

Seroprevalence of hepatitis E virus infection in pregnant women: a systematic review and meta-analysis

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BACKGROUND: Hepatitis E virus (HEV) infection has emerged as a global public health problem that affects millions of people every year.

OBJECTIVE: Systematically review data on the prevalence of HEV IgG antibody among pregnant women around the world.

DATA SOURCES: Potentially relevant studies were identified by a search of PubMed and ScienceDirect, and by a manual search of the reference lists of identified studies.

STUDY SELECTION: Observational studies in English with no age or area restriction. Reviews, duplicate, book chapters, and other irrelevant studies were excluded.

DATA EXTRACTION: Independent searching by two investigators (TA, THM).

DATA SYNTHESIS: In the 6137 retrieved studies, 15 studies met the inclusion criteria. The studies included 7160 pregnant subjects from 11 countries. Most studies were from Africa. Of the 7160 subjects, 1182 were positive to anti-HEV IgG antibody, and only 66 were anti-HEV IgM antibody positive. The highest seroprevalence of anti-HEV IgG antibody (61.29%) was reported in Sudan and the lowest (3.41%) was reported in Italy. The overall pooled prevalence was 16.51% (95% CI: 0.10-0.23). The heterogeneity level was $I^2 = 98\%$; $P \leq .01$.

CONCLUSION: The seroprevalence of anti-HEV IgG antibody among pregnant women differs by geographic location. Further studies are recommended to evaluate incidence, morbidity, and mortality in those areas where the disease is prevalent.

LIMITATIONS: Seroprevalence was only determined for the anti-HEV IgG antibody, which mostly indicates past infection. Heterogeneity was high among the studies in the analysis.

CONFLICT OF INTEREST: None.

Infection with the hepatitis E virus (HEV) is a significant public health problem that occurs in both developing and industrialized countries.¹ Every year, an estimated 20 million cases of HEV are reported worldwide.² In 2015, the World Health Organization (WHO) reported approximately 44 000 deaths attributed to HEV infection worldwide, accounting for 3.3% of mortality due to viral hepatitis.² The mortality rate ranges from 0.2 to 4%,³ but can be significantly higher in at-risk groups such as young children,^{4,5} those with pre-existing liver disease,⁶ and pregnant women.⁷ In pregnant women, the mortality rate reaches 10% to 25% and largely occurs in the third trimester.³

HEV is an icosahedral, non-enveloped, single-strand, positive-sense RNA virus with a 7.2kb genome.^{8,9} According to the 9th Report of the International Committee on the Taxonomy of Viruses (ICTV), HEV is classified in the family Hepeviridae,^{10,11} and includes two genera, *Orthohepevirus* and *Piscihepevirus*.¹¹ The genus *Orthohepevirus*, which infect mammals and birds,¹⁴ contains four species, A, B, C and D.^{11,12} *Orthohepevirus A* species are isolated from humans, pigs, deer, moneese, rabbits, wild boars and camels; *Orthohepevirus B* is isolated from chicken; *Orthohepevirus C* is isolated from rats, Asian musk shrews, ferrets, greater bandicoots, and minks; and *Orthohepevirus D* is isolated from bats.^{11,13} Species A contains eight genotypes (*HEV1*, *HEV2*, *HEV3*, *HEV4*, *HEV5*, *HEV6*, *HEV7* and *HEV8*).^{14,15} Genotypes *HEV1* and *HEV2* are obligate human pathogens.^{15,16} *HEV3*, *HEV4* are endemic in several animal species, causing zoonotic infections in humans.^{15,16} Genotypes *HEV5* and *HEV6* appear to be restricted to wild boars, and genotypes *HEV7* and *HEV8* have been isolated from dromedary and Bactrian camels.^{15,16} In addition, a case of *HEV7* has been reported in a human.¹⁷

The incubation period of HEV ranges from 2 to 10 weeks.² Symptoms of HEV infection include anorexia, fever, jaundice, myalgia, abdominal pain, back pain, rash, arthralgia, nausea, and vomiting.^{2,3,18} HEV infection is not clinically distinguishable from other types of acute viral hepatitis.² HEV infection is responsible for 30% to 70% cases of acute sporadic hepatitis,¹⁹ and is one of the major causes of acute liver failure.²⁰ HEV is mainly transmitted through the fecal-oral route due to contaminated drinking water,^{9,21} and zoonotic transmission.²¹ Foodborne transmission has also been documented.²² Other uncommon routes of HEV transmission have been documented such as vertical transmission,⁷ and blood-borne transmission.²³⁻²⁵

HEV can be diagnosed by detecting anti-HEV antibodies (IgM and IgG) or RNA-based tests for the

detection of HEV RNA in biological specimens such as liver biopsy, serum, and stool.^{26,27} In the past two decades, two recombinant vaccines have been developed by GlaxoSmithKline (Belgium)²⁸ and Xiamen Innovax Biotech (China).²⁹ The only licensed vaccine, HEV 239 Hecolin, has been approved by China but is not yet available commercially.^{30,31} To reduce the number of cases of acute and chronic HEV infection, improvements in preventive measures and control strategies have to be made.³² This meta-analysis aimed to scrutinize the burden and pooled prevalence of HEV IgG antibody in pregnant women around the world to inform researchers and policymakers.

SUBJECTS AND METHODS

Study protocol

During December 2018 and January 2019, we performed a systematic search of the published literature on HEV infection in pregnant women. Well-defined and clear criteria were set before conducting the search. This study was conducted according to the proposed protocol following the "Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA),"³³ so that all the steps were conducted independently by two investigators and discrepancies were discussed and resolved by the third investigator.

Study selection

Observational studies published in 2015 to 2018 on HEV infection in pregnant women around the world were included in this study.³⁴ Only articles published in the English language were included. There was no age nor area restriction. Excluded were reviews, duplicate, book chapters, and other irrelevant studies. Studies with human immunodeficiency virus (HIV) patients or with co-infections, and studies whose required seroprevalence data were not accessible even after a request to the authors were also excluded.

Article search strategies

The search was carried out by two investigators (TA, THM) independently on PubMed and ScienceDirect. The following keywords; "Hepatitis E virus" AND "pregnant women" OR "pregnancy" were used (**Table 1**). We also reviewed and searched the relevant articles from the selected studies manually.

Outcome

Seroprevalence of anti-HEV IgG antibody in pregnant women was the outcome of interest. Country, and chronological time were investigated as predictors of

the outcome. The seroprevalence was calculated by the following formula.

$$\text{Seroprevalence (\%)} = \frac{\text{HEV-infected women}}{\text{Total number of pregnant women}}$$

The operational definition of seroprevalence was 'the presence of anti-HEV antibody (IgG) in the plasma/serum of pregnant women by the ELISA method'.

Source of data and extraction

Included studies on seroprevalence were from China (n=3), Iran (n=2), Ethiopia (n=2), Benin (n=1), Burkina Faso (n=1), Cameroon (n=1), Eritrea (n=1), Italy (n=1), Ghana (n=1), Nigeria (n=1) and Sudan (n=1) (**Figure 1**). The data from included studies were extracted by two investigators (TA, THM) independently, and disagreements and discrepancies were resolved via discussion with the third investigator. The following parameters were extracted for each selected study; author last name(s), country, publication year, study design, sample size, anti-HEV antibody (IgG and IgM), and anti-HEV antibody detection method. The data was entered into Microsoft Excel 2016.

Quality assessment

To assess the quality of the included studies, we used methodological guidelines from the Joanna Briggs Institute (JBI), University of Adelaide.³⁵ The JBI appraisal checklist is used for prevalence studies to assess the possibility of bias in study design, conduct, and analysis. The JBI appraisal checklist is composed of nine items, and the sources of bias are scored either

yes or no. Three investigators independently scored each study for quality assessment and disagreements were discussed between the investigators until a consensus was reached; however, the quality score was not used in the selection of studies for inclusion in the analysis. Studies that obtained scores from 0 to 3 are presented as high risk of bias, 4 to 6 are at moderate risk of bias, and 7 to 9 are at low risk of bias in study design, conduct, and analysis. Publication bias was calculated using a funnel plot and the Egger test.

Statistical analysis

The data were statistically analyzed by using R software for Windows, Version 3.6.0 (for overall pooled prevalence and subgroup analysis), and Stata software for Windows, Version 12.00 (for sensitivity analysis, meta-regression analysis by year of publication and sample size, and publication bias). The pooled prevalence and 95% CI were calculated based on a random effects model, taking into account the possibility of heterogeneity among the included studies. Heterogeneity was assessed using the I^2 statistic, with value ranges from 25% to 50%, 51% to 75%, and >75%, representing low, medium, and high heterogeneity between studies, respectively. Due to the high heterogeneity ($P < .10$) among the included studies, a random effect model was used. Meta-regression analysis was performed to examine the following factors; sample size (continuous variable), and year of study publication (continuous variable). In addition, a sensitivity analysis was also performed by excluding each study to examine whether a single study might influence the study results.³⁶

Table 1. Search terms and history for studies on hepatitis E virus infection in pregnant women.

Database	Step 1	Yielded documents	Step 2	Assessed for eligibility
PubMed	Link: https://www.ncbi.nlm.nih.gov/pubmed/ Keys: (Hepatitis E virus[Title/Abstract] AND pregnant women[Text Word]) AND pregnancy[Text Word])	163	(Hepatitis E virus[Title/Abstract] AND pregnant women[Text Word]) AND pregnancy[Text Word] AND ((Clinical Study[ptyp] OR Observational Study[ptyp] OR Letter[ptyp] OR Journal Article[ptyp]) AND ("2015/01/01"[PDAT] : "2018/12/31"[PDAT]) AND "humans"[MeSH Terms])	39
Science Direct	Link: https://www.sciencedirect.com/search/advanced Keys: *Hepatitis E virus* AND *Pregnant women* AND *Pregnancy*	5952	Filtered the documents	245
Manual search	Searched from the included studies references	22	Filtered the references of eligible studies	17

RESULTS

Search results and characteristics of included studies

Initially, we identified a total of 6137 articles, of which 5952 were identified from ScienceDirect, 163 from PubMed, and 22 articles were identified manually from the references of included studies. Of the total identified articles, 301 articles remained after screening for eligibility. After screening by title and abstract, we selected 15 studies for the meta-analysis.³⁷⁻⁵¹ Articles were excluded on the basis of the following: review articles (n=251); book chapters (n=381); topics other than HEV infection in pregnant women such as HEV infection among blood donors, animal studies, duplicate, published before 2015, insufficient information (n=5193); and other languages (n=11) as described in **Figure 2**. The 15 studies reported on 8337 subjects, of which 1175 subjects were non-pregnant women and were subtracted from the total sample size. In addition, in another study 2 pregnant women were excluded from the analysis by the authors based on invalid results.⁵⁰ Finally, the analysis included data from 7160 pregnant women, and the sample size ranged from 93 to 1331 per study (**Table 2**).

Prevalence of HEV IgG antibody according to region

A study conducted in 2015 in Sudan reported a high seroprevalence of HEV IgG antibody (61.29%) in pregnant women,⁴⁰ while a study from Italy, in 2015, reported the lowest prevalence (3.41%), findings consistent with national data.⁴⁵ Another two studies from Ethiopia also reported a high prevalence of HEV IgG antibody among pregnant women (42.43%⁴⁹ and 31.61%⁴⁶), respectively, as compared to other included studies. In Eritrea, a study conducted in 2016, reported the prevalence of HEV IgG antibody was 26.8%.⁴⁷ In Benin, a study conducted in 2011, 22.3% of total samples were HEV IgG positive, of which 45 (16.19%) were confirmed as positive by immunoblotting (if samples were positive, the test was repeated).⁴¹ Among the three reported studies from China, an increase was observed a reported 11.07% seroprevalence of HEV IgG antibody in 2009-2010,³⁹ 16.26% in 2011-2013,³⁸ and 21.78% in 2013-2014.⁴⁸ In Burkina Faso, a study conducted in 2014 reported that HEV IgG prevalence was 10.61%.⁴⁴ In Iran, studies conducted in 2010-2011 and 2016-2017 reported 7.43%³⁷ and 6.24%,⁵¹ HEV IgG prevalence, respectively. In Cameroon, a study conducted in 2016, reported 9% seroprevalence of HEV IgG antibody.⁴² A study from Nigeria reported 9.89% HEV IgG prevalence.⁴³ In Ghana, HEV IgG prevalence was reported as 12.06%,⁵⁰ (**Table 3**).

Overall pooled prevalence among pregnant

All the included studies were pooled for meta-analysis as presented on the forest plot (**Figure 3**). The estimated pooled prevalence was 16.51% (95% CI: 0.10-0.23). The heterogeneity level among the included studies was reported high. The I statistics ($I^2=98\%$) represents a high and statistically significant heterogeneity level ($P<.01$) (**Figure 3**). HEV IgG antibody seroprevalence ranged from 3.41% (95% CI: 0.02-0.06) to 61.29% (95% CI: 0.51-0.71) (**Table 3 and Figure 3**). Of the total includ-

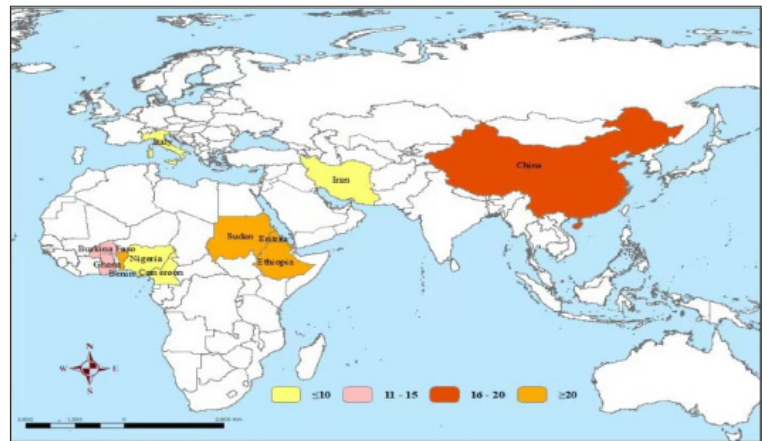


Figure 1. The prevalence of HEV IgG antibody among pregnant women around the world (≤ 10 ; 11-15%; 16-20%, $\geq 20\%$).

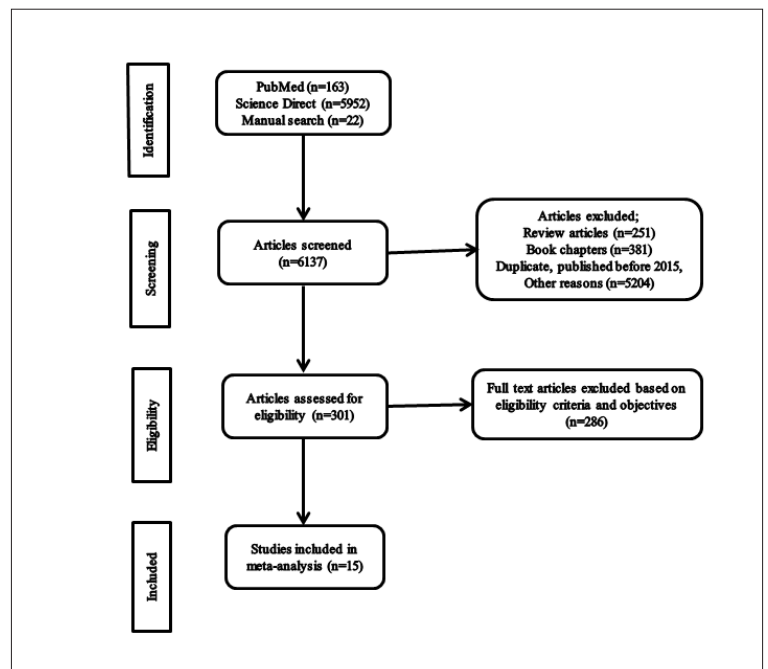


Figure 2. Flow chart showing the processing of the included studies based on PRISMA guidelines.

Table 2. Characteristics of studies in the meta-analysis (n=15).

Study	Year	Sampling year	Country	Pregnant women (n)	Urban (n)	Rural (n)	Age (years)	IgG positive (n)	IgM positive (n)	Study type	Detection method	Ref.
Mamani	2015	2010-2011	Iran	1050	725	325	27.2 (5.6)	78	0	Prospective cross-sectional	DiaPro	37
Gu	2015	2009-2010	China	497	138	359	≤25 ->35	55	3	Cohort	Santa Cruz	39
Cong	2015	2011-2013	China	990	545	445	18-43	161	26	Case-control observational	Wantai	38
Florence	2016	2014	Burkina Faso	179	5	174	≤25 -35	19	0	Cross-sectional	Creative Diagnostic	44
Musa	2016	2015	Sudan	93	16	41	15-45	57	0	Cross-sectional	Soronno	37
De Paschale	2016	2011	Benin	278	0	278	15-41	62	7	NM	DiaPro	41
Noufensi	2016	2016	Cameroon	200	200	0	16-41	18	0	Cross-sectional	Prestige Diagnostics	42
Alkali	2016	2016	Nigeria	182	NM	NM	18-45	18	0	NM	Euroimmun	43
Tekeste	2017	2016	Eritrea	153	NM	NM	15-44	41	0	Cross-sectional Descriptive	Euroimmun	47
La Fauci	2017	2015	Italy	352	352	0	18-≥36	12	0	Hospital based	DiaPro	45
Abebe	2017	2014-2015	Ethiopia	386	386	0	16-40	122	2	Hospital based	Wantai	46
Rui	2018	2013-2014	China	225	NM	NM	20-35	49	8	Case-control observational	Wantai	48
Niguse	2018	2014-2016	Ethiopia	846	356	490	18-50	359	8	Cross-sectional	Wantai	49
Obiri-Yeboah	2018	NM	Ghana	398	341	57	28.0 (5.9)	48	1	Cross-sectional	Tangshan	50
Farshadpour	2018	2016-2017	Iran	1331	1331	0	14-45	83	11	Descriptive cross-sectional	DiaPro	51

Age data are mean (SD) or range. NM: not mentioned..

Table 3. Prevalence rate and quality score of the studies in the meta-analysis by prevalence (n=15).

Study	Sample size (n)	HEV IgG positive (n)	Prevalence (%)	Quality score (average)	Ref.
Musa	93	57	61.29	7	37
Niguse	846	359	42.43	8	49
Abebe	386	122	31.61	8	46
Tekeste	153	41	26.80	6	47
De Paschale	278	62	22.30	7	41
Rui	225	49	21.78	7	48
Cong	990	161	16.26	7	38
Obiri-Yeboah	398	48	12.06	8	50
Gu	497	55	11.07	7	39
Florence	179	19	10.61	6	44
Alkali	182	18	9.89	6	43
Noufensi	200	18	9.00	6	42
Mamani	1050	78	7.43	8	37
Farshadpour	1331	83	6.24	8	51
La Fauci	352	12	3.41	6	45

ed studies, only 7 studies reported IgM antibody, and the pooled rate was 1.33% (95% CI: 0.01-0.02), $I^2=77%$ (**Additional file: Figure S1**).

Subgroup analysis

HEV IgG seroprevalence among pregnant women by

region was high in Africa 22% (95% CI: 0.13-0.34) as compared to other regions (**Figure 4**). The prevalence rate was increased by publication year, 11% (95% CI: 0.08-0.16) in 2015 and 17% (95% CI: 0.08-0.33) in 2018 (**Figure 5**). This increase may be attributed due to different factors, such as studies from different geo-

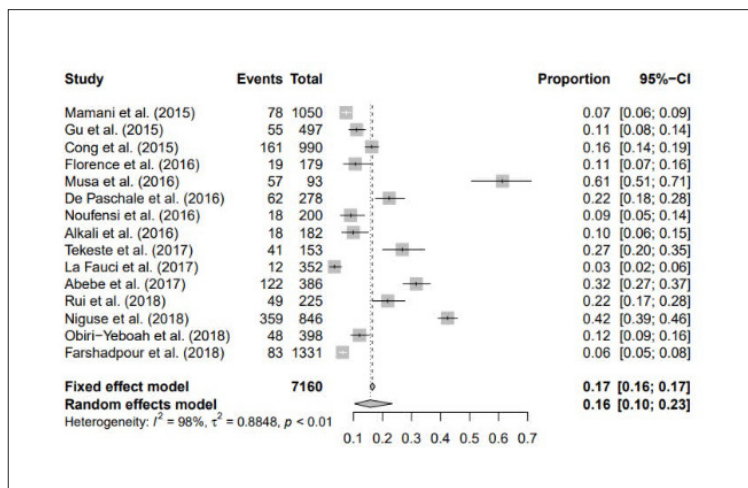


Figure 3. Forest plot meta-analysis of HEV IgG antibody prevalence in pregnant women around the world.

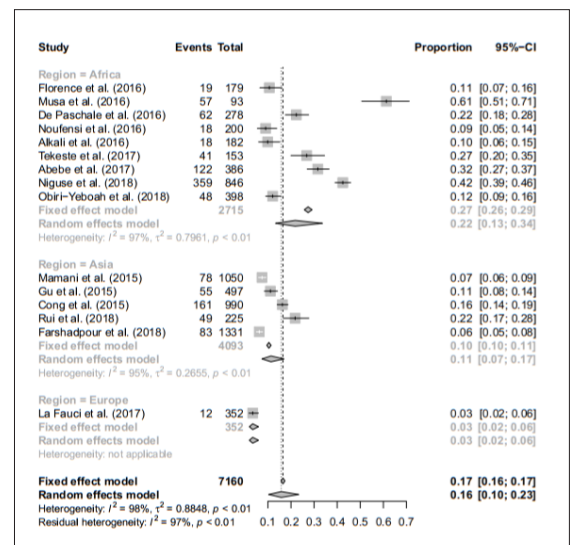


Figure 4. Forest plot of subgroup analysis of HEV IgG antibody prevalence by region.

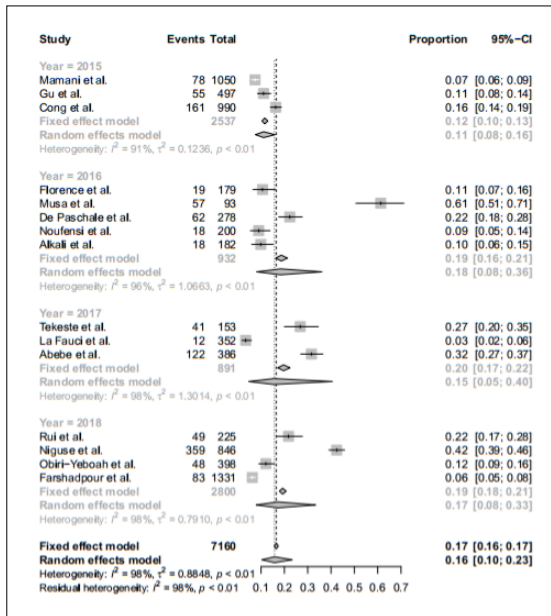


Figure 5. Forest plot of subgroup analysis of HEV IgG antibody prevalence by publication year.

graphical regions, different sample sizes, and different detection methods. The pooled HEV IgG antibody seroprevalence by different ELISA assays showed high variability among included studies ranging from 8% (95% CI: 0.04-0.15) to 27% (95% CI: 0.18-0.38). Dia Pro and Wantai were frequently used commercial assays (Figure 6). The seroprevalence of HEV IgG antibody varied with sample size (Figure 7). The methodological quality scores of the included studies are presented in Table 3. Meta-regression by year of publication ($P=.582$) and sample size ($P=.003$) were calculated (Additional file 1: Figure S2 and S3).

Publication bias

The publication bias was determined using the funnel plot, which showed a dispersed distribution suggesting the possibility of publication bias (Figure 8) as indicated by the Egger test ($P=.007$).

Sensitivity analysis

We also performed a sensitivity analysis by removing one study with a large sample size.⁵¹ The overall HEV IgG antibody pooled rate was 17% (95% CI: 0.11-0.25), with $I^2=98\%$, $P \leq .01$ (Additional file 1: Figure S4 and S5).

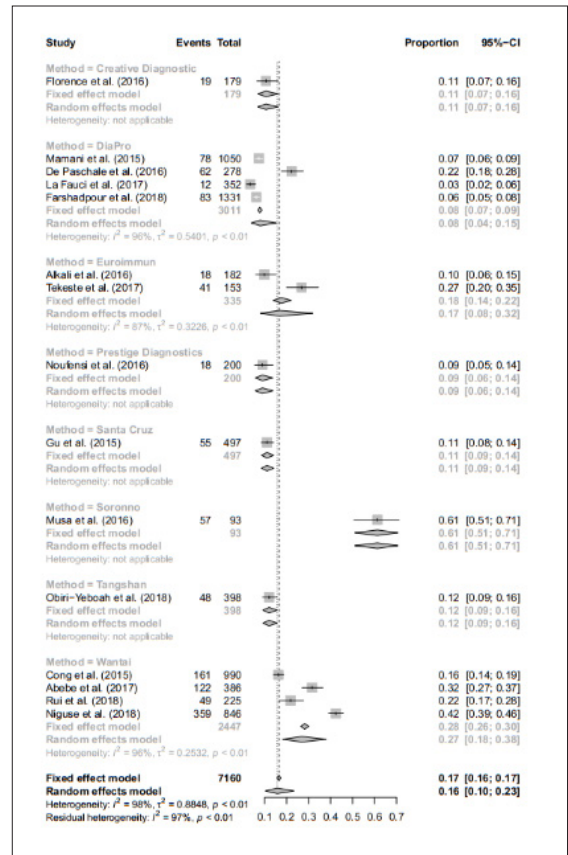


Figure 6. Forest plot of subgroup analysis of HEV IgG antibody prevalence by commercial assay method.

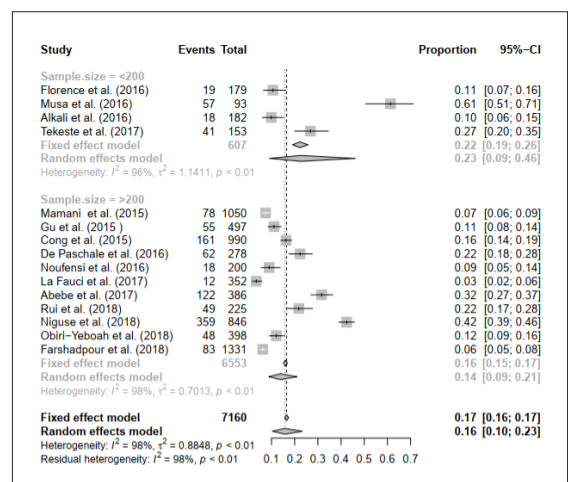


Figure 7. Forest plot of subgroup analysis of HEV IgG antibody prevalence by sample size.

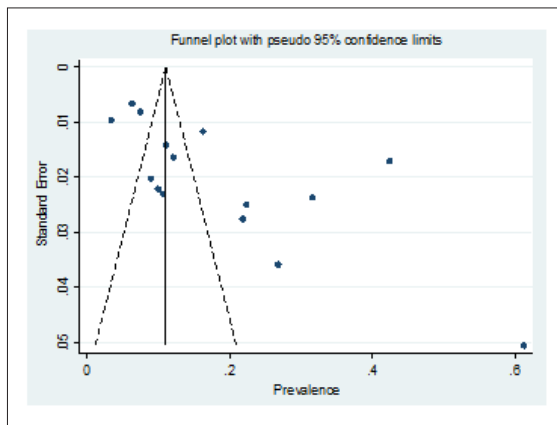


Figure 8. Funnel plot to assess publication bias.

DISCUSSION

HEV is an old and underestimated infection, due to inappropriate diagnosis and lack of awareness among physicians.^{52,53} In recent years, both in developing and developed countries, surveillance and seroprevalence-based research has gained more attention. However, there are significant gaps in the published literature. Therefore, this study aimed to estimate the burden and pooled prevalence of HEV IgG antibody in pregnant women around the world. The information in this report may help researchers and policymakers to better understand the disease distribution in order to launch effective control strategies and preventive measures.

HEV infection is one of the leading causes of fetal and maternal death.⁵⁴ In pregnant women with HEV infection, cytokine gene polymorphisms are associated with adverse pregnancy outcomes.⁵⁵ During the second and third trimester of pregnancy, HEV infection leads to hepatic failure and increases the risk of mortality 30% to 100%.⁷ However, the mechanism of liver injury has not been clarified. Additional research is needed to explore the exact mechanism and determine preventive strategies. A possible reason may relate to the interplay of immunological and hormonal changes that along with high viral load render women more vulnerable to HEV infection.⁵⁶

According to our findings, the prevalence of HEV IgG antibody ranged from 3.4%⁴⁵ to 61.2%.⁴⁰ The observed discrepancies of HEV seroprevalence may be attributable to different assay methods and different geographic regions. Keeping the above factors in mind, we conducted a subgroup analysis by year of publica-

tion, study region, sample size, and assay method. The meta-analysis of the included studies showed that the estimated pooled prevalence of HEV IgG antibody among pregnant women around the world was 16.51%. These results suggest that HEV IgG antibody is endemic in pregnant women.

In Chinese blood donors, the estimated pooled prevalence of HEV IgM antibody was 30%.⁵⁷ However, the finding of our study is higher than a systematic review conducted by Iranian authors reported 5.4% seroprevalence of HEV.⁵⁸ Another meta-analysis conducted among the general population of Iran reported the overall pooled prevalence of HEV was 9.7%.⁵⁹ The estimated seroprevalence of HEV ranged from 0.6% to 52.5% in European countries.⁶⁰ Another systematic review of reports of the Brazilian population reported an overall seroprevalence of HEV infection of 6.0%.⁶¹ Moreover, the pooled prevalence in our study is also higher than that in some primary studies conducted in different countries among pregnant women, such as in Tunisia of 5.1%,⁶² Mexico of 5.7%,⁶³ France of 7.7%,⁶⁴ Pakistan of 8.86%,⁶⁵ Sudan of 10.3%,⁶⁶ and in Serbian blood donors of 15.0%.⁶⁷ On the other hand, a high prevalence of HEV was reported among pregnant women in Egypt of 83.4%,⁶⁸ and India of 60.0%.⁶⁹ In addition, some other studies reported a high prevalence of HEV IgG antibody in Iran, with 46.1% in the adult population.⁷⁰ In a study conducted in German blood donors, only 3 of 13 HEV RNA positive results had detectable IgM antibody titers.⁷¹ Spread of HEV through contaminated blood products remains unknown.⁷¹

This meta-analysis has a relatively large sample size but several limitations. Most of the studies used different ELISA kits for the detection of anti-HEV IgG antibody with different specificity and sensitivity, which may affect the reliability and accuracy of the test. Seroprevalence was only determined by the anti-HEV IgG antibody level, which shows mostly after infection. Furthermore, the studies included in the analysis were observational and varied by baseline characteristics, sample size, and year of sampling.

The consequences of HEV infection—severe liver injury, and high morbidity and mortality rate, especially in pregnant women, have gained the attention of more scientists and researchers. As a result, more focus has been paid to the pathophysiology and immunology of HEV interaction during pregnancy. But it is also important to study genetic and environmental factors, espe-

cially in HEV endemic areas. Immunological research and preventive and management strategies need to be improved to control and stop the disease in the near future. Also, cost-effective vaccination programs are needed in those countries where the disease is endemic.

In conclusion, the seroprevalence of anti-HEV IgG antibody among pregnant women differs by geographic location and is highest in African countries. Further studies are recommended to evaluate the incidence, morbidity, and mortality in those areas where the disease is prevalent. However, necessary actions should be taken to control and prevent HEV infection in gen-

eral and particularly in pregnant women. Special care must be taken in traveling to endemic areas, especially in strictly following drinking water (only bottled water) and food precautions.

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SUPPLEMENT FIGURES:

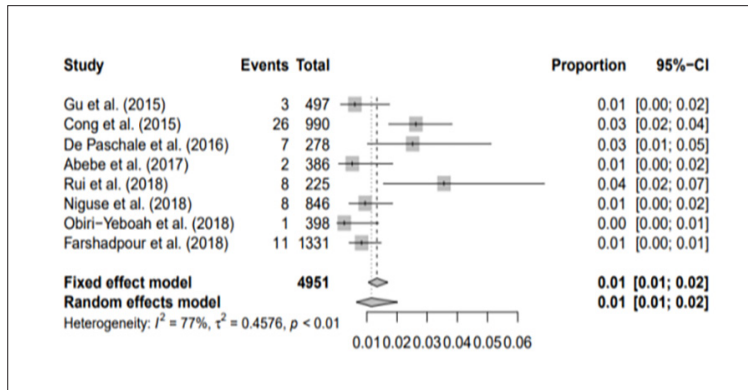


Figure S1. Forest plot of HEV IgM antibody among pregnant women around the world

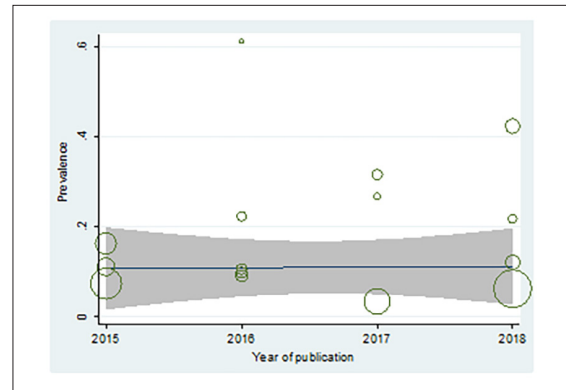


Figure S2. Meta-regression analysis by year of publication ($P=.582$)

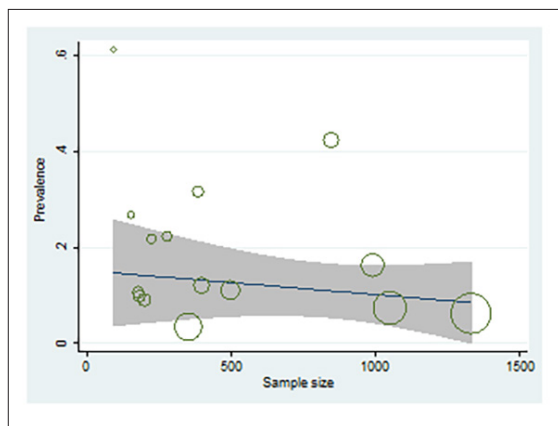


Figure S3. Meta-regression analysis by sample size ($P=.003$)

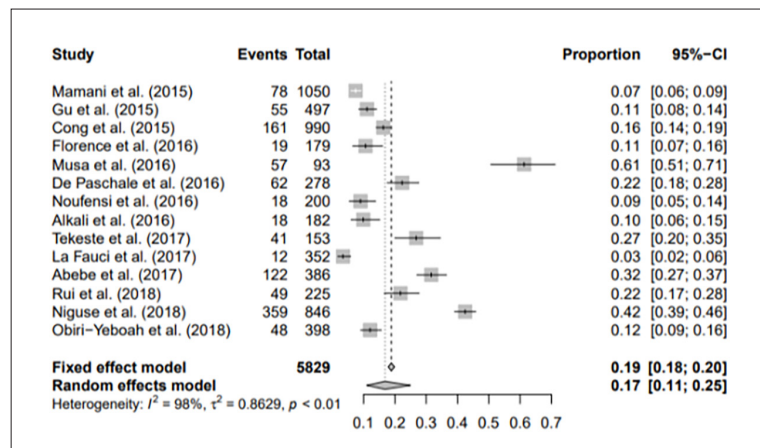


Figure S4. Forest plot of sensitivity analysis.

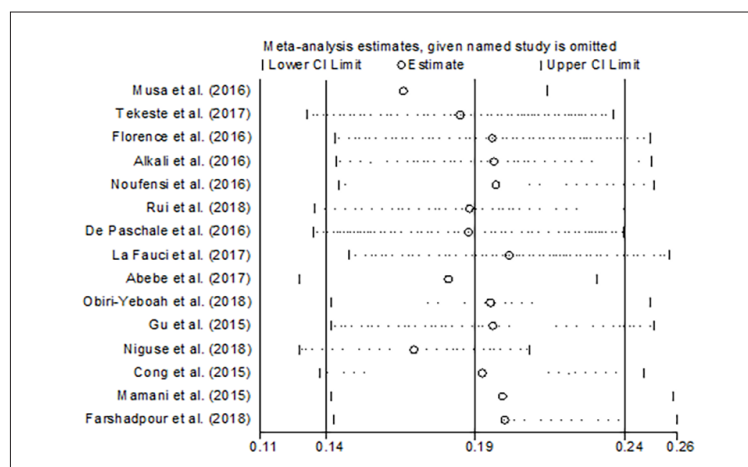


Figure S5. Sensitivity analysis.