropericardium, hakisan hempedu dan bronkitis puyuh. Walaupun jangkitan FAdV telah dikenal pasti di banyak negara, masih terdapat kekurangan pemahaman tentang pengedaran virus ini secara global. Objektif kajian ini adalah untuk mengkaji secara sistematik penerbitan mengenai kes FAdV di seluruh dunia dan meneroka taburan jangkitan berdasarkan jenis FAdV isolate, negara, spesies burung, umur burung dan butiran lain yang berkaitan dari tahun 2011 hingga 2021. Data dikumpulkan daripada Scopus dan PubMed, menggunakan pendekatan sistematik PRISMA. Daripada 678 penerbitan yang ditemui pada mulanya, hanya 101 yang memenuhi kriteria kemasukan dan

dimasukkan dalam ulasan ini. Kajian ini mengenal pasti bahawa jangkitan FAdV kebanyakannya dilaporkan dari negara Asia (66%) dan Eropah (21%). Spesies FAdV yang paling biasa dilaporkan dalam jangkitan ini ialah FAdV-E (33%), diikuti oleh FAdV-C (29%), FAdV-D (27%), dan pada tahap yang lebih rendah daripada FAdV-A (8%) dan FAdV-B(3%). Hepatitis badan inklusi (45%) dan sindrom hepatitis hydropericardium (42%) adalah manifestasi FAdV yang paling umum dilaporkan dalam jangkitan ini. Kebanyakan jangkitan FAdV adalah daripada kalangan ayam pedaging komersial (55%) dan mempengaruhi anak burung berumur kurang daripada satu bulan (43%). Kajian ini menyerlahkan keperluan untuk menjalankan lebih banyak kajian epidemiologi untuk mengenal pasti serotip FAdV yang paling biasa dan sifat patogenik FAdV isolate daripada wabak jangkitan FAdV di seluruh dunia.

Kata kunci: Adenovirus unggas (FAdV), kajian sistematik, hepatitis badan inklusi, sindrom hepatitis hydropericardium, ayam

## ABSTRACT

An abstract of the project paper presented to the Faculty of Veterinary Medicine in partial fulfilment of the course VPD 4999 – Final Year Project.

### **GLOBAL DISTRIBUTION OF FOWL ADENOVIRUS INFECTIONS IN 2011-2021: A SYSTEMATIC REVIEW**

By

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2022

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**Dr Norfitriah binti Mohamed Sohaimi**

Fowl adenoviruses (FAdV) are common infectious agents infecting poultry and wild birds worldwide causing inclusion body hepatitis, hepatitis hydropericardium syndrome, gizzard erosion and quail bronchitis. Although FAdV infections have been identified in many countries, there is still a lack of understanding on the distribution of these viruses globally. The objective of this study was to systematically review publications on FAdV cases worldwide and explore their distribution based on the type of FAdV field isolates, country, avian species, age of birds, and other related details from 2011 to 2021. Data was collated from Scopus and PubMed, using PRISMA systematic approach. Out of 678 publications screened, only 101 met the inclusion criteria and were included in this review. The study identified that FAdV

publications were mainly reported from Asian (66%) and European (21%) countries. The most common FAdV species reported in these outbreaks were FAdV-E (33%), followed by FAdV-C (29%), FAdV-D (27%), and to a lesser extent of FAdV-A (8%) and FAdV-B(3%). Inclusion body hepatitis (45%) and hepatitis hydropericardium syndrome (42%) were the most prominent FAdV manifestation reported in these outbreaks. Most FAdV infections were from commercial broilers (55%) and affected young birds less than one month of age (43%). This study highlights the need for more epidemiological studies to identify prevalent of FAdV serotypes and pathogenicity of isolates from outbreaks of FAdV infections worldwide.

Keywords: Fowl adenovirus (FAdV), systematic review, inclusion body hepatitis, hepatitis hydropericardium syndrome, poultry

## 1.0 INTRODUCTION

Fowl adenoviruses (FAdVs) are group I adenoviruses in genus *Aviadenovirus*, which belongs to the *Adenoviridae* family (Choi et al., (2012). FAdVs have a worldwide distribution and are classified into five species (FAdV-A to FAdV-E) and twelve serotypes (FAdV-1 to 8a and -8b to 11) based on restriction enzyme digest patterns and serum cross-neutralization tests (Zhao et al., 2015).

FAdVs have been associated with a variety of diseases in birds, including inclusion body hepatitis (IBH), hepatitis-hydropericardium syndrome (HHS), respiratory tract disease, and gizzard erosion (Chen et al., 2019).

Epidemiological investigation revealed different serotypes or genotypes of FAdVs were discovered in different geographic regions, indicated that FAdVs have a worldwide distribution (Li et al., 2018). IBH and HHS are the two most prominent diseases related to FAdV infections in chickens (Liu et al., 2016).

Classical IBH affects mostly 3–5-week-old chickens and is characterised by mortality approaching 10% and hepatic necrosis with microscopic eosinophilic or basophilic intranuclear inclusion bodies in hepatocytes (Zhao et al., 2015). Viruses that have previously been found to cause IBH in geographically separate places are mostly caused by FAdV belonging mainly to serotypes FAdV-2, FAdV-11 (species Fowl aviadenovirus D), and FAdV-8a and FAdV-8b (species Fowl aviadenovirus E) (Schachner et al., 2018).

FAdV-4 (species Fowl aviadenovirus C) and FAdV-1 (species Fowl aviadenovirus A) serotypes were identified as causative agents for HHS and gizzard erosion, respectively (Harrach et al., 2019).

HHS is characterised by the accumulation of translucent or straw-coloured fluid in the pericardial sac, nephritis, and hepatitis, as well as a high death rate of 30–70%. Gizzard erosion is commonly found in slaughtered broiler chickens (Zhao et al., 2015).

In recent years, the clinical cases of IBH and HHS have been increasing worldwide, resulting in significant economic losses in many countries, such as China, India, United States, Canada, Hungary, Korea, and Japan (Zhao et al., 2015).

Fowl adenovirus infection of poultry can occur at any age. Young birds experience the greatest clinical and economic consequences. The infection's outcome is influenced by other factors, including the virus strain's virulence and immunosuppressive circumstances (Kiss, et al., 2018).

Fowl adenoviruses are common infectious agents in poultry and wild birds, causing substantial economic losses to the poultry industry worldwide. The diversity and distribution of the most prevalent of FAdV types on the regional level and their pathogenic role under field conditions are still not fully understood. Furthermore, there are limited commercially available vaccines to prevent FAdV infections.

Therefore, it is critical to identify areas of knowledge that need to be reinforced in order to develop regional and vaccination programmes for the prevention, control, and eradication of FAdV infections.

The objective of this study was to systematically review publications on FAdV outbreaks from epidemic countries to describe the distribution of FAdV infections of all avian cases which occurred globally from 2011 to 2021.



## 2.0 MATERIALS AND METHODS

### 2.1 Identifying relevant publications

A systematic review on journal articles on Fowl adenovirus published from January 2011 to August 2021 were performed. The PRISMA method (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses—2010*) were followed. The systematic review included all fowl adenovirus reported cases worldwide. The articles were obtained from PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) and Scopus (<https://www.scopus.com/>) databases.

For the systematization of information, a database was built that included the references of all selected publications, as well as the title, author, year of publication, country or countries where the study was conducted, and language of publication.

### 2.2 Search strategy

The processes for searching, selecting, and collecting the articles in the database were conducted using Boolean connectors and advanced search on the recognized database such as Scopus and PubMed in this study.

Relevant publications were identified using keyword combination: (avian OR fowl) AND (adenovirus OR *Aviadenovirus* OR “inclusion body hepatitis” OR “hydropericardium syndrome” OR “gizzard erosion” OR “quail bronchitis”).

The search queries were set to include above terms in (a) article titles, abstracts, and keywords for Scopus database. (b) titles and abstracts for PubMed.

All searches were performed in September 2021. The search result was limited to articles published from January 2011 to August 2021 and in English language only.

## **2.3 Screening relevant publications**

### **2.3.1 Main inclusion criteria**

The systematic review included all publications on case reports of Fowl adenovirus worldwide. All laboratory-confirmed cases or outbreaks where confirmation was performed by officially indicated methods (histopathology examination, immunohistochemistry, serological, molecular, both serological and molecular, or other virus isolation method) were included. All species (A-E) and serotypes of Group 1 avian adenovirus were included. All avian species of any age were considered, including wild birds; commercial poultry, and backyard domestic poultry.

### **2.3.2 Exclusion criteria**

Notes, letters to editors, review, editorials, and experimental inoculation studies were manually excluded since they are regarded as artificially induced cases rather than naturally occurring cases. Publications related to other groups 2, 3 adenovirus (Siadenovirus, Atadenovirus) were also excluded.

Publications not stating clearly about species or serotype of FAdV isolates, unconfirmed cases of FAdV infections, case reports in humans, or other species different to birds and for mixed of other reasons were not included in the study as they did not have specific outcomes relevant to our systematic review. The selection criteria developed a priori were the following:

#### **1. Year of the publications**

2. Country/city of epidemic
3. Bird species such as commercial birds, backyard flocks, and wild birds
4. Age group of cases
5. Diagnostic methods (serological, molecular, etc)
6. Forms of FAdV infections (IBH, HHS, GE, QBV)
7. FAdV species(A-E) and serotypes (12)
8. Mortality of FAdV infections and isolates
9. Co-infections with other immunosuppressive viral agents (CIAV, IBD, HPAI)
10. Surveillance/vaccination programme administration

#### **2.4 Data collection process and items**

A data extraction sheet was developed by Excel for screening purposes. The articles were selected using a two-stage approach. During the first stage, the publications were selected based on their titles and abstracts, excluding the publications that were not considered relevant for this study.

During the second stage, the full text of the articles that were previously selected in the first phase were reviewed. At this point, the articles that did not meet the previously established criteria were excluded.

## 3.0 RESULTS

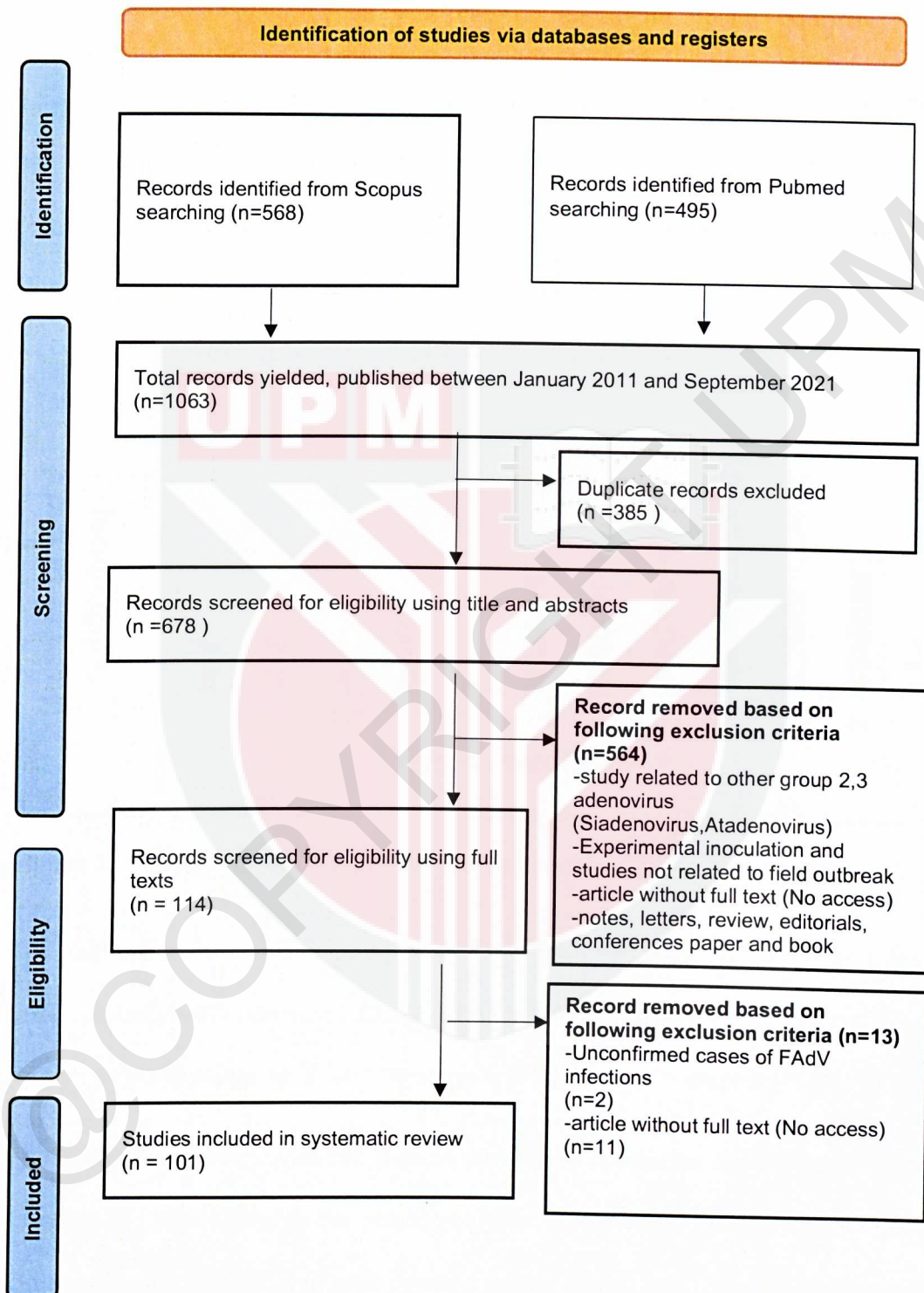
### 3.1 Search results

During the selection process, Scopus yielded 568 records and PubMed yielded 495 records fitting the research strategy criteria.

### 3.2 Study selection

The study selection process is summarised in a flow diagram (Figure 1). The search provided initially 1063 and after eliminating duplicates of 385 articles, 678 articles remained. After the initial review of all these studies by the first and last author on both the title and abstract, 564 articles were discarded after the first screening. After full-text screening and during data extraction process, 13 articles were discarded as they did not meet eligibility criteria.

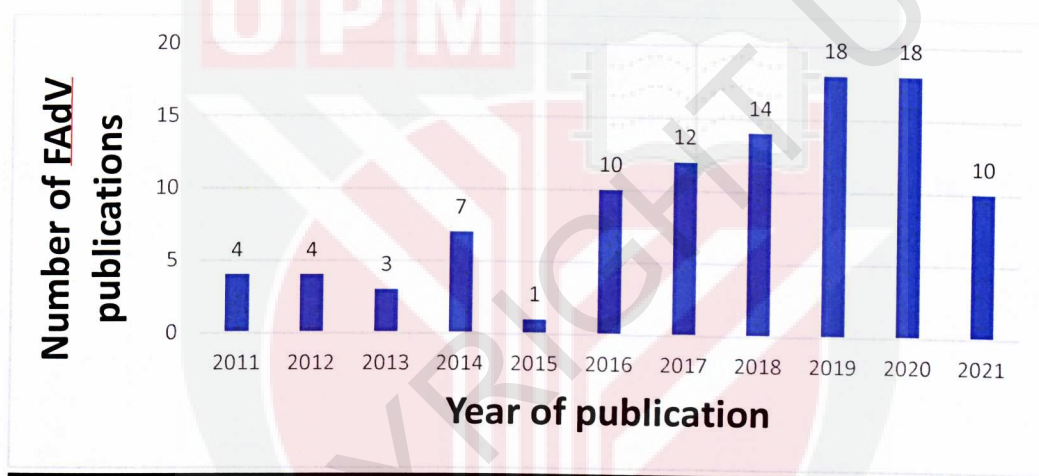
A total of 101 publication articles from the electronic databases mentioned, were eventually deemed eligible for inclusion in this systematic review.



**Figure 1: PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) flowchart diagram showing identification and records selection process of studies for the systematic review**

### 3.3 Distribution of included publications based on years, countries, and continents

The greatest number of publications 18 (17.8%) occurred in both of the years 2020 and 2019, while 14 (13.9%) occurred in 2018, 12 (11.9%) in 2017. 2021 and 2016 recorded the same number of publications which is 10 (9.9%), while 7 (6.9%) in 2014 (Figure 2). 2012 and 2011 recorded the same number of publications which is 4 (4%), while 3 (3%) in 2013, and only 1 publication included in 2015 (Figure 2).



**Figure 2: Number of publications of Fowl adenovirus from 2011 to 2021.**

The publications on FAdV were mainly from Asia 67 (66%), followed by Europe 21(21%), and South America 5 (5%). Africa and North America recorded the lowest number of publications on FAdV, which is 4 (4%) for each continent (Figure 3).

China was the country with the highest number of conducted studies and reported cases of 36 (35.6%) during the period analysed, followed by Poland with 9 (8.9%), India and Iran with 5 (5%) in each country. Japan, Korea, and United States recorded the same number of publications which is 4 (4%). Egypt, Malaysia, and Brazil recorded the same number of publications which is 3 (3%). The remaining 18 countries recorded only 1 or 2 publications for FAdV infections (Figure 4).

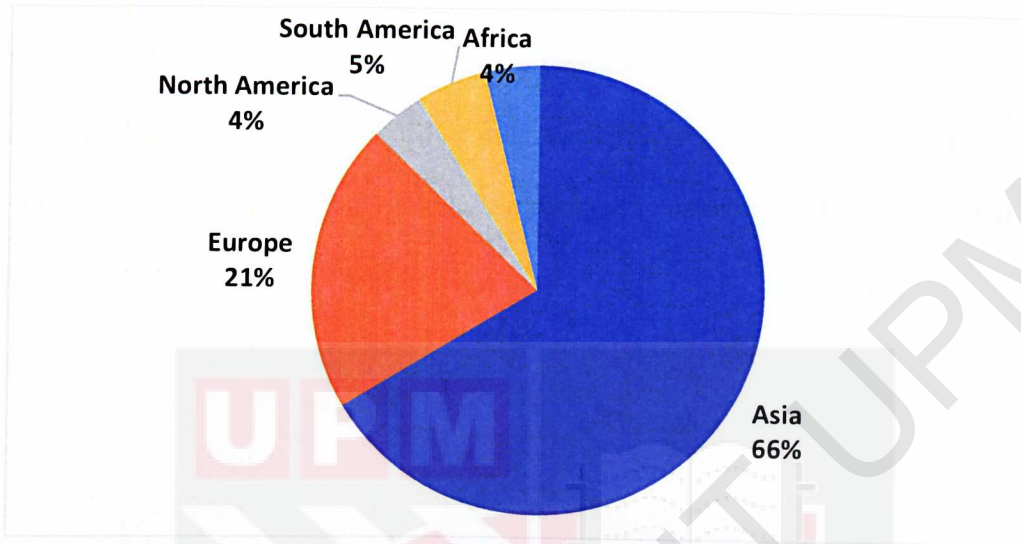


Figure 3: Distribution (%) of FAdV publications based on 5 continents.

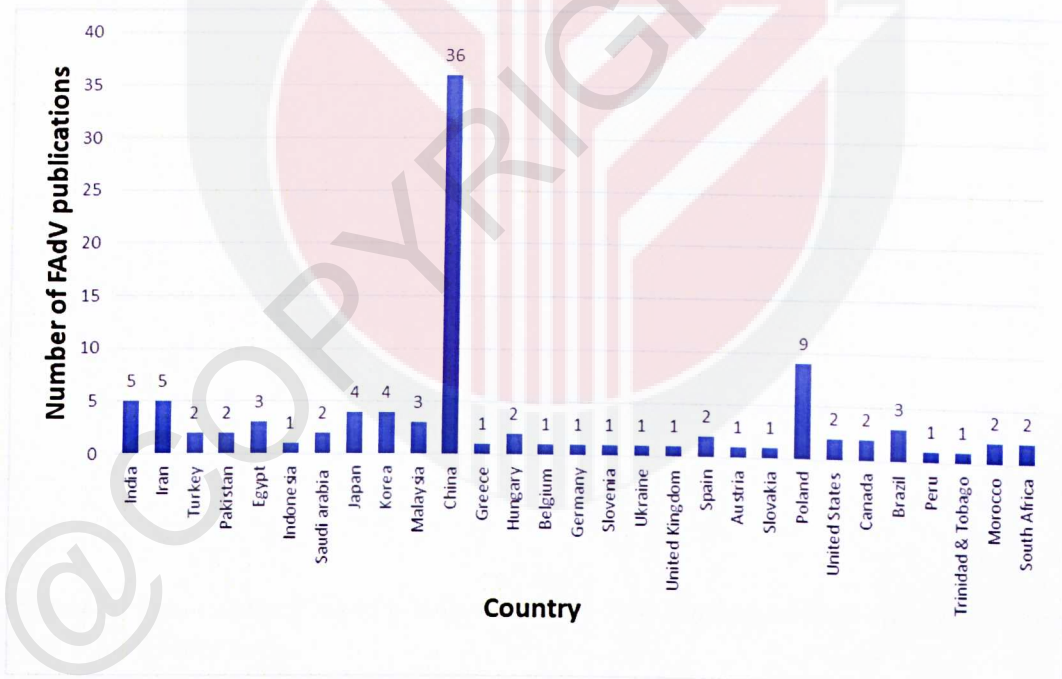
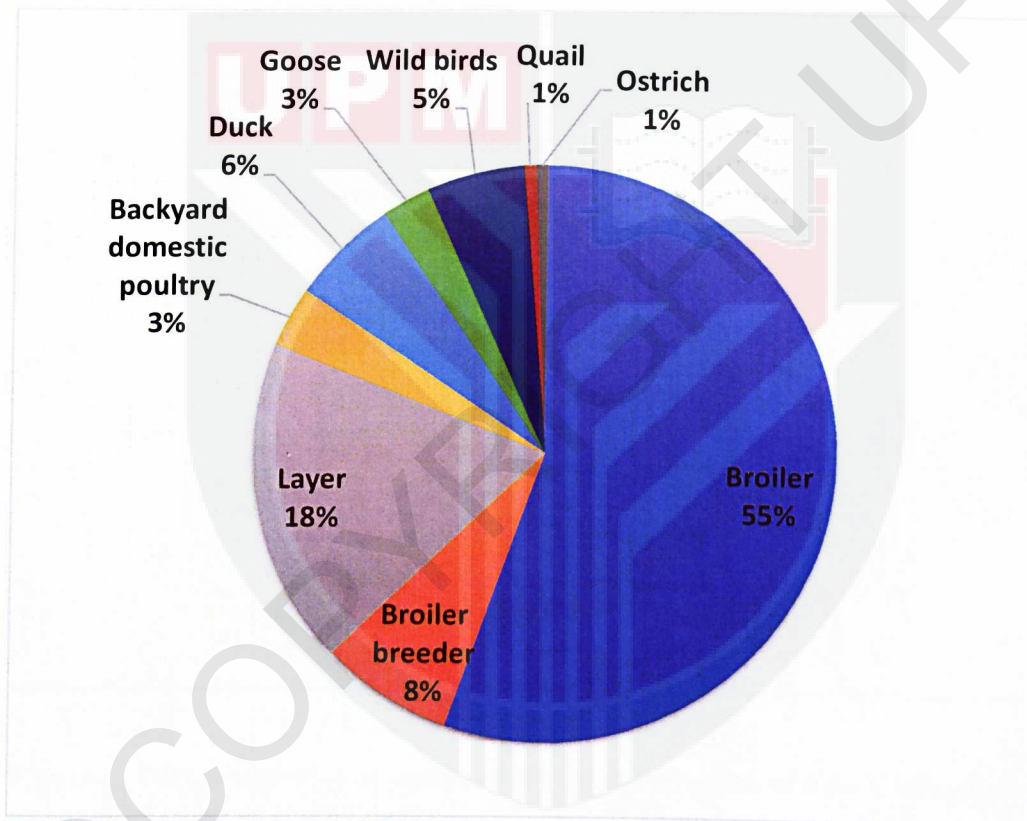


Figure 4: Number of publications reported FAdV cases from 2011-2021: based on 29 countries.

### 3.4 Bird species

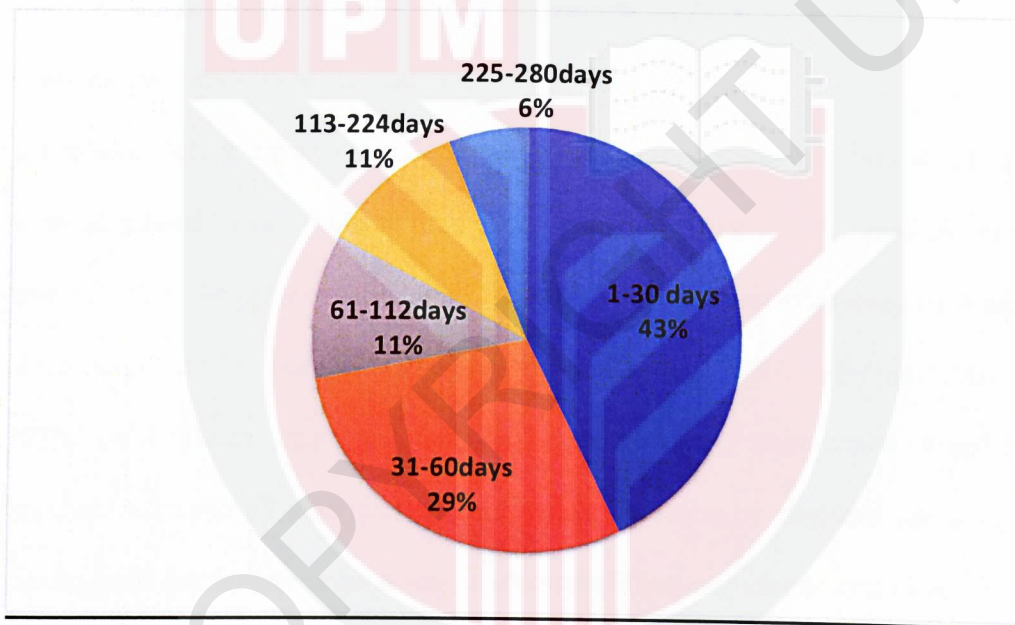
99 (98%) of publications reported the bird species affected. Most of publications show that FAdV infecting broilers (55%), followed by layers (18%), broiler breeder (8%), duck (6%), wild birds (5%), goose (3%), backyard domestic poultry (3%), quail (1%) and ostrich (1%) (Figure 5).



**Figure 5: Percentage (%) of publications on distribution of bird species affected with FAdV infections.**

### 3.5 Bird age

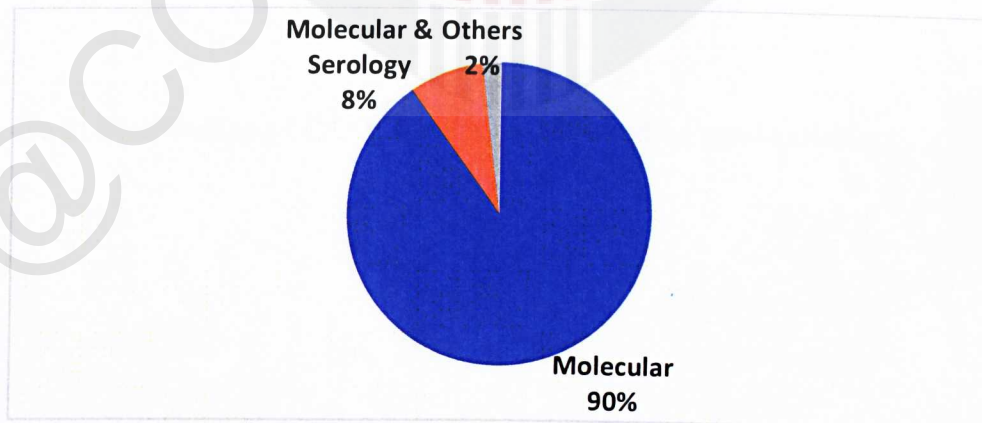
44 (43.6%) of publications specified the age of infected birds from all avian species. The age of FAdV-positive birds with clinical symptoms ranged between 1 and 280 days of age. Among those mentioning the specific case age, majority of birds aged between 1-30days (43%), followed by 31-60 days (29%), 61-112 days (11%), 113-224 days (11%), and 225-280 days (6%) of age (Figure 6).



**Figure 6: Percentage (%) of publications on distribution of FAdV infections by age groups of birds (1-280 days).**

### 3.6 Diagnostic method

Almost all 99 (98%) publications identified field samples by virus isolation, molecular and serology detection. Only 2 (2%) publication diagnosed samples up to histopathological examination and immunohistochemistry only (Figure 7). 54 (53.5%) publications performed virus isolation to diagnose FAdV infections by using SPF embryonated eggs, chick embryo liver culture, chicken kidney cell. Those samples that proved to be positive by virus isolation for FAdV were selected for further analysis by molecular or serology diagnostic method. 91 (90%) publications mentioned field samples were diagnosed by molecular methods. Majority of samples were identified by detection of the hexon gene loop 1 of a major capsid protein gene using PCR, followed by real-time PCR. 8 (8%) publications mentioned field samples were diagnosed by molecular and serology methods (ELISA, VNT and AGID). 98 (97%) publications mentioned that field isolates were further characterized into 5 species (A-E) and 12 serotypes after molecular detection by phylogenetic analysis of hexon gene, nucleotide sequencing, and complete genome characterization.



**Figure 7: Percentage (%) of publications on diagnostic methods for FAdV infections.**

### 3.7 Distribution of FAdV species (A-E) based on publications

The phylogenetic analysis from 97 (96%) publications revealed that the most common FAdV species reported in these outbreaks was FAdV-E (33%), followed by FAdV-C (29%), FAdV-D (27%), and to a lesser extent of FAdV-A (8%) and FAdV-B (3%) (Figure 8). Only 4 (4%) of included articles did not specify FAdV species isolated.

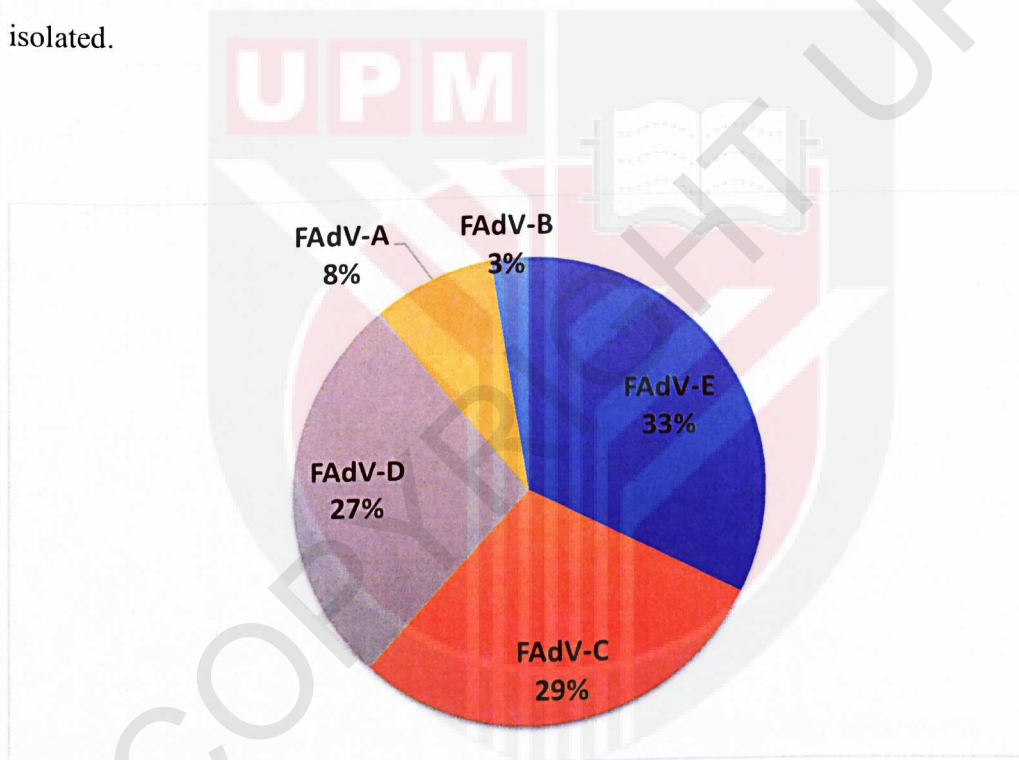


Figure 8: Distribution of FAdV species (A-E) based on publications.

### 3.8 Distribution of forms of FAdV infections based on publications

97 (96%) publications from 27 countries reported forms of disease associated with FAdV infections. Majority of FAdV infections related to 47 (49%) with inclusion body hepatitis, followed by 41 (42%) with hepatitis-hydropericardium syndrome, 8 (8%) with gizzard erosion, and only one publication reported Quail Bronchitis (Figure 9). 4 (4%) of publications did not specify forms of adenovirus infections.

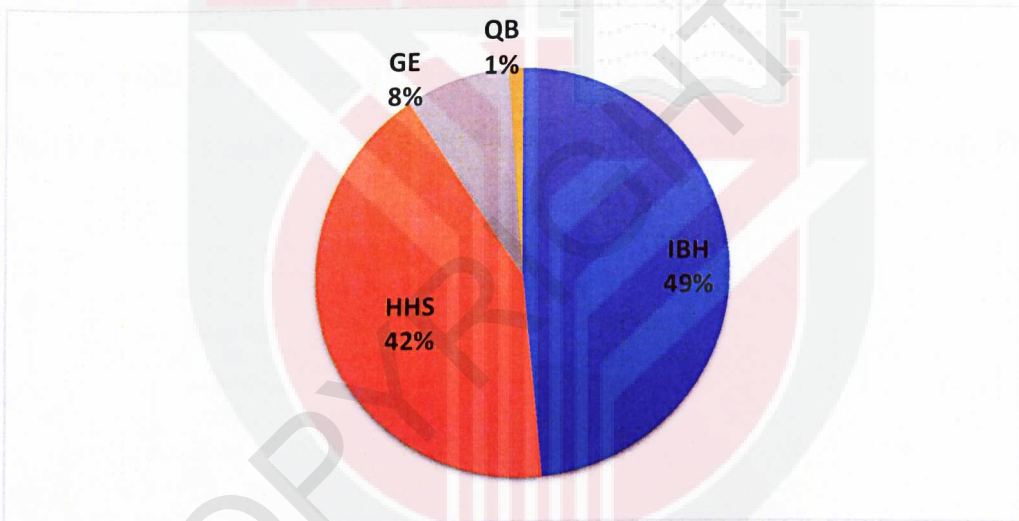
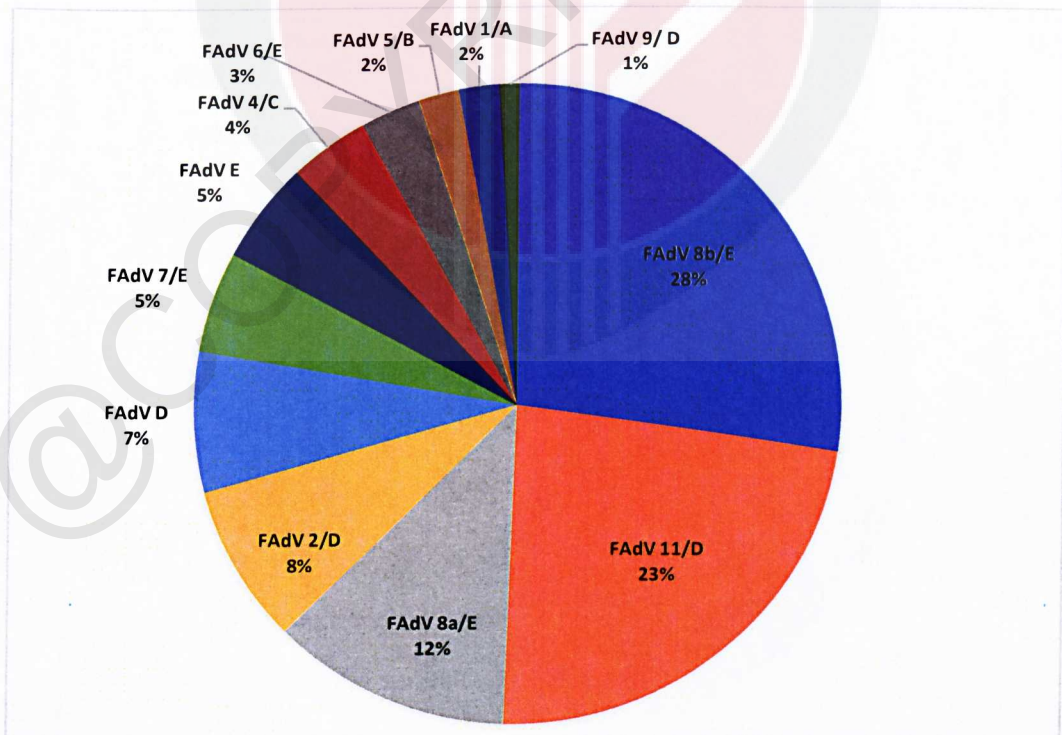


Figure 9: Distribution of forms of FAdV infections based on publications.

### 3.9 Inclusion body hepatitis (IBH)

FAdV-D and FAdV-E strains were identified in 39% and 53% of the total 47 publications of IBH cases included in this study. Majority of serotypes caused IBH were FAdV-8b/E (28%), followed by FAdV-11/D (23%), FAdV-8a/E (12%), FAdV-2/D (8%), FAdV-7/E (5%), FAdV-4/C (4%), FAdV-6/E (3%) respectively (Figure 10).

Few publications reported FAdV-D (7%) and FAdV-E (5%) field isolates in IBH outbreaks but did not specify which serotypes. Other serotypes FAdV-1/A (2%), FAdV-5/B (2%), and FAdV-D/9 (1%) were identified at negligible proportion (Figure 10).

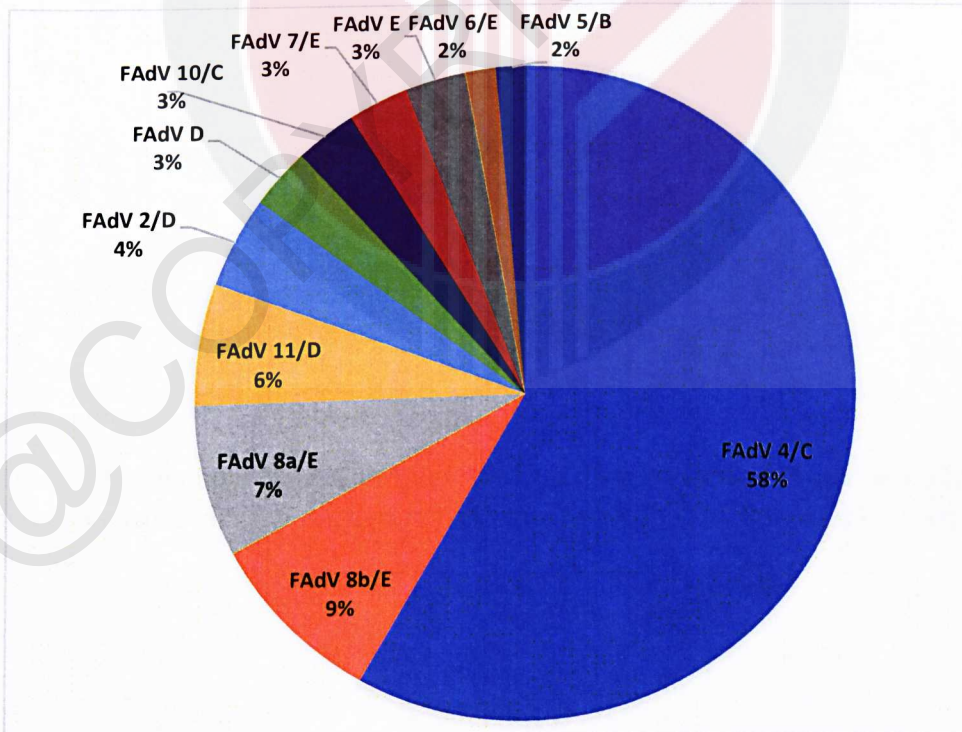


**Figure 10: Percentage (%) of publications on distribution of FAdV species and serotypes causing inclusion body hepatitis (IBH).**

### 3.10 Hepatitis-hydropericardium syndrome (HHS)

FAdV-C (61%), FAdV-E (24%), FAdV-D (13%) were identified from total 41 of HHS publications from 5 Asia countries including China (33), India (2), Korea (2), Pakistan (1), Saudi Arabia (1) and 2 publication from Brazil. Majority of serotypes causing HHS were FAdVs-4/C (58%), followed by FAdV-8b/E (9%), FAdV-8a/E (7%), FAdV-11/D (6%), FAdV-2/D (4%), FAdVs-10/C (3%), FAdV-7/E (3%) (Figure 11).

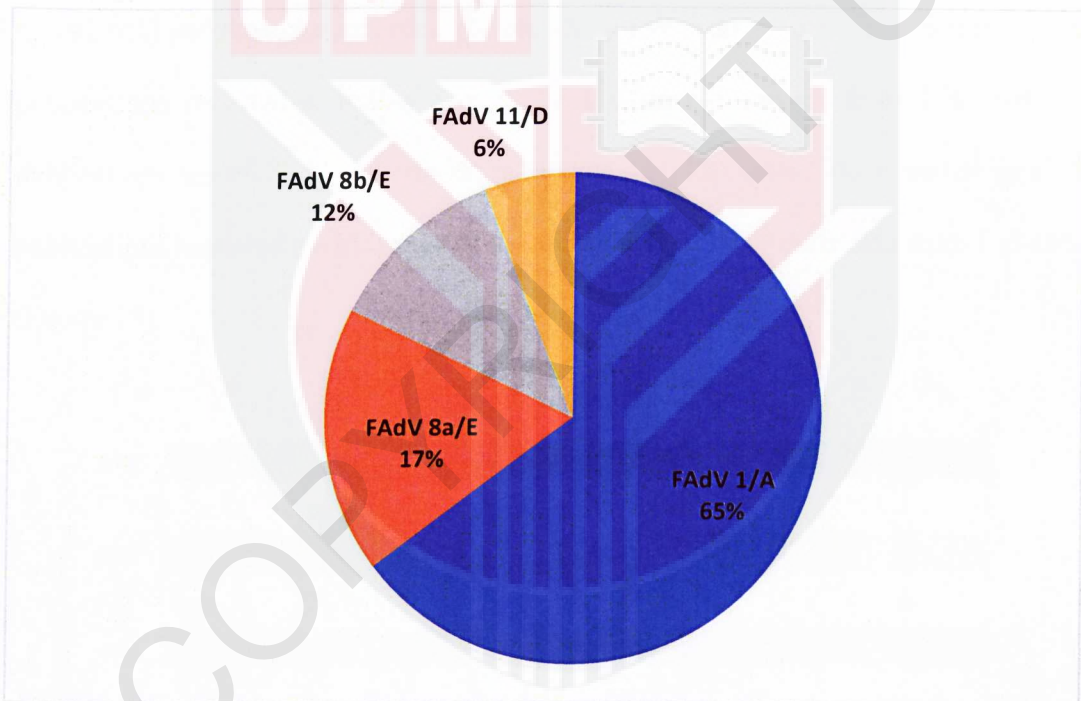
Other publications reported FAdV-D (3%) and FAdV-E (3%) field isolates in HHS outbreak but did not specify which serotypes. Other serotypes FAdV-5/B and FAdV-6/E were identified at a negligible proportion of 2% for each serotype (Figure 11).



**Figure 11: Percentage (%) of publications on distribution of FAdV species and serotypes causing Hepatitis-hydropericardium syndrome (HHS).**

### 3.11 Gizzard erosion and quail bronchitis

Total of 8 publications from 3 Asian countries including Iran (1), Korea (1), Japan (1), and 4 European countries included Poland (2), Hungary (1), United Kingdom (1), Germany (1) reported gizzard erosion outbreaks. FAdV-1/A (65%), FAdV-8a/E (17%), FAdV-8b/E (12%), and FAdV-11/D (6%) were identified from total 8 publications of gizzard erosion (Figure 12).

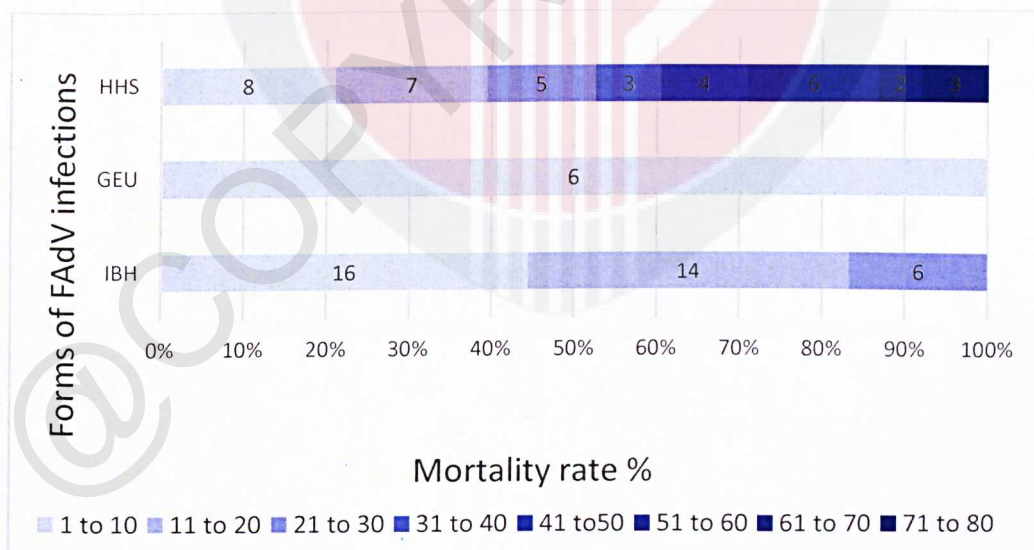


**Figure 12: Percentage (%) of publications on distribution of FAdV species and serotypes causing gizzard erosion mainly due to FAdV-1/A followed by FAdV-8a and -8b/E.**

Another FAdV infection caused by FAdV-1/A was Quail bronchitis, an acute, highly contagious, deadly respiratory disease in immature bobwhite quail caused by quail bronchitis virus. Infected flocks often experienced more than 50% mortality and up to 100% morbidity, and the disease is more severe in young quail less than three weeks old (Singh et al., 2016).

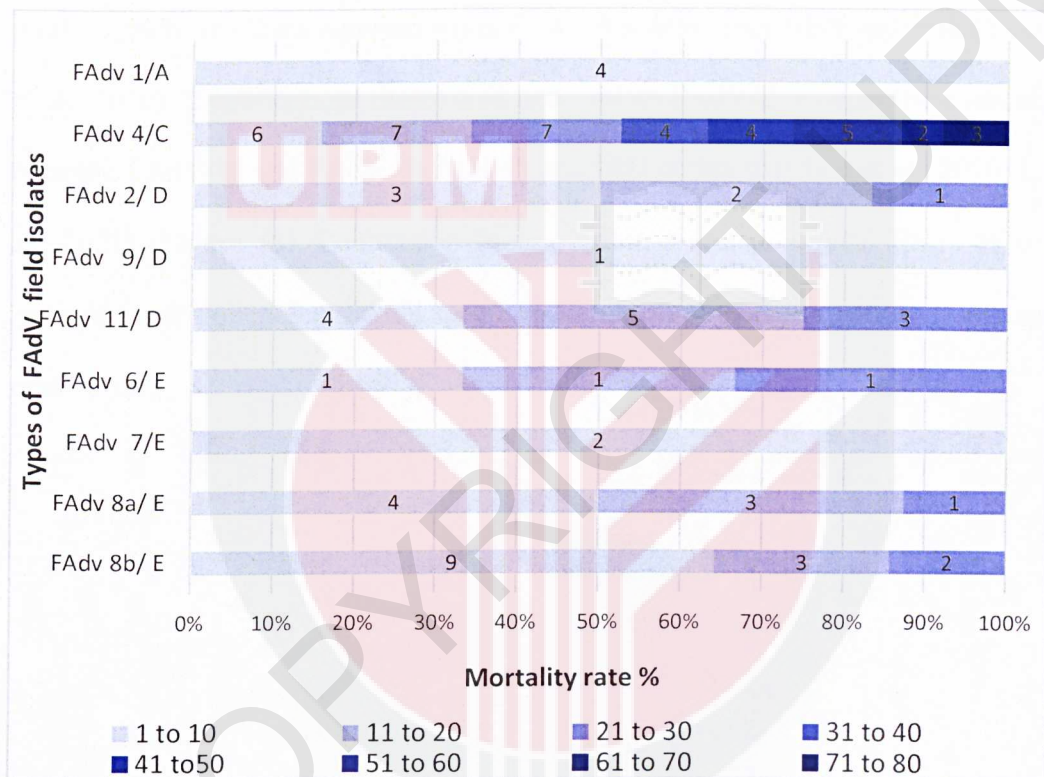
### 3.12 Mortality rate

42 (41.6%) publications recorded the mortality rate from FAdV field outbreaks. 19 publications reported mortality rate of IBH outbreaks ranges from 1 to 30%. 6 publications reported gizzard erosion outbreaks with less than 10% mortality rate. 17 publications recorded a wide range of mortality rates of HHS outbreaks from 1 to 80% (Figure 13).



**Figure 13: Mortality rate based on forms of FAdV infections mainly due to IBH and HHS outbreaks.**

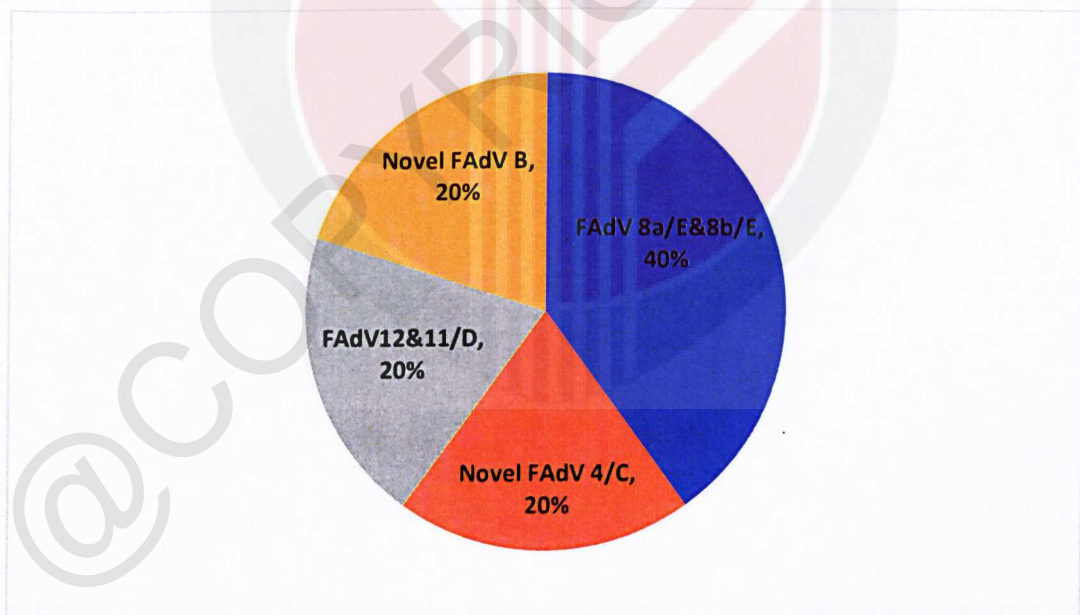
FAdV 4/C recorded the widest ranges, and highest mortality rates which range from 1-80%, followed by FAdV 8a/E, FAdV 8b/E, FAdV 11/D, FAdV 2/D, and FAdV 6/E ranged from 1% to 30% of mortality rates. FAdV 1/A, FAdV 9/D, FAdV 7/E recorded less than 10% mortality rates (Figure 14).



**Figure 14: Mortality rate based on types of field isolates and widest ranges in FAdV-4/C.**

### 3.13 Novel and recombinant FAdV strain

5 (3%) out of 101 publications revealed novel and recombinant isolates were discovered from HHS outbreak. One publication from India discovered new isolates clustered with FAdV-11 and FAdV-12 in HHS outbreak. (Thakor et al., 2012). One publication from China reported novel FAdV-4 strains from HHS outbreak (Yuming et al., 2020). 2 publications discovered new isolate FAdV-E as recombination strain between FAdV-8a and FAdV-8b in HHS and IBH outbreak (Chen et al., 2020; Lv et al., 2021) (Figure 15). Publication from Ukraine revealed a novel FAdV-B strain isolated from broilers but did not specify which form of FAdV infections (Homonnay et al., 2021).

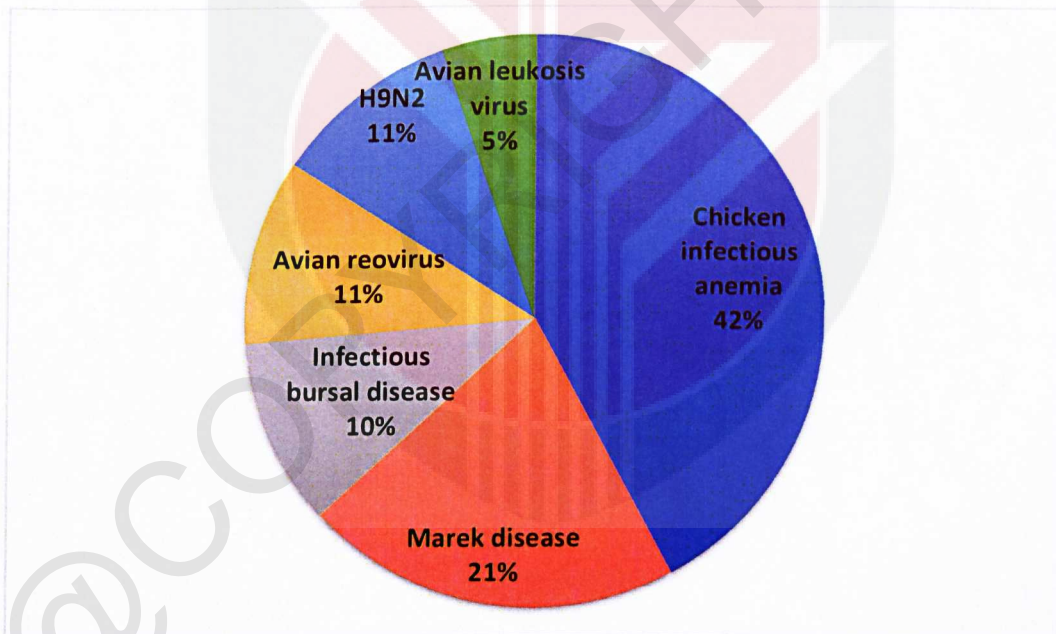


**Figure 15: Percentage (%) of publications on novel and recombinant fowl adenovirus (FAdV) isolates.**

### 3.14 Co-infections with other immunosuppressive viral agents

19 (18.8%) publications revealed the usage of molecular or serology methods to screen for the presence of possible mixed infections such as CIAV, IBDV, H9N2 AIV, and others.

14 (13.9%) publications detected positive FAdV infections complicated with other immunosuppressive viruses. The most frequent coinfection was with CIAV (42%), followed by Marek disease (21%), avian influenza (H9N2) (11%), avian reovirus (11%), infectious bursal disease virus (10%), avian leukosis virus J (5%) (Figure 16).



**Figure 16: Percentage (%) of publications on the distribution of immunosuppressive viruses co-infecting with FAdV infections.**

### 3.15 Vaccination programme

Only 8 (8%) of publications mentioned vaccination programmes were administered to the flock. One publication mentioned broilers were vaccinated with FAdV-4 vaccine against IBH. The remainder 7% of the publications mentioned broilers were vaccinated against infectious bursal disease virus (IBDV), chicken infectious anemia virus (CIAV), infectious bronchitis virus (IBV), Newcastle disease virus (NDV), and infectious laryngotracheitis virus (ILT). For this reason, the value of vaccination could not be reliably evaluated.

#### 4.0 DISCUSSION

In this systematic review, a global dataset spanning ten years was systematically reviewed to investigate the epidemiological profile of FAdV species and their serotypes at the regional level. Our findings suggest that FAdV infections have been widely distributed in different countries, and it is still expanding, causing significant economic losses to the poultry industry worldwide. 101 publications of FAdV infections from 29 countries represented 5 continents were being reviewed.

Asia was the continent with the highest publications on FAdV outbreaks, with most FAdV-positive cases recorded in China (Chen et al., 2019; Rashid et al., 2020), India (Chitradevi et al., 2021), Iran (Mirzazadeh et al., 2021) and Korea (Park et al., 2020) during 2016-2019. The author believed that the increased number of publications on FAdV infections overtime was due to better regional surveillance systems and enhanced laboratory diagnostic methods implemented in all these countries.

Most publications (90%) included in this systematic review originated from commercial poultry farms, mainly attributed to broilers (55%). 3% of publications were originated from backyard domestic poultry. Few publications (7%) indicated that adenovirus strains have been detected in wild bird species such as black grouse, falcon, swan, duck, and peacock, suggesting some wild bird species could act as adenovirus reservoirs (Niczyporuk et al., 2020; Wang et al., 2021). Isolation of poultry adenovirus strains from wild birds reveals that these strains are constantly developing and altering at the molecular level. Direct or indirect transmission between wild and

domestic bird species is also possible (Niczyporuk et al., 2020). Our findings suggested a potential risk of cross-species transmission between domestic and wild birds, emphasising the importance of implementing strict biosecurity measures to prevent mixing different bird species.

The age group of infected birds with clinical symptoms range from 1 to 280 days, suggesting all age groups are susceptible to FAdV infections. Our findings demonstrate that the percentage morbidity in all types of birds aged 1-30 days (43%) and 31-60 days (29%) were significantly higher than other age groups, indicating FAdV infections mostly reported in young birds.

Aviadenoviral infections are characterised by age-related resistance (Mittal et al., 2014). The degree of proliferation of viruses within the host is restricted as the host's age increases, and the mortality rates also reduce consequently (Rahimi & Minoosh, 2015). Chickens around the age of 2-6 weeks are considered the most susceptible age for IBH and HHS. Though the disease has a 10-day incubation period, occurrence of the disease in birds during their first and second weeks of life may be attributable to the presence of virulent FAdV strains in the environment. Improper cleaning or having multiple age groups of flocks will lead to the persistence of FAdVs on the farm (Mittal et al., 2014). Our findings reveal that some clinical cases of FAdV infections have affected chickens of various age groups, and both horizontal and vertical transmission might cause it, but we were unable to determine whether the transmission route was horizontal or vertical in each publication. Therefore, more research is needed to investigate most likely routes of transmission of FAdVs and identify possible risk factors contribute to field outbreak.

All FAdV infections were diagnosed based on case history, pathological post-mortem findings, histopathology together with evaluation of field data, including clinical signs, morbidity and mortality rates, birds age, and others. Serological methods or virus isolation were used to screen field samples. Positive and suspect samples were confirmed with molecular methods in most cases.

In studies conducting phylogenetic analysis reveals that the most prevalent FAdV species reported from outbreaks belong to FAdV-E, FAdV-D and FAdV-C. Our results show the most common FAdV infections reported in these outbreaks were inclusion body hepatitis and hepatitis-hydropericardium syndrome, indicating both FAdV infections have emerged as economically significant diseases.

All 5 continents reported a growing number of IBH outbreaks in various geographical locations, mainly from Asia and Europe for the past 10 years, emphasising the disease's global expansion (Schachner et al., 2018). IBH primarily affects broilers up to five weeks of age in the field, but it has also been reported sporadically in layers and broiler breeders (Schachner et al., 2018). The post-mortem examination revealed hepatomegaly, cholestasis, and hepatitis of liver, splenomegaly, haemorrhages in spleen (Maartens et al., 2014). Large regions of cellular degeneration and necrosis, lymphoid infiltration, and inclusion bodies are common histological findings in livers of IBH affected chicken (Schachner et al., 2018).

Based on included studies, IBH is mainly caused by FAdV-E from serotypes FAdV-8a, FAdV-8b, and FAdVs D from serotypes FAdV-2, FAdV-11. All species A-E and 12 serotypes of FAdVs have been linked to IBH outbreaks (Schachner et al., 2018).

Epidemiological investigations in Korea revealed FAdV 8b/E and 11/D were responsible for clinical IBH (Park et al., 2020). IBH was solely caused by fowl adenovirus serotype 8b in Malaysia (Sabarudin et al., 2021); serotype 2 was related to IBH in Japan (Mase et al., 2012). The increasing number of IBH field reports strongly suggested that the increase in virulence of FAdV field strains, particularly strain FAdV 8b/E over FAdV 8a/E and FAdV 11/D in commercial broilers.

All publications of HHS originated from Asian and South American countries, with a majority of 80.5% publications reported from China. Hydropericardium syndrome (HPS) is a viral infection that affects broiler chickens aged 3 to 5 weeks. (Zhang et al., 2016). Since 2015, HHS epidemics with high mortality rates have been reported in several broiler-producing areas in China (Chen et al., 2019; Pan et al., 2017). Major gross lesion associated with HHS is hydropericardium characterized by pericardial effusion with a clear accumulation of straw-colored pericardial fluid. Other lesions include enlargement and discoloration of the liver with hemorrhagic or necrotic foci (Chen et al., 2019). Our findings indicate most cases of HHS in chickens were caused by FAdV-C (61%), but other species FAdV-D (12%) and FAdV-E (21%) also discovered from HHS field cases at smaller proportion.

Although HHS is a disease that mainly affects chickens, it has been detected in ducks, pigeons, and quails on rare occasions (Abd El-Ghany, 2021). Several publications reported that FAdV-4 were isolated from peacocks (Wang et al., 2021), geese (Wei et al., 2019), ducks (Yu et al., 2018), and ostriches (Changjing et al., 2016). This finding is consistent with previous reports and indicates the potential for interspecies transmission between different bird species.

There are limited number of publications reported GE outbreak worldwide, due to the disease is less visible and clinically difficult to assess. Most affected birds exhibited no apparent symptoms and were only discovered during slaughterhouse inspections (Mirzazadeh et al., 2021). Gizzard erosion (GE) in slaughtered commercial broiler chickens has been observed frequently in European and Asian countries (Mase et al., 2014).

All gizzard erosion outbreak cases were found to be associated with FAdV-1/A, although other species included FAdV-8a/E, FAdV-8b/E, or FAdV-11/D were sporadically isolated from affected gizzards (Schachner et al., 2018) (Figure 12). Post-mortem examination revealed dilated gizzards and proventriculi, loaded with dark brown contents and gizzard wall perforation (Grafl et al., 2018). Histopathology examination identified the presence of intranuclear inclusion bodies in gizzard epithelial cells (Domanska-Blicharz., 2011).

Another FAdV infection caused by FAdV-1/A was Quail bronchitis, an acute, highly contagious, deadly respiratory disease in immature bobwhite quail caused by quail bronchitis virus (QBV). Infected flocks often experience more than 50% mortality and up to 100% morbidity, and the disease is more severe in young quail less than three weeks old (Singh et al., 2016).

Our results also demonstrated a significant difference in the mortality rate of outbreak cases based on the type of field isolates and the form of FAdV infections. Variable mortality rates may be attributed to the viral strain's virulence, the age and susceptibility of the host, and the presence of concomitant immunosuppressive illnesses (Abd El-Ghany, 2021). Studies have shown specific FAdV serotypes are

more virulent than others, and some of the more virulent FAdV serotypes are capable of causing severe clinical signs of disease and high rates of mortality even when co-infecting viruses are not present (Brown et al., 2019).

Gizzard erosion caused by FAdV-1/A reported less than 10% mortality rate (Schade et al., 2013; Lim et al., 2012). IBH, which is mainly caused by FAdV-11/D, FAdV-2/D and FAdV-8a/E, FAdV-8b/E reported mortality rate range from 1-30%, with majority of publications reported 1-10%, followed by 10-20%, and 20-30% mortality rate (Arazi et al., 2020; Hosseini et al., 2020). Virulent strains primarily related to serotypes FAdV8a/E, FAdV8b/E, and FAdV11/D have been linked to significant IBH epidemics in various countries (Brown et al., 2019).

IBH outbreaks in broilers at 3 to 7 weeks of age are marked by a rapid onset of mortality, peaking at 3-5 days post-infection (Maartens et al., 2014). Although FAdV infections often result in a low degree of morbidity, mortality rates typically range from 5% to 10% and occasionally as high as 30% in severe cases (Sabarudin et al., 2021). Immunosuppressive disorders such as infectious bursal disease, chicken infectious anemia, and Marek's disease have been reported to play a role in the spread of IBH and its rising mortality (Abd El-Ghany, 2021). Previous publications reported CIAV-induced immunosuppression is critical in exacerbating IBH-related mortality in broiler chickens (El-Tholoth & Abou El-Azm, 2019).

Hepatitis-hydropericardium syndrome (HHS) is a highly pathogenic and infectious disease that primarily affects young broiler chickens, with a 30 to 80 percent mortality rate, causing significant economic losses to the poultry industry worldwide (Rashid et al., 2020). Our findings reveal mortality rate of HHS, which is mainly caused by

FAdV-4/C, was variable in birds, ranging from 5 to 10% (Park et al., 2011), 10 to 30% (Yu et al., 2018), and 30 to 60% (Zhao et al., 2015; Liu et al., 2016). Few publications reported FAdV 4/C, which isolated from HHS outbreak, caused 60% to 80% mortality in birds, indicating some field strains of FAdV-4/C were highly pathogenic (Zhang et al., 2017; Changjing et al., 2016).

In 2015, China reported an emerged HHS outbreak in layers, caused by novel genotype hypervirulent FAdV-4/C infection in the absence of co-infection, with a 50% mortality rate much higher than previously reported (Pan et al., 2017). Several studies have found that new FAdV-4 isolates contain large deletion and alteration in their genome compared with those of FAdV-4 isolates reported from other countries worldwide (Rashid et al., 2020). The molecular mechanisms underlying the infection and pathogenesis of FAdV-4 is still unknown (Wang et al., 2019).

Differences in pathogenicity across strains within the same serotype could be due to genetic differences between strains or differential susceptibility of chickens (Xia et al., 2017). However, the pathogenic role of FAdV under field conditions remains unknown (Sabarudin et al., 2021). Further evaluation of the genome of new isolates is needed to increase understanding of the pathogenesis of viruses (Rashid et al., 2020).

Our findings demonstrate that most IBH, HHS, and GE cases were not the result of simple FAdV infection but the concurrent infection of multiple FAdV serotypes in flocks simultaneously. The presence of novel isolates could be due to the existence of many FAdV species in flocks, and the shift of virus species composition occurred during isolation, which would provide opportunities for recombination between FAdV strains (Kiss et al., 2018; Lv et al., 2021).

Mixed infections were common in IBH, and HPS cases with two or more FAdV serotypes have been reported previously (Niu et al., 2018). FAdV-1/A and FAdV-8/E infections, as well as FAdV-7/E and FAdV-1/A infections, have previously been documented in IBH-affected flocks, posing a risk of recombinant among different serotypes of FAdV (Mittal et al., 2014). Recombination between viral genomes is becoming more widely recognised as the primary driver of viral evolution, leading to viral pathogenesis changes. However, we have minimal knowledge about recombination of these potentially lethal FAdVs in field strain (Lv et al., 2021).

One serotype may act as a predisposing factor for other serotypes, or both may work together to produce synergistic effects. The presence of multiple serotypes in a single outbreak or flock suggests that there may be limited cross-protection among serotypes. (Mittal et al., 2014). It is currently unknown if mixed FAdV infections have a synergistic effect on the severity of clinical illness. Disease prevention and treatment in practice frequently focuses on the most prevalent epidemic viral serotypes, resulting in outbreaks of other serotypes. Therefore, mixed infection of FAdV with multiple serotypes will pose a significant challenge to disease prevention and treatment (Niu et al., 2018).

Detection of the presence of multiple serotypes in an affected flock is crucial in control FAdV infections. More research is needed to discover the serological relationships between serotypes of field strains (Mittal et al., 2014). Furthermore, advanced laboratory diagnostic approaches for detecting FAdV and distinguishing between disease-associated serotypes are considered essential.

Previous study documented co-infection rates of FAdV-4 and other immunosuppressive viruses were high among tested birds (Yu et al., 2019). Most cases of FAdV coinfecting with immunosuppressive viruses are associated with CIAV, suggest the widespread presence of CIAV infections in chickens (El-Tholoth and Abou El-Azm, 2019; Brown et al., 2019). Our results highlighted the potential need for serotype-specific vaccines and vaccines against CIAV to aid in the control and prevention of CIAV and FAdV associated diseases (Brown et al., 2019). It is suggested to detect immunosuppressive virus infection in FAdV positive chickens due to the high incidence of FAdV co-infections rate.

Vaccine shows promising results in control FAdV infections in birds. Cases of FAdV-4 declined quickly in Korea from 2016 to 2019 after the release of commercial inactivated FAdV-4 vaccines in 2015 (Lai et al., 2021). Vaccines were effective against FAdV-4/C, but they did not provide cross-protection against other IBH-causing serotypes such as FAdV-8b/E and FAdV-11/D (Lai et al., 2021). There is a lack of commercial vaccines to control FAdV infections (Xia et al., 2017). Some countries vaccinated broiler breeders with the autogenous vaccine to prevent disease (Gupta et al., 2018).

Our findings reveal FAdV isolates belong to FAdV-D and FAdV-E have become prevalent in most outbreaks of IBH or HHS in recent years. Further research is required to develop commercial vaccines that will accord protection against FAdV-D and FAdV-E due to lack of cross protection between difference serotypes.

Systematic reviews allow the revision of all scientific evidence on a given topic avoiding selection bias. In this study, we reviewed the current knowledge on FAdV

infections worldwide and identified several knowledge gaps. We also recognised the limitations of this study. The cases identified in this systematic review are likely to underestimate the actual incidence of FAdV due to the limiting timeline of 2011-2021 set by us and difficulties of precisely including data referring to years 2011-2021. The global distribution of FAdV outbreaks or cases mentioned in the scientific literature is likely to be subject to considerable publication bias. Unreported cases of FAdV infections have occurred in some regions of the country. Although an increase in FAdV-related outbreaks frequency has been reported in many countries worldwide, the reported cases are still an under-representation of actual epidemiological situations.

## 5.0 CONCLUSION

Overall, the systematic review strongly suggests that FAdV infections are disseminated worldwide and occur in both developed and developing countries, responsible for causing substantial economic losses to the poultry industry. It is undeniable that more FAdV studies are needed at the regional level to identify and differentiate endemic species and serotypes in regional commercial and wild birds. Efficient epidemiological surveillance systems are needed to identify new FAdV isolates introduced in the region quickly. It is crucial to identify the main risk factors involved in the transmission of FAdV between wild birds and poultry. Moreover, it is necessary to maximize regional efforts for the early detection of FAdV in both local and migratory wildlife and to maintain biosafety and biocontainment barriers to prevent infection in poultry. The factors determining FAdV pathogenicity profiles remain unclear due to limited information on complete genome sequences of FAdV. Currently, the complete nucleotide sequences of FAdV genomes were only available for few isolates. There is still a lack of knowledge about geographic distribution, molecular variation, virulence determinants and recombination of these potentially lethal FAdV in field strain. Finally, we suggest that more comprehensive epidemiological studies need to be carried out to identify dominant FAdV serotypes from field outbreaks worldwide. Further analysis of viral genome, development of new laboratory diagnostic methods for efficient differentiation of FAdV field strains and serotype-specific vaccine against newly emerged FAdV cluster are highly warranted for effective control of FAdV outbreaks.

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