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Source: Environmental Health Insights, 18(2)

Published By: SAGE Publishing

URL: https://doi.org/10.1177/11786302241299370

Zoonotic and Food-Related Hazards Due to Hepatitis A and E in Africa: A Systematic Review and Meta-Analysis

Environmental Health Insights
Volume 18: 1–9
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DOI: 10.1177/11786302241299370

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ABSTRACT

INTRODUCTION: Foodborne infections are caused by a wide spectrum of microbial pathogens, and they pose a significant global health threat, resulting in millions of cases and thousands of fatalities annually. Among these pathogens, human viruses, including Hepatitis A virus (HAV) and Hepatitis E virus (HEV), play a significant role in foodborne viral outbreaks, especially in Africa. This systematic review determined the prevalence of these viruses in livestock and produce in Africa.

METHOD: A systematic search strategy was implemented following the PRISMA guidelines. Databases such as African Journal Online, Web of Science, Scopus, and PubMed were searched from their inception until November 30, 2023. Descriptive statistics and a proportional meta-analysis utilising a random-effects model with a 95% confidence interval were employed in the data analysis. The Cochrane risk-of-bias tool (ROB2) was utilised to evaluate the potential for bias in each study.

RESULTS: The search identified 27 articles that met the inclusion criteria, among which seven focused on HAV, comprising a total of 309 samples, whereas 20 studies focused on HEV, comprising a total of 4238 samples. Egypt had the highest number of studies, followed by Cameroon and Nigeria. The meta-analysis revealed an overall prevalence of 33.8% (95% CI: 17.0–50.6) for HAV in ducks and shellfish and 22.0% (95% CI: 12.1–31.8) for HEV in various livestock. Genotype 3 was identified as the predominant genotype, for both HAV and HEV.

CONCLUSION: This review revealed a high prevalence of HAV and HEV in livestock populations in Africa, shedding light on the potential risks associated with zoonotic and/or food-related infections. There is a need for continued surveillance and monitoring of these viruses in both animals and food products to mitigate the risk of foodborne outbreaks and protect human health.

KEYWORDS: Hepatitis A, Hepatitis E, zoonotic, domestic animal, transmission, prevalence, Africa, food safety, swine

RECEIVED: July 4, 2024. **ACCEPTED:** October 27, 2024.

TYPE: Review

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by the National Institutes of Health, USA, through the "Application of Data Science to Build Research Capacity in Zoonoses and Food-Borne Infections in West Africa (DS-ZOOFOOD) Training Programme" hosted at the Department of Medical Microbiology, University of Ghana Medical School (Grant Number: UE5TW012566). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Every year, foodborne infections affect approximately 600 million people globally, resulting in nearly 420 000 preventable deaths.[1] These diseases stem from various harmful agents, including bacteria, viruses, and parasites, that can taint food and make it hazardous to eat.[2] Notably, human-afflicting viruses are significant contributors to health issues and economic impacts.[3] Hepatitis A virus (HAV) and Hepatitis E virus (HEV) cause approximately five million cases of acute viral hepatitis worldwide each year.[4]

Although both viruses are classified as small RNA viruses, they have distinct genetic differences and structures.[5] HAV is a small, positive-sense RNA virus belonging to the *Hepatovirus* genus within the *Picornaviridae* family.[5] It presents in two distinct forms: nonenveloped virions found in faeces and quasienveloped virions (eHAVs), which exit infected cells without causing cell damage.[6] These eHAV virions can be detected in the blood of infected individuals and in the supernatant of infected cell cultures.[7] Contaminated shellfish, poor sanitation, and close contact with infected individuals are common transmission routes of HAV.[8,9] HAV causes acute liver infection, which is characterised by liver inflammation, with symptoms ranging from mild to severe.[10] Prolonged jaundice and itching due to bile flow obstruction can also occur.[11] Children under six years of age typically remain asymptomatic.[12] However, individuals with compromised immune systems and expectant mothers are at an increased risk of experiencing severe clinical hepatitis.[13]

HEV, on the other hand, has a single-stranded RNA genome with positive polarity and is enveloped within capsid proteins, forming an icosahedral structure.[14] It belongs to the *Hepeviridae* family, which comprises two main genera: *Parahepevirinae*, which includes *Piscihepesvirus*, such as the cutthroat trout virus, and *Orthohepevirinae*, which is further divided into four species.[15,16] These species include (I) *Paslahepevirus*, which encompasses HEV variants found in humans, pigs, wild boars, deer, mongooses, rabbits, and camels, (II) *Avihepevirus*, which is found in chickens, sparrows, and little egret, (III) *Rocahepevirus*, which includes HEV variants from rats, greater bandicoots, Asian musk shrews, ferrets,

and minks, and (IV) *Chirohepevirus*, which is found in bats.[15,16] Five genotypes of HEV can infect humans, with HEV-1 and HEV-2 being prevalent in Africa, Asia, and the Middle East, and primarily transmitted through the consumption of faeces-contaminated water.[17,18] The primary reservoirs for the zoonotic strains HEV-3 and HEV-4 include deer, wild boars, and pigs,[19-21] whereas HEV-7 has been found in camels.[22,23] Recently, *Rocahepevirus ratti* strains have been found to be capable of infecting humans. These strains are carried primarily by rats, which frequently come into contact with pigs on swine farms.[24]

The consumption of undercooked or raw meat products, including sausages, liver, and unpasteurised milk, has led to reported cases of HEV-3 and HEV-4 infections in developed nations.[25,26] Similarly, outbreaks have occurred periodically in developing nations across Asia and Africa through the faecal-oral route, often involving the consumption of contaminated pork.[18,27,28] Using pigs as a model for HEV infection, Yadav et al.[29] revealed that infectious HEV was present in sperm, suggesting a potential route of sexual transmission. In one human study in Egypt, however, HEV RNA and HEV Ag were not found in the semen of infertile men and acute Hepatitis E (AHE) patients, although HEV markers were present in the urine of HEV-1 patients.[30] However, a recent study in Germany detected infectious HEV-3 in patients' ejaculate[31]; similarly, HEV RNA was found in 28.1% of semen samples from Chinese infertile men, with all the isolates belonging to the HEV-4 variant,[32] suggesting that HEV-positive ejaculate may pose a risk of transmission to sexual partners.

HEV causes chronic liver disease and severe complications, with symptoms including fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, and jaundice.[33] Acute kidney injury and glomerulonephritis have also been reported in some HEV cases.[34,35] The study by Elkhawaga et al.[36] represents the first report of abnormal renal function in AHE Genotype 1 infection in Egypt, based on an evaluation of kidney function tests (KFTs) in affected patients. While HAV vaccines are easily accessible and recommended for travelers to regions with high HAV prevalence, individuals with chronic liver disease, and other vulnerable groups,[37,38] there is only one recombinant HEV vaccine, Hecolin, which is currently exclusively available in China and Pakistan.[39] Despite the significance of HAVs and HEVs in relation to zoonotic and food-related infections, a systematic review on the subject in Africa that provides comprehensive information to guide preventive, control, and management efforts has not been performed. This systematic review, therefore, evaluated the prevalence of HAV and HEV in major livestock species and produce in Africa.

Methods

PRISMA guidelines

To guarantee a methodical and transparent approach to our literature search and evaluation, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[40] A thorough checklist and flow diagram for record identification, screening, and evaluation are provided by the PRISMA standards.

Search strategy

We conducted an extensive literature search using African Journal Online, Web of Science, Scopus, and PubMed to gather all published studies evaluating the prevalence of HAV and HEV in Africa published from inception to November 30, 2023. Additionally, we explored the reference lists of pertinent articles to identify any additional studies for inclusion in our review. The search terms used included ("hepatitis A," OR "hepatitis E") AND ("foodborne" OR "animals" OR "livestock" OR "vegetables" OR "fruits") AND ("Algeria" OR "Angola" OR "Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cabo Verde" OR "Cameroon" OR "Central African Republic" OR "Chad" OR "Comoros" OR "Congo" OR "Cote d'Ivoire" OR "DR Congo" OR "Djibouti" OR "Egypt" OR "Equatorial Guinea" OR "Eritrea" OR "Eswatini" OR "Ethiopia" OR "Gabon" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea Bissau" OR "Kenya" OR "Lesotho" OR "Liberia" OR "Libya" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Mayotte" OR "Morocco" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Reunion" OR "Rwanda" OR "Saint Helena" OR "Sao Tome and Principe" OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sudan" OR "Tanzania" OR "Togo" OR "Tunisia" OR "Uganda" OR "Western Sahara" OR "Zambia" OR "Zimbabwe"). We did not place any restrictions on population groups or outcome measures to ensure the inclusion of all relevant studies.

Inclusion and exclusion criteria

To identify relevant studies, a thorough two-step screening was conducted. The first step involved assessing titles and abstracts to remove any duplicates or unrelated studies. The second step was a more in-depth evaluation of the remaining full-text research articles, which determined their suitability for inclusion in the review. The studies were evaluated on the basis of predefined inclusion and exclusion criteria. Eligible studies included those that reported the prevalence of HAV and HEV in livestock in Africa, as well as studies investigating the presence of HAV and HEV in plants, fruits, and vegetables. On the other hand, studies reporting the prevalence of HAV and HEV in humans, studies focusing on waterborne transmission of HAV and HEV, and reviews were excluded. The screening process involved two independent reviewers, and Mendeley Desktop, Version 1.19.8, was used to manage the search results and identify any duplicate records from the databases.

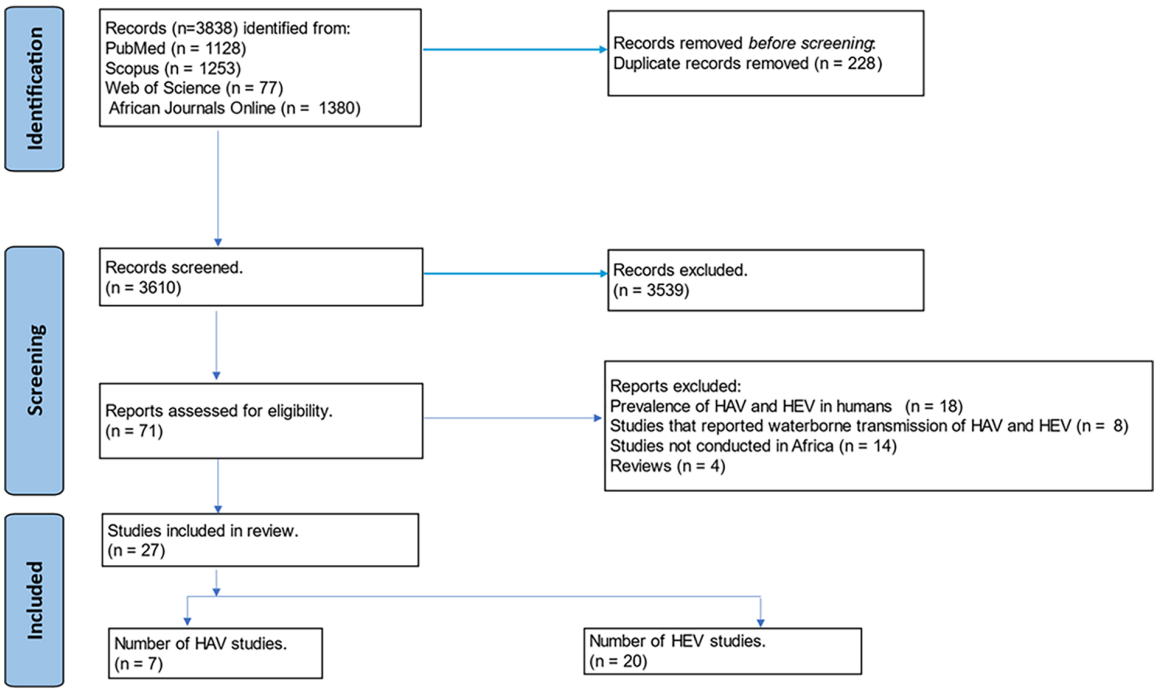

Figure 1. The PRISMA flow diagram for the study selection process.

Data extraction

The data from the reviewed studies were organised and managed using Microsoft Excel 2019, Version 2405. The extracted information included various details about the articles, such as the author(s), year and country, sampling location, sample collected, species or population type, diagnostic assays used for HAV and HEV detection, target genomic regions, number of positive cases, prevalence (%), and identified HAV and HEV genotypes. To ensure accurate extraction of relevant data related to the study characteristics and outcomes of interest, two authors independently utilised a predesigned data abstraction format created in Microsoft Excel 2019, Version 2405.

Evaluation of bias

The Robvis tool[41] was used to visually represent the outcomes of the risk-of-bias assessment conducted on each study using the Cochrane risk-of-bias tool (ROB2).[42] This assessment focused on five key bias domains: randomisation, deviations from interventions, missing outcome data, outcome measurement, and the selection of reported results. Each of these domains was given a classification of low-risk, high-risk, or some concerns. A study was considered low-risk if all domains received a low-risk designation, high-risk if at least one domain was labeled high-risk, and some concerns if there were concerns in one or more domains.

Statistical analysis

Descriptive statistics and a proportional meta-analysis with a random chance model were employed for the data analysis. The analysis was conducted using R software, Version 4.3.3 (2024). The metaprop package was used to calculate the overall prevalence, accompanied by a 95% confidence interval. Pooled prevalence ratios were estimated using a random-effects analysis, and differences in the data were evaluated using a Chi-square test. Unfortunately, conducting a subgroup analysis was not feasible because of the inclusion of studies with mixed animal populations. To evaluate publication bias, the "metabias" command and a funnel plot were used.

Results

Search results

The initial online database search yielded a total of 3838 publications from the inception of the databases up to November 30, 2023 (Figure 1). After removing duplicates, 3610 records remained and were screened on the basis of their titles and abstracts. A total of 3539 articles were excluded because they did not meet the established inclusion criteria for the review. Next, 71 full-text articles were assessed for eligibility, and 27 articles met the inclusion criteria for the review. These 27 articles[43-69] provided information on the detection of HAV and HEV in various animal populations, including swine, cattle, goats, chickens, rabbits, monkeys, camels, ducks, shellfish, fruits, and vegetables, in Africa (Supplemental Tables S1 and S2).

Study distribution

A total of 12 out of 58 African countries have investigated the detection of HAV and HEV in animal populations and produce. Figure 2 illustrates the distribution of these studies across different countries. Egypt had the greatest number of studies,

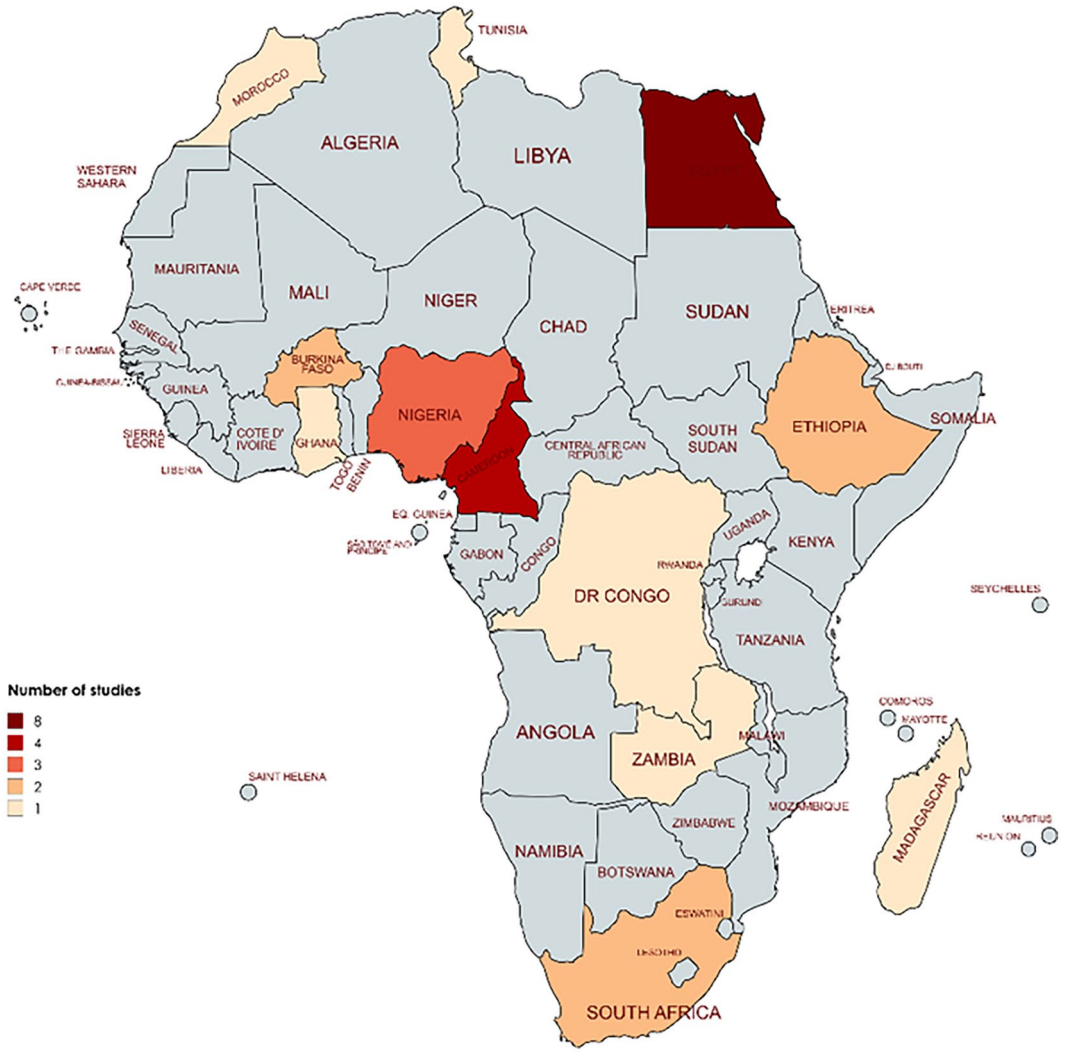

Figure 2. Distribution of included studies across countries in Africa.

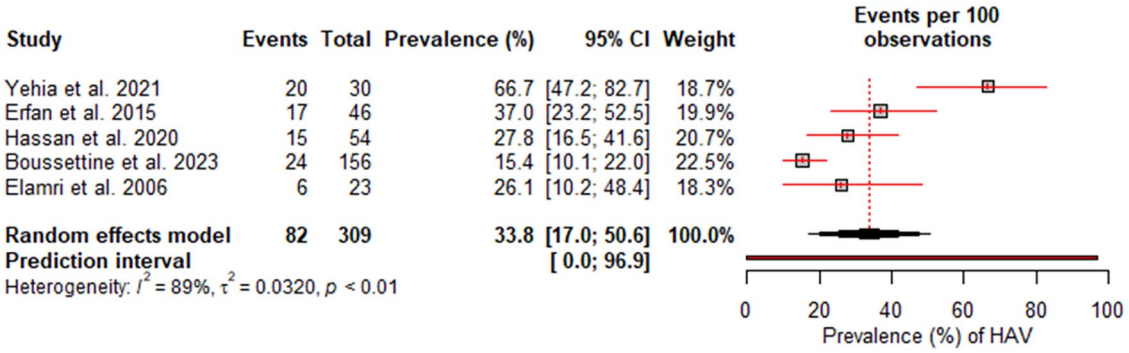

Figure 3. Forest plot for the pooled prevalence (%) of HAV in ducks and shellfish.[44-47,49]

with a total of eight, followed by Cameroon, with four studies, and then Nigeria, with three studies.

Detection and prevalence of HAV

Seven studies (26%) detected the presence of HAV, all in North African countries, including Egypt, Morocco, and Tunisia.[43-49] Among these studies, four focused on ducks[43,44,47,49], two focused on shellfish,[45,46] and one identified HAV in fruits and vegetables.[48] HAV was detected via RT-PCR, which primarily targets the VP1 gene. The identified HAV genotypes included Genotype 1 and Genotype 3. Prevalence data were available in five studies,[44-47,49] comprising a total of 309 samples, 82 of which tested positive for HAV. The meta-analysis indicated that the overall prevalence of HAV in ducks and shellfish was 33.8% (17.0–50.6, 95% CI), with a random effect and a p value of $<.05$ (Figure 3). An I^2 value of 89% indicated significant heterogeneity among the studies.

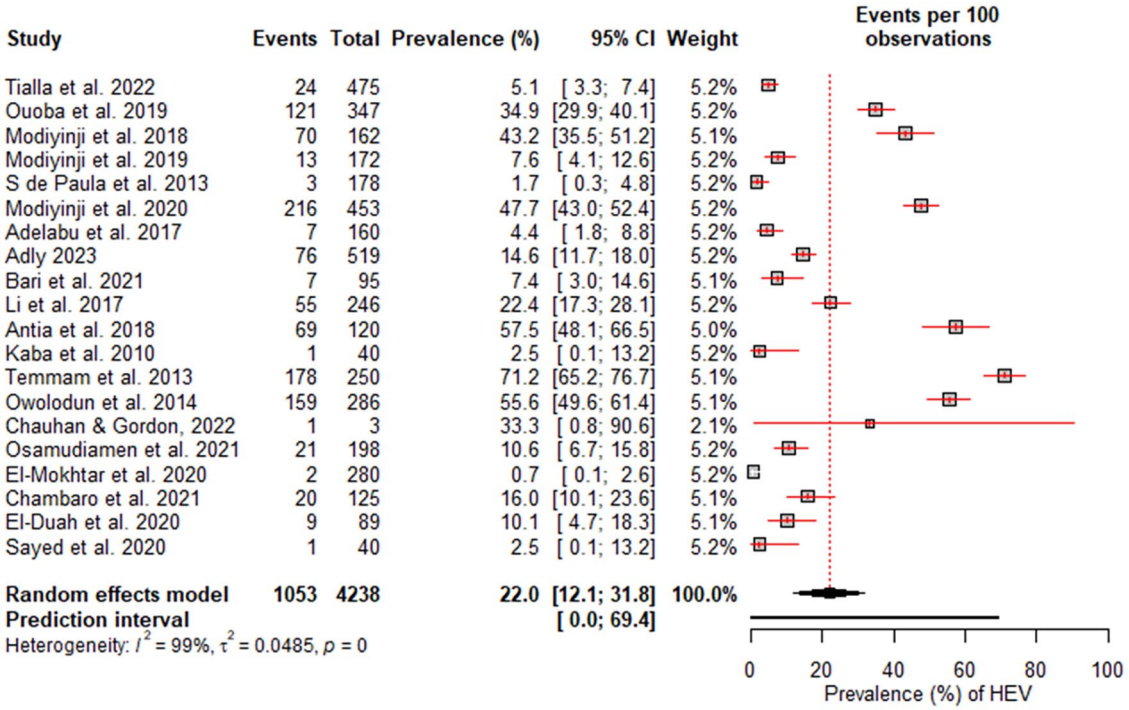

Figure 4. Forest plot for the pooled prevalence (%) of HEV in various livestock (pigs, chickens, rabbits, hares, cattle, sheep, goats, cows, camels, and monkeys).[50-69]

Detection and prevalence of HEV

The majority of the studies in this review, 20 (74%)[50-69] detected the presence of HEV in livestock, primarily in western Africa. Ten of these studies[50,52,53,58,60,61,65-68] focused on pigs, whereas the remaining studies focused on rabbits, hares, cattle, cows, sheep, goats, chickens, camels, and monkeys. Four studies used ELISA[53-55,59], six used RT-PCR (targeting the ORF1, ORF2, and ORF3 regions),[52,56,60,61,63,67] and the others used both methods for the detection of HEV. Genotype 3 was the most prevalent genotype, identified in 18 studies,[50-56,58-62,64-69] with one study[63] identifying Genotype 2. Prevalence data from 20 studies[50-69] and 4238 samples revealed an overall HEV prevalence of 22.0% (12.1–31.8, 95% CI) in various livestock (Figure 4). An I^2 value of 99% indicated high heterogeneity among the studies.

Publication bias

The funnel plot displayed a slight asymmetrical distribution upon visual examination (Supplemental Figures S1 and S2). The results of the Egger linear regression test were not statistically significant, providing support for the absence of small study effects. A regression-based Egger test with a p value $<.05$ indicated potential reporting bias.

Risk of bias

Figure 5 shows a comprehensive assessment of the risk of bias for the 27 studies included in this systematic review. The assessment categorises the risk of bias into three levels: low-risk (represented by green), some concerns (indicated by yellow), and high-risk (shown in red). The predominance of low-risk ratings in all evaluated domains indicates that the studies demonstrate strong methodological integrity and reliability.

Discussion

This review focused on investigating the detection and prevalence of HAV and HEV in African countries. The meta-analysis revealed an overall prevalence of 33.8% for HAV in ducks and shellfish and 22.0% for HEV in various livestock. These results are comparable to those of a meta-analysis in Africa, which reported a 23.4% prevalence of HEV Immunoglobulin G antibodies in animals[17] and higher than a global meta-analysis that reported a 2% prevalence of HEV in ruminants,[70] as well as a meta-analysis that reported a 12% prevalence of HAV in ducks in mainland China.[71]

Notably, the reporting of HAV cases in Africa remains low, with a predominant focus on HAV outbreaks in ducks, especially in North Africa. This indicates a geographical bias in the studies conducted on HAV in Africa. In addition to ducks, shellfish have also been identified as a potential source of HAV contamination.[45,46] Moreover, a study conducted in Egypt reported the presence of HAV in strawberries and green leafy vegetables, suggesting a potential risk of produce contamination.[48] RT-PCR, which targets the VP1 gene, was commonly used as a method for HAV detection, probably because of its high sensitivity and specificity in identifying HAV RNA.[72]

While the available studies had a limited focus on HAV, the majority of the studies focused predominantly on HEV. These studies detected the presence of the HEV in livestock,

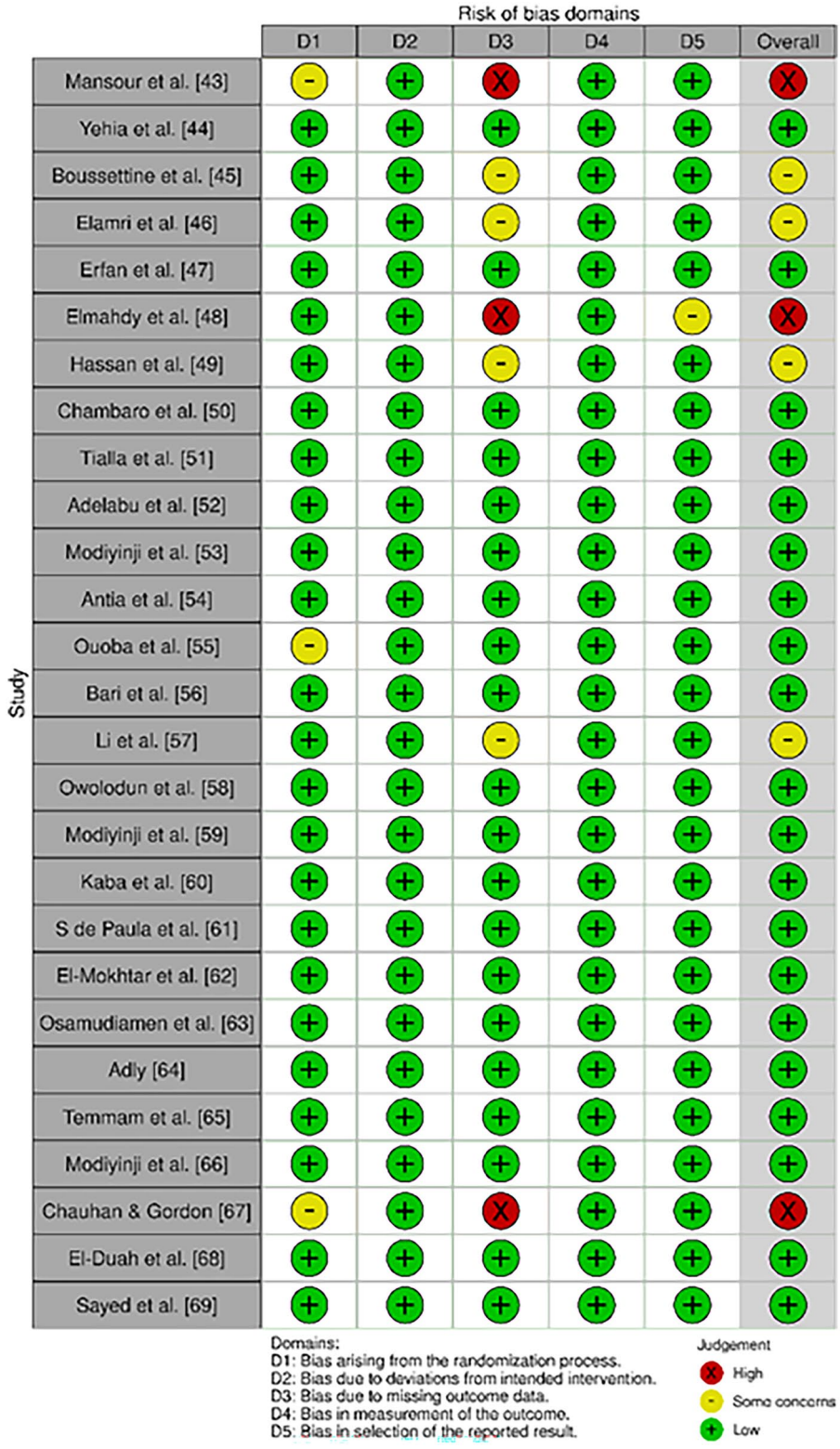

Figure 5. Risk of bias assessment of the 27 studies.[43-69]

primarily in western Africa. The use of both ELISA and RT-PCR for HEV detection demonstrates the different approaches employed to identify the virus, with ELISA being useful for detecting HEV antibodies.[73] We found that pigs were the primary focus, underscoring their importance as reservoirs for transmitting HEV to humans. Although we did not conduct a subgroup analysis, the meta-analysis by Modiyinji et al.[17] revealed a higher seroprevalence of immunoglobulin G antibodies of 37.8% among pigs in Africa. The primary mode of transmission of HEV is the faecal-oral route, which typically occurs when contaminated food or water containing faecal matter carrying the virus is consumed.[74] Swine

production practices in Africa exhibit considerable variation, ranging from large-scale commercial operations to small-scale communal systems.[75] In communal systems, in which pigs have the freedom to roam and access water sources, there is a high potential for water contamination with pig faeces and urine, creating a route for transmission to humans.[76]

Our review revealed the existence of three prominent genotypes of the hepatitis virus: Genotype 1, Genotype 2, and Genotype 3. Interestingly, Genotype 1 was found only in HAV, whereas Genotype 2 was exclusive to HEV. The codetection of HAV Genotypes 1 and 3 implies the presence of both local and imported strains. Genotype 1 is commonly associated with human outbreaks, whereas Genotype 3 is often found in animal reservoirs.[18] The varying genotypes of HAV and HEV found in these studies demonstrate the genetic variability of these viruses. Notably, Genotype 3 was the most common genotype detected, which aligns with its global distribution pattern.[70] The high occurrence of HEV Genotype 3 in African pigs highlights the potential for zoonotic transmission to individuals who come into contact with these animals. The first documented case of HEV Genotype 3 in South Africa involved a transplant patient with an underlying medical condition.[77] Several studies conducted in South Africa have investigated the presence of HEV in human populations. For example, a study by Madden et al.[78] revealed a high incidence of HEV (27.9% anti-HEV IgG) among patients aged 30 years and older without liver disease. Since these patients did not have any contact with pigs, it was suspected that the transmission might be foodborne, possibly through the consumption of pork.[78] While HEV in swine has been recognised as the primary source of human infection, HEV subtypes capable of infecting humans have also been found in goats.[62] However, the extent of their contribution to the transmission of HEV to humans remains poorly studied. It is currently unclear whether goats act as natural reservoirs for the virus or if they become infected through inadvertent exposure to strains originating from pigs. Additionally, other domestic livestock, such as sheep, rabbits, hares, cows, chickens, camels, and monkeys, should not be disregarded as potential reservoirs of infection.

Our review revealed that HAV and HEV are increasingly acknowledged as significant pathogens in Africa; yet, there is a significant knowledge gap regarding their infection in animals, despite the availability of data on human outbreaks in most African countries.[28,79] The potential zoonotic risk of HAV and HEV transmission from livestock in sub-Saharan Africa remains poorly understood due to a lack of sequence information.[68] This review underscores the need for continued surveillance and monitoring of HAV and HEV in animals and food products to prevent foodborne outbreaks. Implementing control measures, promoting good agricultural and hygienic practices, and prioritising vaccination are crucial for reducing the transmission of these viruses within the food chain, particularly among high-risk groups.[80] To protect public health and minimise the impact of HAV and HEV infections, it is essential to prioritise these preventive measures and conduct further research to understand the dynamics of these viruses in animal reservoirs. Adopting a One Health approach, which considers the interconnectedness of humans, animals, and the environment, is vital to addressing the challenges posed by HAV and HEV infections in Africa.

This review has several strengths, including its comprehensive coverage, methodological consistency, genotyping information, and use of meta-analysis. However, there are a few limitations to consider. This review's focus on North African countries and Western Africa for HAV and HEV detection may limit the generalisability of the findings to other regions in Africa. Additionally, the emphasis on specific animal species, such as ducks and pigs, may overlook the potential presence of HAV and HEV in other animals. The significant heterogeneity among the included studies, resulting from variations in study design, sample sizes, geographic locations, and diagnostic methods, could affect the interpretability and generalisability of the results. Furthermore, publication bias may impact the overall interpretation and presentation of the prevalence and detection rates, as studies with positive or significant results are more likely to be published.

Conclusion

This review illuminates the findings of HAV and HEV detection across different regions of Africa and various animal hosts, indicating their zoonotic potential and foodborne transmission risk. The predominance of Genotype 3 across different animal hosts suggests a persistent and pervasive risk to both animal and human health, highlighting significant public health concerns. The high prevalence, coupled with notable heterogeneity among studies, underscores the need for targeted, and comprehensive interventions. These should include enhanced surveillance, public health measures, vaccination programmes, collaborative research initiatives, and improved environmental controls to effectively mitigate the transmission of HAV and HEV.

Acknowledgements

Not applicable.

Author Contributions

Conceptualisation, E.S.D., F.C.N.K., and A.O.; methodology, A.O., E.S.D., I.B., F.C.N.K., and K.W.C.S.; validation, A.O., E.S.D., F.C.N.K., and K.W.C.S.; formal analysis, A.O., F.C.N.K., E.S.D., I.B., and K.W.C.S.; investigation, A.O., E.S.D., I.B., F.C.N.K., and K.W.C.S.; resources, A.O., E.S.D., I.B., and K.W.C.S.; data curation, A.O., E.S.D., I.B., and K.W.C.S.; writing—original draft preparation, A.O., E.S.D., I.B., F.C.N.K., and K.W.C.S.; writing—review and editing, A.O., E.S.D., I.B., F.C.N.K., and K.W.C.S; visualisation, A.O., E.S.D., F.C.N.K., I.B., and K.W.C.S; supervision, E.S.D. and K.W.C.S.; project administration, E.S.D., and A.O.; funding acquisition, E.S.D. All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

All the authors have given their consent for the publication of this manuscript.

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Availability of Data and Materials

All the supporting data are presented in the manuscript and supplementary files.

Supplemental Material

Supplemental material for this article is available online.

REFERENCES

1. Todd E. Food-borne disease prevention and risk assessment. *Int J Environ Res Public Health*. 2020;17:5129.
2. Elbehiry A, Abalkhail A, Marzouk E, et al. An overview of the public health challenges in diagnosing and controlling human foodborne pathogens. *Vaccines*. 2023;11:725.
3. O'Shea H, Blacklaws B, Collins P, McKillen J, Fitzgerald R. Viruses associated with foodborne infections. *Reference Module in Life Sciences*. Elsevier;2019:B978-0-12-809633-8.90273-5.
4. Nemes K, Persson S, Simonsson M. Hepatitis A virus and hepatitis E virus as food- and waterborne pathogens—transmission routes and methods for detection in food. *Viruses*. 2023;15:1725.
5. Gholizadeh O, Akbarzadeh S, Ghazanfari Hashemi M, et al. Hepatitis A: viral structure, classification, life cycle, clinical symptoms, diagnosis error, and vaccination. *Can J Infect Dis Med Microbiol*. 2023;2023:1-17.
6. Yin X, Ambardekar C, Lu Y, Feng Z. Distinct entry mechanisms for nonenveloped and quasi-enveloped hepatitis E viruses. *J Virol*. 2016;90:4232-4242.
7. Rivera-Serrano EE, González-López O, Das A, Lemon SM. Cellular entry and uncoating of naked and quasi-enveloped human hepatoviruses. *eLife*. 2019;8:e43983.
8. Rao A, Wanjari MB, Prasad R, Munjewar PK, Sharma R. From mystery to clarity: uncovering the possible cause of hepatitis outbreak in children. *Cureus*. 2023;15:e38388.
9. Yan B, Chen P, Feng Y, et al. A community-wide epidemic of hepatitis A virus genotype IA associated with consumption of shellfish in Yantai, Eastern China, January to March 2020. *Hum Vaccin Immunother*. 2022;18:2106081.
10. Shin EC, Jeong SH. Natural history, clinical manifestations, and pathogenesis of hepatitis A. *Cold Spring Harb Perspect Med*. 2018;8:a031708.
11. Alebaji MB, Mehair AS, Shahrour OI, et al. Prolonged cholestasis following acute hepatitis A infection: case report and a review of Literature. *Cureus*. 2023;15(5):e38511.
12. Yassin NA, El-Houchi SZ, Abd El-Shafy SF, et al. Frequency of Hepatitis A virus as a cause of anicteric hepatitis in children under 5 years: a common yet under-recognized cause. *Egypt Pediatr Assoc Gazette*. 2022;70:41.
13. Aggarwal R, Goel A. Natural history, clinical manifestations, and pathogenesis of hepatitis E virus genotype 1 and 2 infections. *Cold Spring Harb Perspect Med*. 2019;9:a032136.
14. Oechslin N, Moradpour D, Gouttenoire J. On the host side of the hepatitis E virus life cycle. *Cells*. 2020;9:1294.
15. Purdy MA, Drexler JF, Meng XJ, et al. ICTV Virus taxonomy profile: Hepeviridae 2022. *J Gen Virol*. 2022;103:001778.
16. Smith D, Simmonds P, Jameel S, et al. Consensus proposals for classification of the family Hepeviridae. *J Gen Virol*. 2014;95:2223-2232.
17. Modiyinji AF, Bigna JJ, Kenmoe S, et al. Epidemiology of hepatitis E virus infection in animals in Africa: a systematic review and meta-analysis. *BMC Vet Res*. 2021;17:50.
18. Khuroo MS, Khuroo MS, Khuroo NS. Transmission of hepatitis E virus in developing countries. *Viruses*. 2016;8:253.
19. Priemer G, Cierniak F, Wolf C, et al. Co-circulation of different Hepatitis E virus genotype 3 subtypes in pigs and wild boar in North-East Germany, 2019. *Pathogens*. 2022;11:773.
20. Pires H, Cardoso L, Lopes AP, et al. Prevalence and risk factors for hepatitis E virus in wild boar and red deer in Portugal. *Microorganisms*. 2023;11:2576.
21. Karlsen AA, Kichatova VS, Kyuregyan KK, Mikhailov MI. Phylodynamic analysis suggests that deer species may Be a true reservoir for hepatitis E virus genotypes 3 and 4. *Microorganisms*. 2023;11:375.
22. Sarani A, Ravanbakhsh A, Kamaladini H. First detection of hepatitis E virus in dromedary camels from Iran. *Vet Med Sci*. 2023;9:1812-1817.
23. Sridhar S, Teng JLL, Chiu TH, Lau SKP, Woo PCY. Hepatitis E virus genotypes and evolution: emergence of camel hepatitis E variants. *Int J Mol Sci*. 2017;18:869.
24. Yadav KK, Boley PA, Lee CM, et al. Rat hepatitis E virus cross-species infection and transmission in pigs. *PNAS Nexus*. 2024;3:ae259.
25. Di Profio F, Sarchese V, Palombieri A, et al. Current knowledge of hepatitis E virus (HEV) epidemiology in ruminants. *Pathogens*. 2022;11:1124.
26. Songtanin B, Molehin AJ, Brittan K, Manatsathit W, Nugent K. Hepatitis E virus infections: epidemiology, genetic diversity, and clinical considerations. *Viruses*. 2023;15:1389.
27. Yeboah R, Sylverken AA, Owusu M, et al. Sero-molecular epidemiology of hepatitis E virus in pigs and human contacts in Ghana. *One Health Outlook*. 2021;3:13.
28. Bagulo H, Majekodunmi AO, Welburn SC. Hepatitis E in Sub Saharan Africa - A significant emerging disease. *One Health*. 2020;11:100186.
29. Yadav KK, Boley PA, Laocharoensuk T, et al. Infectious hepatitis E virus is associated with the mature sperm head. *PLoS Pathog*. 2024;20:e1012240.
30. El-Mokhtar MA, Seddik MI, Osman AOB, et al. No evidence of HEV genotype 1 infections harming the male reproductive system. *Virology*. 2021;554:37-41.
31. Schemmerer M, Bock HH, Schattenberg JM, et al. Proof of infectivity of hepatitis E virus particles from the ejaculate of chronically infected patients. *J Med Virol*. 2024;96:e29735.
32. Huang F, Long F, Yu W, et al. High prevalence of hepatitis E virus in semen of infertile male and causes testis damage. *Gut*. 2018;67:1199-1201.
33. Xin S, Xiao L. Clinical Manifestations of Hepatitis E. *Ann Int Med Dent Res*. 2016;948:175-189.
34. Cheema SS, Cheema MF, Gilani S, Cheema SR. Immunoglobulin A nephropathy associated with acute hepatitis E infection: first case report. *Clin Nephrol Case Stud*. 2023;11:95-98.
35. Kumar KJ, Velamala S, Kumar K, Manjunath VG. Acute kidney injury as a rare complication of acute hepatitis E in a child; a case report. *Middle East J Dig Dis*. 2022;14:141-144.
36. Elkhawaga AA, El-Mokhtar MA, Mahmoud AA, et al. First report on abnormal renal function in acute hepatitis E genotype 1 infection. *Pathogens*. 2023;12:687.
37. Migueres M, Lhomme S, Izopet J. Hepatitis A: epidemiology, high-risk groups, prevention and research on antiviral treatment. *Viruses*. 2021;13:1900.
38. Wu D, Guo CY. Epidemiology and prevention of hepatitis A in travelers. *J Travel Med*. 2013;20:394-399.
39. Lynch JA, Lim JK, Asaga PEP, et al. Hepatitis E vaccine-illuminating the barriers to use. *PLoS Negl Trop Dis*. 2023;17:e0010969.
40. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
41. Mcguinness L, Higgins J. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. 2020. Accessed June 11, 2024. https://doi.org/10.1002/jrsm.1411
42. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;l4898:366. doi:10.1136/bmj.l4898
43. Mansour SMG, Mohamed FF, ElBakrey RM, et al. Outbreaks of duck hepatitis A virus in Egyptian duckling flocks. *Avian Dis*. 2019;63:68-74.
44. Yehia N, Erfan AM, Omar SE, Soliman MA. Dual circulation of duck hepatitis A virus genotypes 1 and 3 in Egypt. *Avian Dis*. 2021;65:1-9.
45. Boussettine R, Hassou N, Maanan M, Bessi H, Ennaji MM. Hepatitis A virus detection by RT-qPCR in shellfish samples from three Moroccan Atlantic coastal areas: Dakhla, Oualidia, and Moulay Bousselham. *Lett Appl Microbiol*. 2023;76:ovac059.
46. Elamri DE, Aouni M, Parnaudeau S, Le Guyader FS. Detection of human enteric viruses in shellfish collected in Tunisia. *Lett Appl Microbiol*. 2006;43:399-404.
47. Erfan AM, Selim AA, Moursi MK, Nasef SA, Abdelwhab EM. Epidemiology and molecular characterisation of duck hepatitis A virus from different duck breeds in Egypt. *Vet Microbiol*. 2015;177:347-352.
48. Elmahdy EM, Shaheen MNF, Mahmoud LHI, Hammad IA, Soliman ERS. Detection of Norovirus and Hepatitis A virus in strawberry and green leafy vegetables by using RT-qPCR in Egypt. *Food Environ Virol*. 2022;14:178-189.

49. Hassan TIR, Eid AAM, Ghanem IAI, et al. First Report of Duck Hepatitis A Virus 3 from duckling flocks of Egypt. *Avian Dis*. 2020;64:269-276.
50. Chambaro HM, Sasaki M, Muleya W, et al. Hepatitis E virus infection in pigs: a first report from Zambia. *Emerg Microbes Infect*. 2021;10:2169-2172.
51. Tialla D, Cissé A, Ouédraogo GA, et al. Prevalence of hepatitis E virus antibodies in cattle in Burkina Faso associated with swine mixed farming. *J Vet Sci*. 2022;23:e33.
52. Adelabu OA, Chuks Iweriebor B, Nwodo UU, Obi LC, Okoh AI. Incidence and molecular characterization of Hepatitis E virus from swine in Eastern Cape, South Africa. *Adv Virol*. 2017;2017:1-7.
53. Modiyinji AF, Atsama MA, Monamele GC, Nola M, Njouom R. High seroprevalence of hepatitis E among pigs suggests an animal reservoir in Cameroon. *J Infect Dev Ctries*. 2018;12:676-679.
54. Antia RE, Adekola AA, Jubril AJ, Ohore OG, Emikpe BO. Hepatitis E virus infection seroprevalence and the associated risk factors in animals raised in Ibadan, Nigeria. *J Immunoassay Immunochem*. 2018;39:509-520.
55. Ouoba JB, Traore KA, Rouamba H, et al. Prevalence of anti-hepatitis E virus antibodies in domestic animal from three representative provinces of Burkina Faso. *Vet Anim Sci*. 2019;7:100059.
56. Bari FD, Wodaje HB, Said U, et al. First molecular detection of hepatitis E virus genome in camel and pig faecal samples in Ethiopia. *Virol J*. 2021;18:160.
57. Li TC, Yoshizaki S, Zhou X, et al. Serological evidence of hepatitis E virus infection in dromedary camels in Ethiopia. *J Virol Methods*. 2017;246: 34-37.
58. Owolodun OA, Gerber PF, Giménez-Lirola LG, Kwaga JKP, Opriessnig T. First report of hepatitis E virus circulation in domestic pigs in Nigeria. *Am* Soc *Trop Med Hyg*. 2014;91:699-704.
59. Modiyinji AF, Amougou Atsama M, Monamele Chavely G, Nola M, Njouom R. Detection of hepatitis E virus antibodies among Cercopithecidae and Hominidae monkeys in Cameroon. *J Med Primatol*. 2019;48:364-366.
60. Kaba M, Colson P, Musongela JP, Tshilolo L, Davoust B. Detection of hepatitis E virus of genotype 3 in a farm pig in Kinshasa (Democratic Republic of the Congo). *Infect Genet Evol*. 2010;10:154-157.
61. Salete de Paula V, Wiele M, Mbunkah AH, et al. Hepatitis E virus genotype 3 strains in domestic pigs, Cameroon. *Emerg Infect Dis*. 2013;19:686-688.
62. El-Mokhtar MA, Elkhawaga AA, Sayed IM. Assessment of hepatitis E virus (HEV) in the edible goat products pointed out a risk for human infection in Upper Egypt. *Int J Food Microbiol*. 2020;330:108784.
63. Osamudiamen FT, Akanbi OA, Zander S, et al. Identification of a putative novel genotype of avian hepatitis e virus from apparently healthy chickens in Southwestern Nigeria. *Viruses*. 2021;13:954.
64. El-Adly AM. Serological and genetic diversity of hepatitis E virus among rabbits population in Egypt. *Open Vet J*. 2023;13:515-522.
65. Temmam S, Besnard L, Andriamandimby SF, et al. High prevalence of hepatitis E in humans and pigs and evidence of genotype-3 virus in swine, Madagascar. *Am* Soc *Trop Med Hyg*. 2013;88:329-338.
66. Modiyinji AF, Sanding GMAM, Atsama MA, et al. Serological and molecular investigation of hepatitis E virus in pigs reservoirs from Cameroon reveals elevated seroprevalence and presence of genotype 3. *PLoS One*. 2020;15:e0229073.
67. Chauhan RP, Gordon ML. Characterization of a near full-length hepatitis E virus genome of subtype 3c generated from naturally infected South African backyard pigs. *Pathogens*. 2022;11:1030.
68. El-Duah P, Dei D, Binger T, et al. Detection and genomic characterization of hepatitis E virus genotype 3 from pigs in Ghana, Africa. *One Health Outlook*. 2020;2:1-9.
69. Sayed IM, Elkhawaga AA, El-Mokhtar MA. Circulation of hepatitis E virus (HEV) and/or HEV-like agent in non-mixed dairy farms could represent a potential source of infection for Egyptian people. *Int J Food Microbiol*. 2020;317:108479.
70. Santos-Silva S, López-López P, Gonçalves HMR, et al. A systematic review and meta-analysis on Hepatitis E virus detection in farmed ruminants. *Pathogens*. 2023;12:550.
71. Zhou S, Li S, Wang Y, Li X, Zhang T. Duck hepatitis A virus prevalence in Mainland China between 2009 and 2021: a systematic review and meta-analysis. *Prev Vet Med*. 2022;208:105730.
72. Persson S, Alm E, Karlsson M, et al. A new assay for quantitative detection of hepatitis A virus. *J Virol Methods*. 2021;288:114010.
73. Zhao Q, Sun Y, Zhao J, et al. Development and application of an indirect ELISA for detection of antibodies against avian hepatitis E virus. *J Virol Methods*. 2013;187:32-36.
74. Treagus S, Wright C, Baker-Austin C, Longdon B, Lowther J. The foodborne transmission of Hepatitis E virus to humans. *Food Environ Virol*. 2021;13:127-145.
75. Adesehinwa AOK, Boladuro BA, Dunmade AS, et al. Invited review - pig production in Africa: current status, challenges, prospects and opportunities. *Anim Biosci*. 2024;37:730-741.
76. Bagulo H, Majekodunmi AO, Welburn SC, Bimi L. Hepatitis E seroprevalence and risk factors in humans and pig in Ghana. *BMC Infect Dis*. 2022;22:132.
77. Andersson MI, Stead PA, Maponga T, van der Plas H, Preiser W. Hepatitis E virus infection: an underdiagnosed infection in transplant patients in Southern Africa? *J Clin Virol*. 2015;70:23-25.
78. Madden RG, Wallace S, Sonderup M, et al. Hepatitis E virus: Western Cape, South Africa. *World J Gastroenterol*. 2016;22:9853-9859.
79. Patterson J, Abdullahi L, Hussey GD, Muloiwa R, Kagina BM. A systematic review of the epidemiology of hepatitis A in Africa. *BMC Infect Dis*. 2019;19:651.
80. Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of hepatitis A virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, 2020. *MMWR Recomm Rep*. 2020;69:1-38.