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Literature Review

A Systematic Review of the Prevalence of Avian Hepatitis E Virus in Bird's Husbandry Worldwide, 2000-2023 Prevalence of Avian Hepatitis E Virus

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Abstract: Avian Hepatitis E virus (aHEV) constitutes a serious animal health problem and involves significant losses in poultry production; however, epidemiological evidence is scattered. Analyze the prevalence of aHEV infection in bird husbandry and its histopathological and phylogenetic characteristics based on scientific publications worldwide from 2000-2023.Systematic review applying the Johanna Briggs Institute guidelines and the PRISMA guide. Exhaustiveness, reproducibility, and evaluation of the methodological quality were guaranteed. Random effect meta-analyses were performed estimating the prevalence of aHEV by ELISA and RT-PCR. Heterogeneity was evaluated with $I^{2,}$ publication bias with the Begg statistic, and sensitivity using the influence graph.342 publications were identified, and 22 complied with the protocol; 10 used ELISA, 6 RT-PCR, and 6 both tests. The majority of studies were conducted in Asia; from America, only three studies were found in the United States. Seroprevalence in studies using ELISA ranged from 7.7-52.0%, with a pooled measure of 32.2.1% (95% CI: 31.4-33.1) in 12,287 birds. The molecular prevalence fluctuated between 5.1-74.4%, and the combined measurement in 3584 birds was 14.0% (95% CI 12.8-15.1). Statistically significant differences were found in the combined seroprevalence of in-house ELISA compared with the commercial one. Seroprevalence was 50% higher in adult birds (OR 1.5; 95% CI 1.1-2.2). In terms of molecular prevalence, statistical differences were found between asymptomatic and symptomatic birds. This study describes the main phylogenetic and histopathological findings of aHEV. The prevalence of aHEV in poultry production around the world is high, and there is wide variability in exposure to the virus and infection in birds. The presentation of signs and symptoms associated with the infection is also variable. The absence of studies in Latin America, despite the demonstration of the circulation of aHEV in the United States, makes it imperative to develop epidemiological studies in this region.

Keywords: Meta-Analysis, Prevalence, Systematic Review, Seroprevalence, Avian Hepatitis E Virus, Phylogenetic, Histopathology

Introduction

According to the Food and Agriculture Organization of the United Nations (FAO), global chicken meat production has doubled since the beginning of the century, going from approximately 9 million tons in 1961 to approximately 133 million tons in 2020, surpassing pork meat production. In addition, egg production also increased, from 954 billion in 2000 to 1.6 billion in 2020 (Food and Agriculture Organization of the United Nations, 2016) In this context, avian diseases that increase deaths or decrease egg production or bird weight are relevant because they affect the economies of multiple nations.

Hepatitis E virus (HEV) is the most common cause of acute hepatitis in humans, and due to its genetic variability, it has various animal hosts (Kenney, 2019) Some of its genotypes are zoonotic, transmitted mainly by the fecal-oral route, with serious implications for animal production and health (Thiry *et al*., 2017) HEV viruses are classified within the *Hepevirideae* family, which is

divided into *Parahepevirinae* subfamilies that affect fish and *Orthohepevirinae* that affect a wide variety of hosts such as humans, pigs, and birds. The last subfamily is divided into four genera, including the genus *Avihepevirus*, which has two species: *Avihepevirus egretti*, which affects wild aquatic birds, and *Avihepevirus magniiecur*, which affects bird husbandry (Sun *et al*., 2019)

Avian Hepatitis E Virus (aHEV) is the main cause of hepatitis-splenomegaly syndrome (HSS), Big Liver and Spleen disease (BLS), and is one of the main causes of hepatic rupture hemorrhage syndrome (HRHS) (Haqshenas *et al*., 2001; Payne *et al*., 1999; Su *et al*., 2020a). These diseases affect birds' husbandry and are characterized by inducing inflammation and fragility in the liver and spleen, as well as regression of the ovaries and abdomen with bloody fluid. Although there is a percentage of infected birds without clinical signs, there is commonly an increase in mortality and a decrease in production in the affected flocks (Handlinger and Williams, 1998; Su *et al*., 2018).

In several investigations, the prevalence of aHEV in chickens has been determined, evidencing a high variability with frequencies ranging between 7.7-52.0% for specific antibodies against the virus, and between 5.4-74.4% for the detection of the genome (Serageldeen and Nabila, 2016; Su *et al*., 2019). These data vary significantly depending on the diagnostic test, sample evaluated, study region, type of accommodation, age, immune status, or diet (Serageldeen and Nabila, 2016; Su *et al*., 2019).

The evidence on this topic is scattered, only narrative reviews focus on the history of its discovery, genomic organization, clinical presentations, and transmission (Sun *et al*., 2019; Julian, 2005; Yugo *et al*., 2016). There is no systematic review on the prevalence of aHEV, which would allow grouping the available evidence, quantifying the degree of heterogeneity in the magnitude of this infection, identifying factors associated, and gaps in this field, among other issues that denote the advantages of systematic reviews. Therefore, the objective of this study was to analyze the prevalence of aHEV infection in poultry based on global scientific publications between 2000-2023.

Materials and Methods

Type of Study and Question PICo (Population of Interest and Context

A systematic review was conducted following the recommendations of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and Joanna Briggs Institute (JBI).

The population was bird husbandry. The condition of interest was the prevalence of aHEV (exposure or seroprevalence, infection, or molecular prevalence), their associated factors, and histopathological and phylogenetic characterization. The context was at a global level, between 2000-2023.

Data Sources and Literature Search Strategy

Searches were conducted in PubMed, Science Direct, Scielo, and Lilacs. To choose the search terms, DeCS and MeSH thesauri were consulted, and a pearl harvest was applied, using this process the following terms were identified: Hepatitis E virus or aHEV, poultry, avian, birds, rupture hemorrhage syndrome, or hepatitis splenomegaly syndrome. This was complemented with a manual search with the specific name of species of poultry, without finding additional studies that complied with the protocol. The search was performed without language or time restrictions, the retrospective limit of the year 2000 was based on the decade in which the first study was conducted, and prospectively, the last update of the protocol was applied in February 2024 (Table 1).

Table 1: Search syntax

PubMed	1. (Hepatitis E virus[Title/Abstract]) OR (aHEV [Title/Abstract]) AND (avian[Title/Abstract]) 2. (Hepatitis E virus[Title/Abstract]) OR (aHEV [Title/Abstract]) AND (birds[Title/Abstract]) 3. (Hepatitis E virus[Title/Abstract]) OR (aHEV [Title/Abstract]) AND (poultry[Title/Abstract]) 4. (Hepatitis E virus[Title/Abstract]) OR (aHEV [Title/Abstract]) AND (rupture hemorrhage syndrome[Title/Abstract]) 5. (Hepatitis E virus[Title/Abstract]) OR (aHEV [Title/Abstract]) AND (hepatitis-splenomegaly syndrome[Title/Abstract])
Science Direct	6. Title, abstract, keywords: Hepatitis E virus OR aHEV AND avian 7. Title, abstract, keywords: Hepatitis E virus OR aHEV AND birds 8. Title, abstract, keywords: Hepatitis E virus OR aHEV AND poultry 9. Title, abstract, keywords: Hepatitis E virus OR aHEV AND rupture hemorrhage syndrome 10. Title, abstract, keywords: Hepatitis E virus OR aHEV AND hepatitis-splenomegaly yndrome
SciELO and Lilacs	11. (ti :((ab:(hepatitis E virus)))) OR (ti :((ab:(aHEV)))) AND (ti :((ab:(avian)))) 12. (ti :((ab:(hepatitis E virus)))) OR (ti :((ab:(aHEV)))) AND (ti :((ab:(birds)))) 13. (ti :((ab:(hepatitis E virus)))) OR (ti :((ab:(aHEV)))) AND (ti :((ab:(poultry)))) 14. (ti :((ab:(hepatitis E virus)))) OR (ti :((ab:(aHEV)))) AND (ti :((ab:(rupture haemorrhage yndrome)))) 15. (ti :((ab:(hepatitis E virus)))) OR (ti :((ab:(aHEV)))) AND (ti :((ab:(hepatitis-splenomegaly syndrome))))

Eligibility Criteria

The search results were exported to a reference manager to eliminate duplicates. Then, the title and abstract of each article were read to apply the following inclusion criteria: Original articles, observational prevalence studies, whose population included poultry, and an explanation of the aHEV detection technique. A complete reading of full papers was conducted to apply the following exclusion criteria: Studies that only analyze dead birds (since aHEV is the cause of mortality, it is expected that in these studies the values will be overestimated), studies not available in full text, classified as prevalence studies but with fewer than 14 cases (which correspond to a series of cases), and those that used diagnostic tests with validity problems.

Data Extraction from the Included Studies

In manuscripts that fulfilled the previous phases, the following data were extracted: Title, year, country, type of production, symptoms, alteration in production, mortality, number of birds and flocks, type of sample, detection method, breed, type of housing, number of positives (flocks and birds), vaccination, coinfections, genotype, phylogenetic analysis, histology, and associated factors. It should be clarified that the majority did not make an exhaustive report on these variables (data was missing). In addition, items evaluating methodological quality were included in the extraction.

Reproducibility and Quality Assessment of the Studies

All manuscripts included in this review were independently analyzed and recorded by two researchers. Discrepancies were resolved by consensus or referral to a third researcher. For methodological quality, the guidelines established by the JBI for epidemiological studies that reported information on prevalence and incidence were followed, as well as the nine items in the methods section of the STROBE guide for cross-sectional studies (von Elm *et al*., 2008; Manuel, 2018).

Analysis of Information

A qualitative synthesis of the variables extracted from each manuscript was performed. Random effects meta-analyses were performed for seroprevalence (with studies that used ELISA) and for molecular prevalence (with studies that used RT-PCR). Meta-regressions were also carried out for the variables reported in at least three groups, estimating the combined measure according to symptomatology (asymptomatic Vs birds with hepatomegaly and/or splenomegaly), the sample used (liver Vs feces), breed, and country. In these meta-analyses, the evaluation of heterogeneity was carried out with the I^2 statistic, publication bias using the Begg statistic, and the sensitivity with the estimation of the combined measure eliminating each study in successive phases (graphical method of influences). The final results were reported as the prevalence of each study and the combined prevalence, with 95% confidence intervals.

Results

Methodological Quality and Description of the Studies

The application of the search terms generated 28,787, which were reduced to 341 by restricting to title/abstract, and 22 manuscripts met the selection criteria (Fig. 1).

Based on the SROBE and JBI guidelines, a similar proportion of quality criteria were met in a range between 33-56%; the least explicit items in the research were the calculation of the sample size, eligibility of the birds, definition of the exposure variables, and control of biases (Table 2).

In the included studies, 10 used ELISA (immunoglobulin detection *y*), six used RT-PCR, and six used both tests. In ELISA, 56% (9/16) were in-house tests using the ORF2 antigen of the virus and the rest used the commercial big liver and spleen disease kit. The antibody test kit (BLS CK 131, BioChek, Berkshire, United Kingdom) has a sensitivity and specificity of 98%. In the studies using RT-PCR, 50% (6/12) were nested; the most used was Sun's protocol (Sun *et al*., 2004) for the detection of the genes that encode the helicase (ORF1) and viral capsid (ORF2).

The description of other variables was deficient: (i) only half (n = 11/22) report the breed or genetic line, Hy-Lyne Brown (n = 6/11) being more frequent, (ii) 27% (6/22) describe the type of accommodation, six include cage and three add the floor, (iii) 27% (6/22) describe coinfections with *Campylobacter sp*. (n = 1), Fowl Adenovirus (n = 2), Marek's disease virus (n = 1), avian leukosis virus, reticuloendotheliosis virus and chicken infectious anemia virus (n = 2).

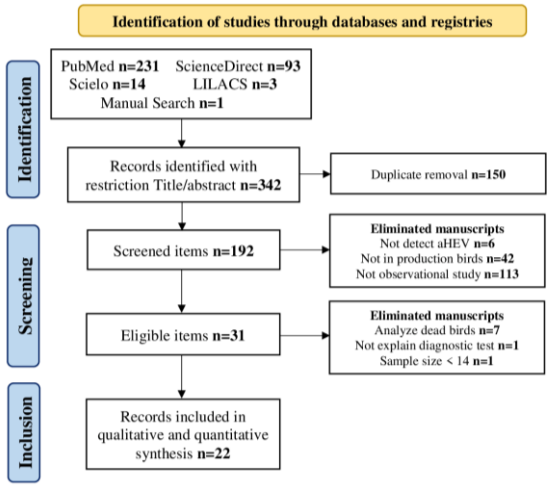

Fig. 1: Flowchart of the search and selection of studies

Table 2: Description of the included studies

Author	Year	Country	# Flocks	Production	Symptoms	JBI Score
ELISA						
Sun *et al*. (2016)	2002	USA	76	No data	No data	3/9
Kwon *et al*. (2012)	2012	Korea	35	Laying Hens and Broiler chikens	No data	3/9
Hsu and Tsai (2014)[a]	2013	Taiwan	61	Laying Hens	Asymptomatic	4/9
Crespo *et al*. (2015)	2015	USA	10	Laying Hens	H.S.[c]	4/9
Serageldeen and Nabila (2016)	2016	Egypt	24		Asymptomatic	5/9
Matczuk *et al*. (2019)[a]	2019	Poland	57	Laying Hens and Broiler chikens	No data	4/9
Sun *et al*. (2020)	2020	China	6	Laying Hens	H.S.[c]	5/9
Osamudiamen *et al*. (2021a)[a]	2021	Nigeria	36	Laying Hens	Asymptomatic	5/9
Razmyar *et al*. (2021)[a]	2021	Iran	34	Laying Hens and Broiler chikens	No data	3/9
Hou *et al*. (2023)[a]	2023	China	1	Laying Hens	H.S.[c]	5/9
RT-PCR						
Yang *et al*. (2016)	2016	China	1	Laying Hens	H.S.[c]	3/9
Su *et al*. (2019)[b]	2019	China	24	Laying Hens	H.S.[c]	4/9
Su *et al*. (2020b)[b]	2020	China	No data	Laying Hens and Broiler chikens	Asymptomatic	3/9
Osamudiamen *et al*. (2021b)[b]	2021	Nigeria	36	Laying Hens	Asymptomatic	5/9
Liu *et al*. (2022)	2022	China	12	Laying Hens	Asymptomatic	3/9
Siedlecka *et al*. (2022)	2022	Poland	336	Laying Hens and Broiler chikens	No data	4/9
ELISA and RT-PCR						
Peralta *et al*. (2009)	2009	Spain	29	Laying Hens	Asymptomatic	4/9
Troxler *et al*. (2014)[a]	2014	Poland	1	Broiler chikens	Asymptomatic	4/9
Gerber *et al*. (2015)	2015	USA	62	Laying Hens	Asymptomatic	5/9
Sun *et al*. (2016)[b]	2016	China	14	Laying Hens and Broiler chikens	H.S.[c]	5/9
Liu *et al*. (2017)[b]	2017	China	4	Laying Hens	Asymptomatic	3/9
Zhao *et al*. (2017)[b]	2017	China	7	Laying Hens	No data	5/9

[a]Commercial ELISA (others used in-house ELISA). [b]nRT -PCR. [c]Hepatitis and/or splenomegaly

Infection Prevalence

All studies reported data on infection per shed. Using in-house ELISA, the seroprevalence in 243 flocks was 78.6% (95% CI = 73.2-84.0); using commercial ELISA, 215 flocks were analyzed in which the seroprevalence was 73.0% (95% CI = 66.9-79.2); without statistically significant differences according to ELISA type. With ELISA in 458 flocks analyzed, the seroprevalence was 76.0% (95% CI = 72.0-80.8). With RT-PCR, the molecular prevalence was 60.2% (95% CI = 51.3-69.0) in 128 flocks (Fig. 2). In these meta-analyses, the I^2 was greater than 0.50, evidencing heterogeneity.

In the analyses by birds, the seroprevalence with in-house ELISA was 36.0% (95% CI = 34.9-37.1) in 7108 birds, whereas using commercial ELISA it was 27.1% (95% CI = 25.9-28.3) in 1404 birds. The molecular prevalence in 3584 birds evaluated with RT-PCR was 14.0% (95% CI = 12.8-15.1) with three studies reporting very high prevalence (Su *et al*., 2019; Sun *et al*., 2016; Yang *et al*., 2016) in sick birds or affected by outbreaks (Fig. 3). In these analyses I^2 was greater than 0.50, indicating heterogeneity; no publication bias was reported, and in the sensitivity analyses, changes were presented in the combined measures by eliminating some studies. Meta-regressions by symptomatology, sample, and other related factors were performed.

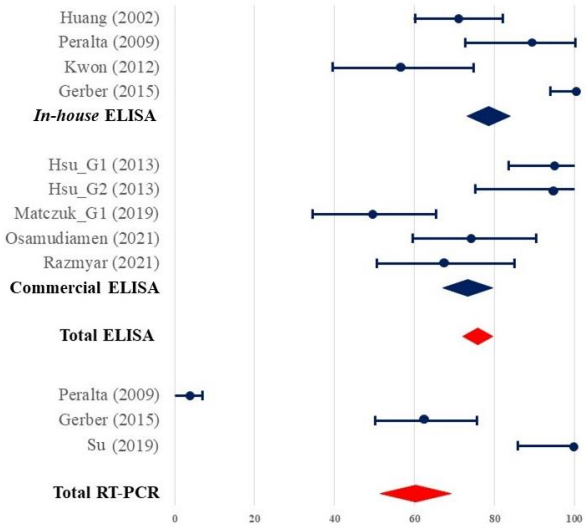

Fig. 2: Prevalence of infection by flocks in individual studies and combined prevalence according to the diagnostic test Note: The graph does not include individual measurements of studies with fewer than 14 flocks. G1: Laying hens. G2: Broiler

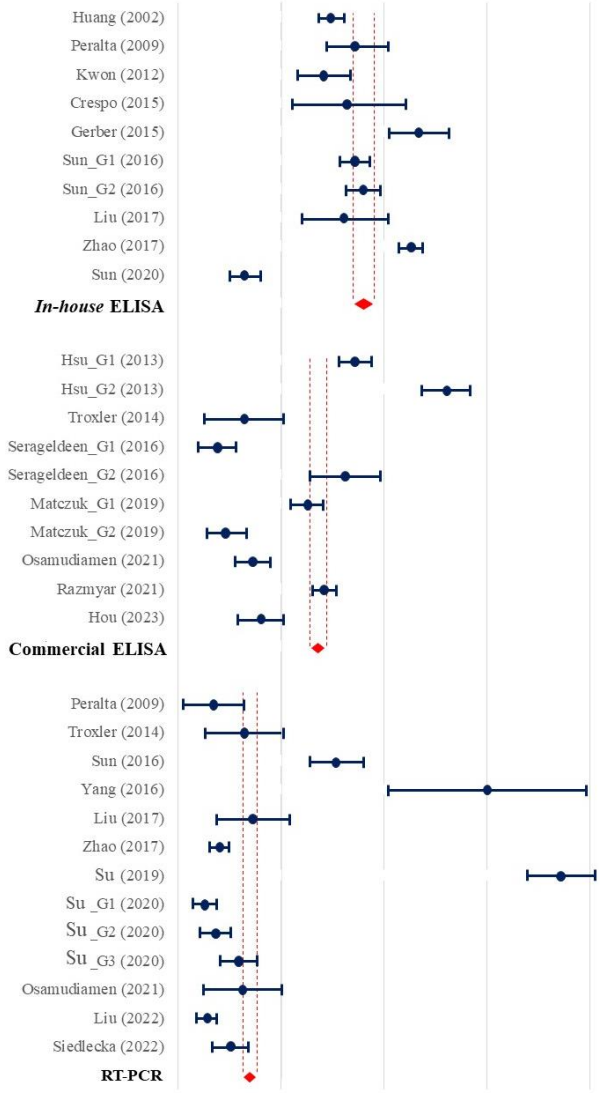

Fig. 3: Prevalence of infection in birds evaluated according to the diagnostic test

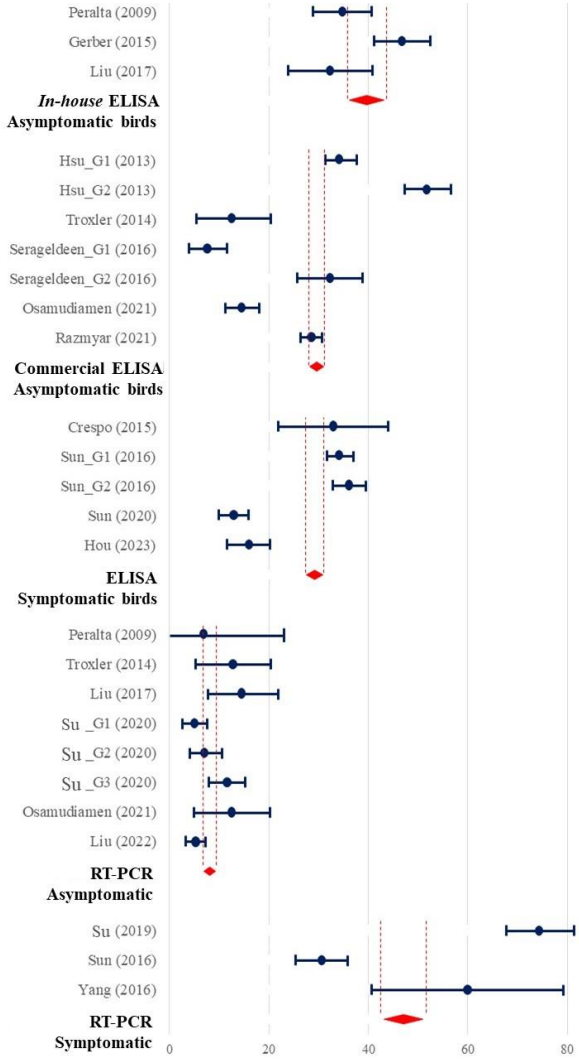

Fig. 4: Meta-regressions of the prevalence of infection in birds according to symptoms and diagnostic tests

In 699 asymptomatic birds evaluated with in-house ELISA, the seroprevalence was 39.6% (95% CI = 35.9-43.3), which is statistically higher than that found in 3845 asymptomatic birds using commercial ELISA with positive results of 29.5% (95% CI = 28.1-31.0). In 2554 symptomatic birds evaluated with in-house ELISA, the seroprevalence was 30.8% (95% CI = 29.0-32.7) when adding 300 symptomatic birds of the study by Hou *et al.* (2023) evaluated with commercial ELISA, it was 29.3%. (95% CI = 27.6-31.0). In 1874 asymptomatic birds evaluated with RT-PCR, the molecular prevalence was 8.0% (95% CI = 7.0-9.0), and in 533 symptomatic birds evaluated with this test it was 47.1% (95% CI = 42.8-51.4) (Fig. 4). There was no publication bias in these analyses (Begg $p>0.05$); in the sensitivity analysis, none of the studies changed the combined measure.

With RT-PCR, the meta-analyses in all the subgroups showed a molecular prevalence of around 10%, except for symptomatic birds with 47.1% (95% CI = 42.8-51.4), and in the liver was 32.8% (95% CI = 29.6-36.0). With commercial or *in-house* ELISA, no high variations were found in any subgroup analyzed (Table 3).

Other Associated Factors and Outcomes

Some factors of poultry production, such as the density of birds in the farms examined, the type of housing, the vaccines applied, and coinfections, were reported in some studies. However, for these variables, it was not possible to perform a grouped analysis given the high diversity in the definition, measurement, and reporting of results.

Table 3: Seroprevalence and molecular prevalence in subgroups studied

	Evaluated birds	Positive birds	% (CI95%)
In-house ELISA			
Total	7108	2558	36.0 (34.9-37.1)
Asymptomatic	699	277	39.6 (35.9-43.3)
Symptomatic	2554	788	30.9 (29.0-32.7)
China	4884	1832	37.5 (36.1-38.9)
United States	1665	551	33.1 (30.8-35.4)
Breed Hy-line Brown	2889	1132	39.2 (37.4-41.0)
Commercial ELISA			
Total	5179	1404	27.1 (25.9-28.3)
Asymptomatic	3845	1136	29.5 (28.1-31.0)
Poland	1120	231	20.6 (18.2-23.0)
Breed Hy-line Brown	1334	268	20.1 (17.9-22.3)
RT-PCR			
Total	3584	501	14.0 (12.8-15.1)
Asymptomatic	1874	149	8.0 (6.7-9.2)
Symptomatic	533	251	47.1 (42.8-51.4)
Fecal	1068	96	9.0 (7.2-10.7)
Liver	869	285	32.8 (29.6-36.0)
China	2469	412	16.7 (15.2-18.2)
Poland	422	45	10.7 (7.6-13.7)

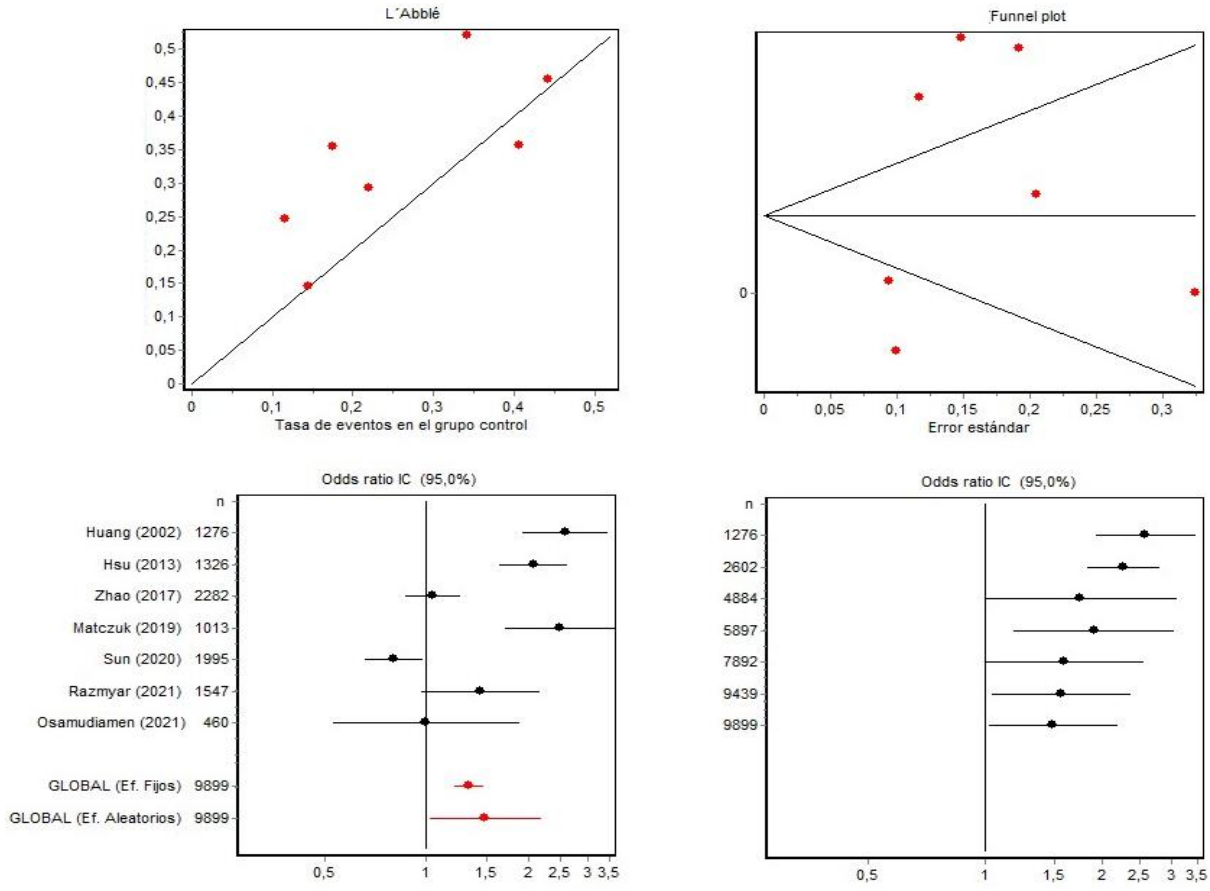

Fig. 5: Meta-regression of seroprevalence HEV according to age

Seven studies compared the seroprevalence of the virus in birds younger than 25 weeks old versus those older in a population of 9899 birds, finding an odds ratio of 1.5 (95 % CI = 1.1-2.2), indicating a higher occurrence of the event in older birds. In this meta-regression, heterogeneity was found (RI coefficient or proportion of the total variance due to the

variance between studies of 0.93; p Q = <0.001*)*, no publication bias was present (p Begg = 1.00; p Egger = 0.374), and there were no sensitivity problems for the combined measure (Fig. 5).

In 54% (n = 12) of the studies, it was indicated that the infection did not affect egg production and in 41% (n = 9) decreases between 5-40% in production were recorded. Furthermore, 59% (n = 13) of the studies indicated that aHEV was not related to the mortality of the populations studied, whereas 32% (n = 7) reported mortality rates between 1-15%.

Phylogenetic Analysis and Histopathology

In the 16 studies that performed phylogenetic analyses, 25.0% (n = 4) found genotype 3, particularly in works located in China (n = 3) and Poland (n = 1). Genotype 2 was reported in 5 studies: USA (n = 2), Poland (n = 2) and Nigeria (n = 1). Genotypes 1 and 4 were identified in Korea (n = 1) and Poland (n = 1) respectively. In addition, the phylogenetic analyses of five investigations (China n = 4, and Nigeria n = 1) failed to group the sequences detected in any of the four genotypes previously reported and were declared as new genotypes. Most of the phylogenetic analyses were performed with the sequences obtained with the amplification of the helicase and capsid genes reported by (Sun *et al*., 2004). Two studies applied complete sequencing of the virus using Primer walking. Three manuscripts did not report the sequence alignment algorithms, however, the most used were Crustal w (n = 9), BLAST (n = 3), and MAFFT (n = 1). To construct the phylogenetic trees, the maximum likelihood (ML) method was used in three studies, the Neighbor method J in nine, and both in two. The maximum parsimony method was used in only one investigation. Only two studies declared the nucleotide substitution method with which statistical inference was performed. In the genetic trees, the outgroups were not considered in nine analyses, and in the rest, other HEV sequences found in mammals were used. The vast majority of works (n = 12) used exclusively the sequences reported in birds with the representatives of each genotype.

Only five studies reported histopathological aspects, among which the following were highlighted: Infiltrated lymphocytes and inflammatory mononuclear cells, lymphoid aggregates in central and periportal veins, multinucleated giant cells, without fat deposit hemorrhage, severe hepatic degeneration, necrosis, lymphocytosis with focal hyperplasia in lobes, moderate to severe lesions, and in some cases necrosis. These findings indicate inflammatory mechanisms compatible with acute pathological events.

Discussion

AHEV has been associated with BLS, HSS, HRHS, and subclinical infections in chickens (Haqshenas *et al*., 2001; Su *et al*., 2020b) The virus is endemic in several countries and has caused significant economic losses in the global poultry industry. AHEV was first characterized in China in 2010, but multiple studies have indicated that it is common on several continents. According to this review, half of the studies were conducted in Asia, mainly in China, which is explained for its leadership in the production and marketing of poultry for consumption worldwide, and multiple outbreaks of HRHS in different provinces of the country since 2016 (Su *et al*., 2018). In Europe (Spain and Poland), Africa (Nigeria and Egypt), and America (USA), similar studies have been conducted but at a very low frequency, which indicates an evident need for research on the subject in multiple regions where the poultry industry constitutes an important line in the economy.

Despite the relevance of the information in the included studies, the methodological quality reveals shortcomings in their design, particularly in the definition of eligibility criteria, exposure variables, and bias control. Contextual information about the conditions of the animals is omitted in most studies; they do not report the type of housing and other factors that can explain the presence of the infection and generate information to reach a better understanding of the presentation of outbreaks. These aspects should be improved in further research on this virus.

The results evidenced a higher seroprevalence in studies using in-house ELISA than commercial ELISA. Although performance analyses of ELISA tests have not been reported, the specificity and sensitivity of commercial techniques and home methods are usually different, which may also contribute to the heterogeneity of prevalences between studies. This situation demands greater rigor to control the risk of false positives (improve specificity) in the in house-ELISA.

The combined prevalence by flocks using ELISA was 76.0%, while the frequency by birds was 32.2%; these results are similar to a study from China (Liu *et al*., 2017) which reported a prevalence of 32.3% with variations by type of accommodation: 54.1% in cage and 12.2% in litter. This indicates that the type of housing is a differential factor in the exposure of animals to the virus. Using the same test, the seroprevalence in asymptomatic and symptomatic birds was similar, indicating that exposure to the virus is variable and that testing only indicates exposure to the virus but is not useful for predicting disease.

The molecular prevalence (viral genome detection) in birds was 16%, similar to a study from China that reported 14.5% (Liu *et al*., 2017). However, it is important to mention that molecular detection fluctuated between 5-74%; in this case, the prevalence was associated with symptomatology; the presence of the viral genome is more frequent in affected birds (47%) compared with asymptomatic birds (8%). In addition to the symptoms, it is important to evaluate the differential distribution of

genotypes; in this sense, four different genotypes were initially proposed to correlate with the different geographical locations where they were identified (Matczuk *et al*., 2019; Osamudiamen *et al*., 2021; Morrow *et al*., 2008) however, seven additional genotypes have recently been proposed based on whole-genome analysis of aHEV strains identified in China (Thiry *et al*., 2017; Liu *et al*., 2020) and Poland (Matos *et al*., 2022).

Although the analyses by age show higher seroprevalence in older birds, the association of infection with age is not conclusive (Matczuk *et al*., 2019; Sun *et al*., 2020); Siedlecka *et al*., 2022; Troxler *et al*., 2014). The presence of genetic material has been demonstrated in egg yolks from apparently healthy hens (Liu *et al*., 2022) and in day-old chicks from 5-week-old broiler breeders (Troxler *et al*., 2014), which reinforces the hypothesis of vertical transmission of the virus. Sun *et al*. showed that, under natural conditions, birds begin to seroconvert by week 12 of life, and antibodies last for more than 30 weeks (Sun *et al*., 2004). However, under experimental conditions, it has been determined that antibodies against AHEV peak between 3 and 4 weeks, coinciding with the disappearance of the virus from the bloodstream (Thiry *et al*., 2017; Sun *et al*., 2019). The disappearance of viremia corresponds to an increase in the anti-HEV IgG titer, although the virus may continue to replicate in other sites of the gastrointestinal system (Billam *et al*., 2005)

Finally, it should be indicated that the mechanisms of aHEV causing liver damage are not completely clear. It has been suggested that liver damage is caused by the immune response to the virus and not by direct virus replication in hepatocytes. The microscopic lesions of the liver reported in the included studies indicate acute inflammation processes. However, the presence of these lesions in the livers of asymptomatic birds (Liu *et al*., 2017) and the absence of the viral genome in animals with clinical symptoms (Carnaccini *et al*., 2016; Wang *et al*., 2023) indicate that aHEV infection is likely to be an important, but not the only, factor for the development of clinical HS syndrome.

Conclusion

The prevalence of aHEV infection is high and heterogeneous in poultry production countries. The presentation of signs and symptoms associated with the infection is also variable. The absence of studies in Latin America, despite the demonstration of the circulation of aHEV in the United States, makes it imperative to develop epidemiological studies in this region. The characterization of associated factors with the infection must be studied in more detail in countries endemic for the infection, as well as in those that have similar production conditions, but no systematic searches have been carried out on the circulation of those reported in the studies compiled by this review. Viral genotypes 2-3 are currently the most isolated, with a notable increase in sequencing in China in recent years.

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Author's Contributions

All authors realized substantial contributions to the conception and design of the study; the acquisition, analysis, and interpretation of data; the writing and critical review of the manuscript, and the approbation of the version to be published. All authors are responsible for all aspects of the manuscript ensuring the accuracy of the paper.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all the other authors have read and approved the manuscript and that no ethical issues are involved.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

Registration and Protocol

The protocol was sent for evaluation and registration in progress but the site directors indicated that, due to the high number of protocols to be evaluated, only agents with demonstrated zoonotic potential will be registered in reviews of animal studies.

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