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GLOBAL SEROPREVALENCE OF ANTI-HEV IgG AND IgM ANTIBODIES AMONG PREGNANT WOMEN: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Introduction Hepatitis E virus (HEV) represents a significant public health concern during pregnancy, being associated with severe maternal and fetal complications. This meta-analysis aimed to estimate the global seroprevalence of anti-HEV IgG and IgM antibodies among pregnant women.

Materials and methods A systematic review and meta-analysis were conducted in accordance with PRISMA guidelines. Observational studies were identified in PubMed, Scopus, and Web of Science. Pooled seroprevalence estimates were calculated using a random-effects model. Heterogeneity was assessed using Cochran's Q and the I^2 statistic, while publication bias was evaluated by funnel plots and Egger's regression test.

Results Thirty studies from diverse geographic regions were included. The pooled global seroprevalence of anti-HEV IgG was 11.76% (95% CI: 9.45–14.54), indicating widespread prior exposure. Anti-HEV IgM seroprevalence, reflecting recent infection, was 1.07% (95% CI: 0.61–1.86). Substantial heterogeneity was observed for both markers (I^2 > 95%), reflecting marked regional variability. No statistically significant small-study effects were detected by Egger's regression (p > 0.05).

Conclusions HEV exposure among pregnant women is common globally, with pronounced regional differences, whereas recent infection appears relatively rare at the global level. These findings highlight the need for region-specific surveillance, improved diagnostic standardization, and targeted preventive strategies to reduce HEV-related risks during pregnancy.

Keywords HEV, IgG, IgM, seroprevalence, pregnancy.

SEROPREVALENȚA GLOBALĂ A ANTICORPILOR IGG ȘI IGM ANTI-HEV LA FEMEILE ÎNSĂRCINATE: O ANALIZĂ SISTEMATICĂ ȘI O META-ANALIZĂ

Introducere Virusul hepatitei E (HEV) reprezintă o problemă importantă de sănătate publică în timpul sarcinii, fiind asociat cu complicații materne și fetale severe. Scopul acestei meta-analize a fost estimarea seroprevalenței globale a anticorpilor anti-HEV IgG și IgM la femeile însărcinate.

Materiale și metode A fost realizată o revizuire sistematică și o meta-analiză conform ghidului PRISMA. Studiile observaționale au fost identificate în PubMed, Scopus și Web of Science. Seroprevalențele combinate au fost calculate utilizând un model cu efecte aleatorii. Heterogenitatea a fost evaluată prin testul Q al lui Cochran și indicele I^2, iar biasul de publicare prin funnel plots și testul Egger.

Rezultate Au fost incluse 30 de studii din regiuni geografice diverse. Seroprevalența globală combinată anti-HEV IgG a fost de 11,76% (IC 95%: 9,45–14,54), indicând o expunere larg răspândită. Seroprevalența anti-HEV IgM a fost de 1,07% (IC 95%: 0,61–1,86). Heterogenitatea a fost foarte ridicată pentru ambii markeri (I^2 > 95%). Nu a fost identificat un bias de publicare semnificativ.

Concluzii Expunerea la VHE în rândul femeilor însărcinate este frecventă la nivel global, cu variații regionale importante, în timp ce infecția recentă este relativ rară. Rezultatele subliniază necesitatea unor strategii de supraveghere și prevenție adaptate contextului regional.

Cuvinte-cheie HEV, IgG, IgM, seroprevalență, sarcină.

INTRODUCTION

Hepatitis E virus (HEV) represents a growing public health concern, particularly in the context of pregnancy, where its clinical consequences can be disproportionately severe. HEV is primarily transmitted through the fecal–oral route and is endemic in many low- and middle-income countries, with outbreaks frequently associated with inadequate sanitation and contaminated water sources (1). Globally, HEV is estimated to cause approximately 20 million infections each year, resulting in about 3.3 million symptomatic cases and more than 50,000 deaths annually (1).

Pregnant women, especially during the third trimester, are at significantly increased risk of severe HEV-related complications, including fulminant hepatic failure, preterm labor, stillbirth, and elevated maternal mortality (2, 3). Despite these well-documented clinical risks, the global burden of HEV infection among pregnant women remains incompletely characterized, with substantial regional variation in seroprevalence and inconsistent reporting across studies.

This meta-analysis aims to address these gaps by systematically evaluating the global seroprevalence of anti-HEV IgG and IgM antibodies among pregnant women. By synthesizing data from diverse geographic regions, this study provides a comprehensive overview of HEV exposure and recent infection patterns during pregnancy, thereby contributing evidence to support improved surveillance strategies and public health prioritization in this vulnerable population.

MATERIALS AND METHODS

Study Design and Reporting Framework

This study was conducted as a systematic review and meta-analysis of observational studies reporting the seroprevalence of HEV antibodies among pregnant women. The methodology and reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Data Sources and Search Strategy

A systematic literature search was conducted in PubMed, Scopus, and Web of Science to identify relevant studies reporting HEV seroprevalence among pregnant women. The search covered all articles published up to January 10, 2025 and was conducted and reported in accordance with the PRISMA guidelines. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to HEV infection and pregnancy, including “hepatitis E”, “HEV”, “seroprevalence”, “pregnant women”, “anti-HEV IgG”, and “anti-HEV IgM”.

The PubMed search strategy was as follows:

((“Hepatitis E”[Mesh] OR “hepatitis E virus” OR HEV) AND (“Pregnancy”[Mesh] OR pregnant OR pregnancy OR pregnant women) AND (seroprevalence OR prevalence OR “anti-HEV IgG” OR “anti-HEV IgM”)).

Search strategies were adapted for Scopus and Web of Science using database-specific syntax. The search was restricted to observational studies (cross-sectional, cohort, or case–control designs) published in the English language. Additional records were identified through manual screening of reference lists from relevant articles and review papers to ensure comprehensive coverage of the available literature.

Subsequently, titles and abstracts were screened for relevance, followed by full-text assessment of potentially eligible studies. All full-text articles retrieved after screening met the predefined inclusion criteria and were therefore included in the final meta-analysis. The study selection process and reasons for exclusion are summarized in the PRISMA flow diagram (fig. 1).

The review protocol was not prospectively registered in PROSPERO, as this meta-analysis was conducted as part of an institutional research project with a predefined scope and timeline. The absence of protocol registration is acknowledged, and all methodological decisions were defined a priori and applied consistently across included studies.

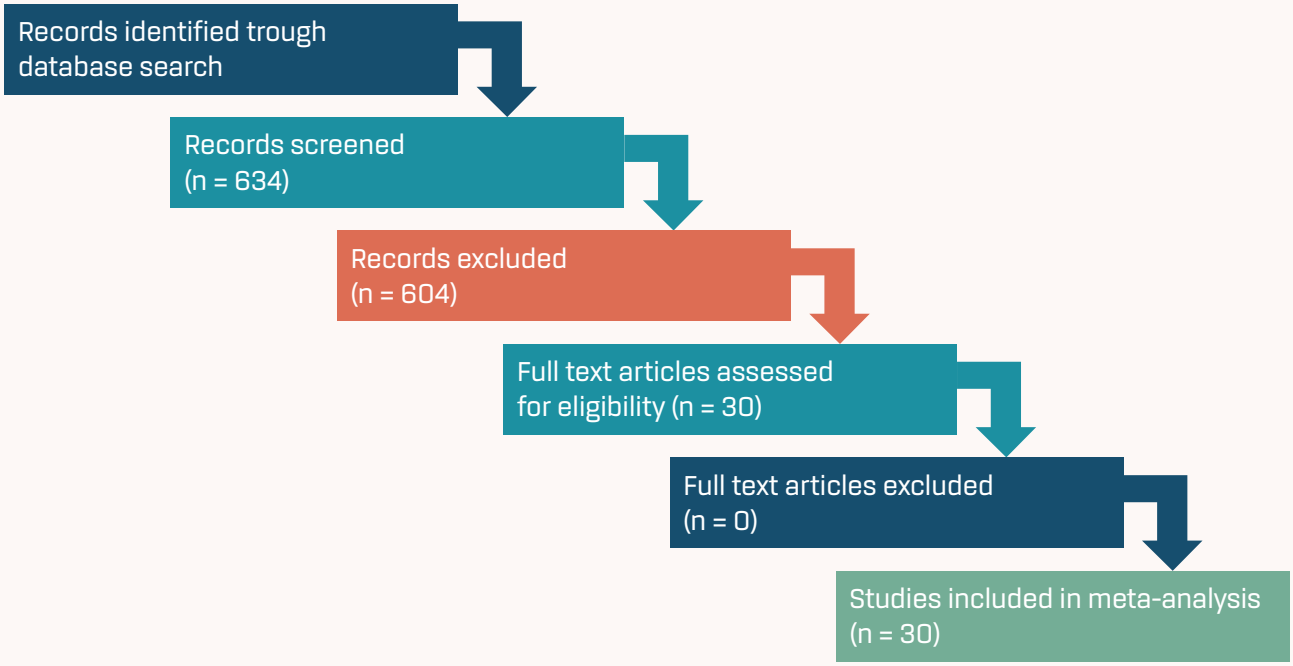

Figure 1. PRISMA flow diagram of study selection. Records were identified through database searching (PubMed, Scopus, and Web of Science). Titles and abstracts were screened for eligibility, followed by full-text assessment. All full-text articles retrieved after screening met the predefined eligibility criteria and were included in the final meta-analysis.

Eligibility Criteria

Studies were included if they met the following criteria:

- Reported the seroprevalence of anti-HEV IgG and/or anti-HEV IgM antibodies among pregnant women;
- Used ELISA or other validated serological assays for HEV antibody detection;
- Provided sufficient data to allow calculation of prevalence estimates (number of positive cases and total sample size, or equivalent information);
- Were original observational studies (cross-sectional, cohort, or case–control);
- Were published in English.

Studies were excluded if they:

- Focused on non-pregnant populations;
- Lacked extractable seroprevalence data;
- Were case reports, reviews, editorials, or conference abstracts.

Study Selection

All identified records were screened independently by two reviewers. Titles and abstracts were first assessed for relevance, followed by full-text evaluation of potentially eligible articles. Any discrepancies between reviewers were resolved through discussion and consensus. The study selection process is summarized using a PRISMA flow diagram.

Data Extraction

From each included study, the following data were extracted using a standardized form:

- Country and study setting;
- Year of publication;
- Sample size (number of pregnant women tested);
- Number or proportion of anti-HEV IgG–positive cases;
- Number or proportion of anti-HEV IgM–positive cases;
- Type of serological assay used.

When overall HEV seroprevalence among pregnant women was not explicitly reported, prevalence estimates were extracted from the largest available subgroup that best reflected the general pregnant population included in the study. This approach was predefined before data extraction and applied consistently across studies. Priority was given to population-based samples or subgroups including all tested pregnant women, whereas clinically selected or high-risk subgroups (e.g., symptomatic cases or women with acute hepatitis) were excluded to reduce selection bias and improve comparability.

Quality Assessment

The methodological quality of included studies was assessed using a domain-based evaluation framework adapted from the Newcastle–Ottawa Scale (NOS) for observational studies (4). Rather than generating a cumulative numeric score, this approach focused on key methodological domains directly relevant to prevalence estimation, including sample representativeness, diagnostic accuracy of the serological assays, and data completeness.

Although the Joanna Briggs Institute (JBI) critical appraisal tools are commonly recommended for prevalence studies, we chose a domain-based framework adapted from the Newcastle–Ottawa Scale (NOS). This decision was made to maintain consistency with previous HEV seroprevalence meta-analyses and to place greater emphasis on diagnostic validity and population representativeness.

Based on the overall methodological rigor across these domains, studies were classified qualitatively as high, moderate, or low quality. This qualitative categorization was applied to facilitate comparison across studies and to support sensitivity analyses, rather than to derive a cumulative numeric score. Any discrepancies in quality assessment were resolved through discussion and consensus between reviewers.

The detailed results of the quality assessment for each included study are presented below (tab. 1).

Table 1. Domain-based quality assessment framework adapted from the Newcastle–Ottawa Scale (NOS).

Country/Study	Sample Representativeness	Diagnostic Accuracy	Data Completeness	Overall Quality
Argentina (5)	Moderate	Moderate (ELISA Diapro)	Moderate	Moderate
China (6)	High (Large sample)	High (ELISA Wantai)	High	High
Nigeria (7)	Low (Small sample)	Moderate (ELISA Canoga Park)	Moderate	Low to Moderate
Cambodia (8)	High	High (Validated methods)	High	High
South Africa (9)	Moderate	High	High	High
Germany (10)	Low (Small sample)	High	Moderate	Moderate
Senegal (11)	High	High	High	High
Iran (12)	Moderate	Moderate (ELISA Diapro)	High	Moderate to High
China (13)	High (Very large sample)	High	High	High
Pakistan (14)	Low (Very small sample)	Moderate (MicroLISA)	Moderate	Low to Moderate
China* (15)	Moderate	High	Moderate	Moderate
Nigeria (16)	Low (Small sample)	Moderate (ELISA Diapro)	High	Moderate
China (17)	Moderate	High	High	High
Haiti (18)	High	High	High	High
Benin (19)	Moderate	Moderate (ELISA Diapro)	High	Moderate to High
Ghana (20)	Moderate	High	High	High
Ethiopia (21)	Moderate	High	High	High
Ethiopia (22)	High	High	High	High
China (23)	Moderate	High	High	High
China (24)	High	High	High	High
Iran (25)	High	Moderate (ELISA Diapro)	High	High
Turkey (26)	Moderate	Moderate (MicroELISA)	Moderate	Moderate
Spain (27)	High	Moderate (ELISA Diapro)	High	High
Tunisia (28)	Moderate	Moderate (ELISA Globe Diagnostic SRL)	Moderate	Moderate
Kyrgyzstan (29)	High	High	High	High
France (30)	Moderate	High	High	High
Croatia (31)	Low (Very small sample)	High	Moderate	Moderate
China (32)	Moderate	High	High	High
Thailand (33)	Low (Very small sample)	High	Moderate	Low to Moderate
Vietnam (34)	Moderate	High	High	High

**Note:* For the study conducted in Qinhuangdao, China, overall HEV seroprevalence among pregnant women was not explicitly reported. Therefore, prevalence estimates were derived from the largest available subgroup representing the general pregnant population included in the study. Clinically selected subgroups were not used for prevalence extraction, in accordance with the predefined data extraction criteria described in the Methods section.

Statistical analysis

For each included study, seroprevalence was calculated as the proportion of positive cases among the total number of tested pregnant women. Study-level 95% confidence intervals (CIs) were computed using the Wilson method, which provides stable estimates for proportions, including studies with small sample sizes. For studies reporting zero seropositive events, confidence intervals were not displayed in descriptive tables to avoid misinterpretation and visual clutter, as such intervals are typically extremely wide and uninformative. Nevertheless, zero-event studies were retained in the meta-analysis and incorporated into the pooled estimates using variance-stabilizing transformations.

Pooled seroprevalence estimates for anti-HEV IgG and anti-HEV IgM were calculated using random-effects meta-analysis to account for substantial between-study heterogeneity related to geographic region, population characteristics, and diagnostic methods. Proportions were stabilized using the Freeman–Tukey double arcsine transformation prior to pooling. Between-study variance (τ^2) was estimated using the DerSimonian–Laird method, and pooled confidence intervals were calculated using the standard random-effects model.

Statistical heterogeneity was assessed using Cochran's Q test and quantified with the I^2 statistic, which represents the proportion of total variability attributable to true between-study heterogeneity rather than sampling error. For anti-HEV IgM, studies reporting zero events were included in the pooled prevalence estimation but were excluded from heterogeneity testing and other standard error–based diagnostics to ensure statistical stability; this distinction is reflected in the reported degrees of freedom for heterogeneity analyses.

To explore potential sources of heterogeneity a priori, exploratory subgroup analyses were planned based on geographic region and serological assay type, as these variables were available for most included studies (Tab. 2). Subgroup analyses were conducted descriptively due to substantial residual heterogeneity and unequal numbers of studies across subgroups. Formal meta-regression was not performed because of incomplete reporting of relevant covariates and limited statistical power within individual subgroups.

Sensitivity and Bias Assessment

Sensitivity analyses were performed to evaluate the influence of studies with extreme prevalence values or very small sample sizes on the pooled estimates. Publication bias was explored through visual inspection of funnel plots and formally assessed using Egger's regression test, with the acknowledgment that such methods have limited power and interpretability in meta-analyses of prevalence, particularly in the presence of substantial heterogeneity.

All statistical analyses were performed using R software (version 4.2.2), employing the meta and metafor packages.

RESULTS

The characteristics of the studies included, which evaluated the seroprevalence of anti-HEV IgG and IgM antibodies among pregnant women across different countries, along with the corresponding references [4–33], are summarized (tab. 2). The included studies provide insights into the epidemiology of HEV infection, diagnostic methodologies used, and regional disparities in seroprevalence.

Table 2. Global Seroprevalence of Anti-HEV IgG and IgM in Pregnant Women

Country/Study	Number of tested pregnant women (samples)	Seroprevalence of Anti-HEV IgG	Seroprevalence of Anti-HEV IgM	Testing method
Argentina (5)	202	8.4% (95% CI: 5.3%–13.1%)	1.0% (95% CI: 0.3%–3.5%)	ELISA Diapro
China (6)	4244	10.5% (95% CI: 9.6%–11.4%)	0.4% (95% CI: 0.2%–0.6%)	ELISA Wantai
Nigeria (7)	200	22.0% (95% CI: 16.8%–28.2%)	15.0% (95% CI: 10.7%–20.6%)	ELISA Canoga Park
Siem Reap, Cambodia (8)	1565	11.6% (95% CI: 10.1%–13.2%)	2.6% (95% CI: 1.9%–3.5%)	ELISA, RecomLine LIA, from Mikrogen
Pretoria, South Africa (9)	384	3.1% (95% CI: 1.8%–5.4%)	0	ELISA Wantai
Germany (10)	62	9.7% (95% CI: 4.5%–19.5%)	0	ELISA Wantai
Senegal (11)	1227	7.4% (95% CI: 6.1%–9.0%)	0.5% (95% CI: 0.2%–1.1%)	ELISA Wantai
Ilam, West of Iran (12)	420	4.3% (95% CI: 2.7%–6.7%)	0.5% (95% CI: 0.1%–1.7%)	ELISA Diapro
China (13)	19,762	11.4% (95% CI: 10.9%–11.8%)	0.1% (95% CI: 0.1%–0.2%)	ELISA Wantai
Pakistan, capital (14)	90	60.0% (95% CI: 49.7%–69.5%)	13.3% (95% CI: 7.8%–21.9%)	MicroLISA
Qinhuangdao, China (15)	365	20.3% (95% CI: 16.6%–24.7%)	4.1% (95% CI: 2.5%–6.7%)	ELISA Wantai
Ibadan, Nigeria (16)	230	17.0% (95% CI: 12.7%–22.3%)	4.8% (95% CI: 2.7%–8.4%)	ELISA Diapro
Qingdao and Weihai, China (17)	990	16.2% (95% CI: 13.9%–18.5%)	2.6% (95% CI: 1.8%–3.8%)	ELISA Wantai
Haiti (18)	1279	10.3% (95% CI: 8.4%–12.3%)	0.3% (95% CI: 0.2%–0.3%)	ELISA Wantai
Benin (19)	278	16.2% (95% CI: 12.3%–21.0%)	1.4% (95% CI: 0.6%–3.6%)	ELISA Diapro
Ghana, Cape Coast Metropolis (20)	393	12.2% (95% CI: 9.3%–15.8%)	0.2% (95% CI: 0.0%–1.4%)	ELISA INNOVITA
Addis Ababa, Ethiopia (21)	386	31.6% (95% CI: 27.2%–36.4%)	0.5% (95% CI: 0.1%–1.9%)	ELISA Wantai
Tigray, Northern Ethiopia (22)	846	42.4% (95% CI: 39.1%–45.8%)	0.9% (95% CI: 0.5%–1.9%)	ELISA Wantai
Jiangsu, China (23)	497	11.1% (95% CI: 8.6%–14.1%)	0.6% (95% CI: 0.2%–1.8%)	ELISA Wantai
Inner Mongolia, China (24)	3278	6.0% (95% CI: 5.2%–6.9%)	0.3% (95% CI: 0.2%–0.6%)	ELISA Wantai
Iran (25)	1331	6.2% (95% CI: 5.1%–7.7%)	0.8% (95% CI: 0.5%–1.5%)	ELISA Diapro
Turkey (26)	245	12.6% (95% CI: 9.1%–17.4%)	0	microELISA Virotech GmbH, Germany

Country/Study	Number of tested pregnant women (samples)	Seroprevalence of Anti-HEV IgG	Seroprevalence of Anti-HEV IgM	Testing method
Madrid, Spain (27)	1,040	3.6% (95% CI: 2.7%–5.0%)	0.7% (95% CI: 0.3%–1.4%)	ELISA Diapro
Tunisia (28)	404	12.1% (95% CI: 9.3%–15.7%)	0	ELISA (Globe Diagnostic SRL
Kyrgyzstan (29)	1472	5.9% (95% CI: 4.8%–7.2%)	4.8% (95% CI: 3.4%–5.5%)	ELISA NPO "Diagnostic Systems"
France (30)	315	7.7% (95% CI: 4.7%–10.8%)	0	ELISA Wantai
Croatia (31)	118	1.7% (95% CI: 0.2%–5.9%)	0	ELISA; Euroimmun
Yunnan, China (32)	293	10.2% (95% CI: 7.3%–14.2%)	1.4% (95% CI: 0.5%–3.5%)	ELISA Wantai
Thailand (33)	17	41.2% (95% CI: 21.6%–64.0%)	11.8% (95% CI: 3.3%–34.3%)	ELISA; Euroimmun
Vietnam (34)	183	7.6% (95% CI: 4.6%–12.4%)	2.1% (95% CI: 0.9%–5.5%)	ELISA Wantai

Note: Confidence intervals were not reported for zero-event studies.

Study Selection and Characteristics

A total of 30 observational studies reporting seroprevalence of HEV antibodies among pregnant women were included in the final meta-analysis. The publication years of the included studies ranged from 2004 to 2024. The studies were conducted across multiple geographic regions, including Africa, Asia, and Europe, and encompassed a wide range of sample sizes, from small cohorts ($n < 100$) to large population-based studies ($n > 10,000$).

Overall, data from 42,116 pregnant women were available for the analysis of anti-HEV IgG seroprevalence, while 42,022 pregnant women contributed data to the analysis of anti-HEV IgM seroprevalence. All included studies employed validated serological assays, predominantly ELISA-based methods, although the specific commercial kits varied across studies.

Analysis of the Data

The seroprevalence of anti-HEV IgG among pregnant women demonstrated pronounced geographic variability, ranging from 1.7% in Croatia to 60.0% in Pakistan, indicating substantial differences in cumulative exposure across settings. Using a random-effects model, the pooled global seroprevalence of anti-HEV IgG was 11.76% (95% CI: 9.45–14.54). Substantial heterogeneity was observed (Cochran's $Q = 1281.4$, $df = 29$, $p < 0.001$; $I^2 = 97.74\%$), suggesting that most variability reflects true between-study differences rather than sampling error.

Exploratory subgroup assessment suggested marked variability in anti-HEV IgG seroprevalence across geographic regions. Higher prevalence estimates were predominantly observed in studies from South Asia and sub-Saharan Africa, whereas lower estimates were more common in European populations. Differences were also noted according to the serological assay used, with studies employing Wantai-based ELISA tests frequently reporting higher seroprevalence than those using other commercial platforms. However,

substantial heterogeneity persisted within subgroups, indicating that no single factor fully accounted for the observed variability.

A forest plot summarizing individual study estimates and the pooled IgG seroprevalence is presented in Figure 2.

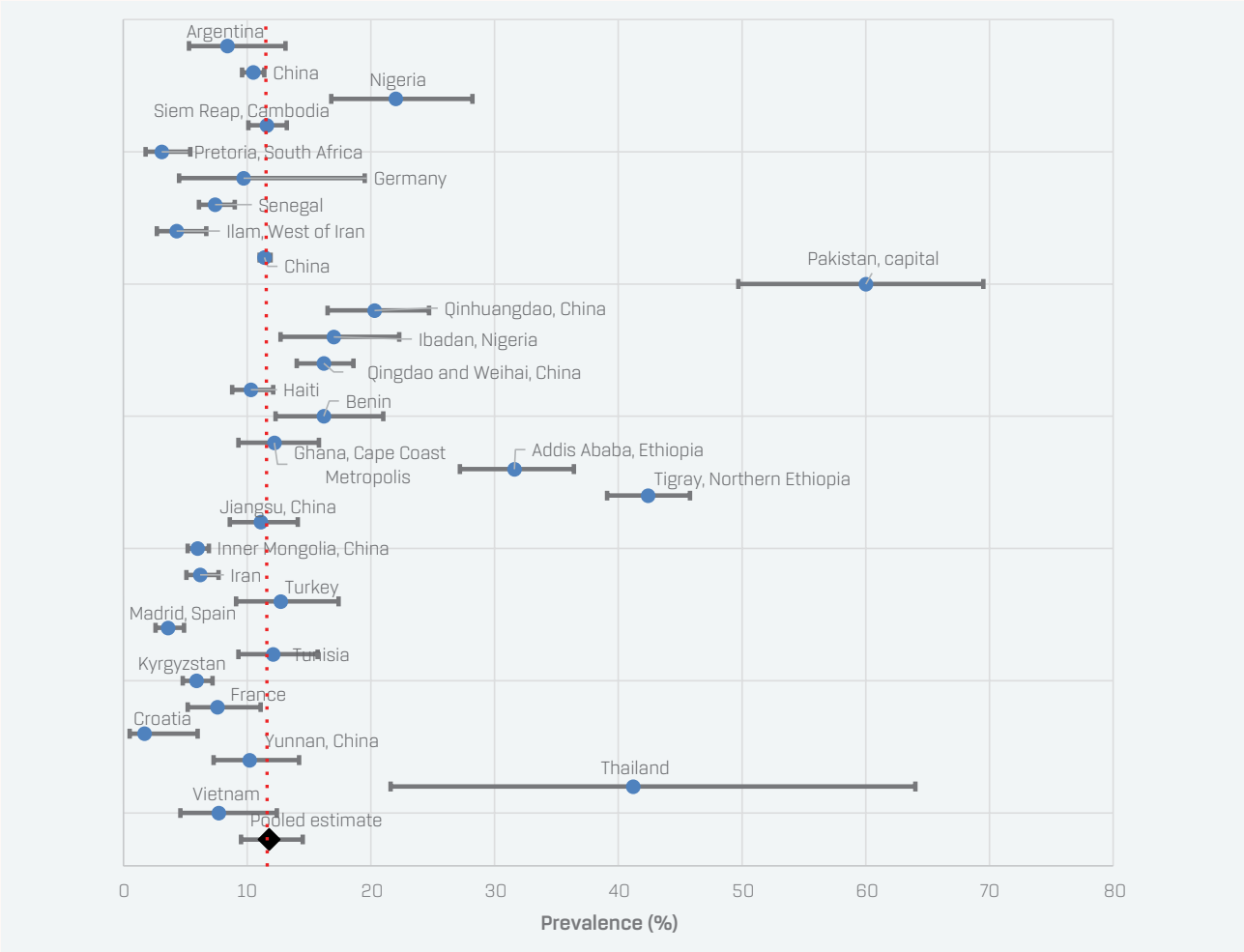

Figure 2. Forest plot of anti-HEV IgG seroprevalence among pregnant women across included studies.

Sensitivity analyses excluding studies with extremely high prevalence values and/or very small sample sizes resulted in only minor changes to the pooled estimate, while heterogeneity remained high. Specifically, the pooled anti-HEV IgG estimate varied by less than 1.0 percentage point after exclusion of these studies, indicating that the observed variability is driven by genuine epidemiological differences rather than by single influential studies.

In contrast, anti-HEV IgM seroprevalence, a marker of recent or acute HEV infection, was low in most included studies, frequently below 1%. Nevertheless, several countries reported markedly higher IgM prevalence, including Nigeria (15.0%), Pakistan (13.3%), and Thailand (11.8%), indicating ongoing transmission or recent outbreaks in these settings. Using a random-effects model, the pooled global seroprevalence of anti-HEV IgM was estimated at 1.07% (95% CI: 0.61–1.86). Heterogeneity remained considerable (Cochran's Q = 570.9, df = 23, $p < 0.001$; $I^2 = 95.97\%$), reflecting substantial variability in recent HEV exposure across study populations.

Exploratory subgroup assessment for anti-HEV IgM suggested higher prevalence estimates in studies from South Asia and sub-Saharan Africa compared with other regions; however, interpretation was limited by the low overall prevalence, frequent zero-event studies, and the small number of studies within individual subgroups. Accordingly, no robust subgroup-specific pooled estimates were derived for IgM.

Anti-HEV IgM data were available in 24 studies. Heterogeneity statistics for IgM were therefore calculated based on studies reporting non-zero prevalence values, as the inclusion of zero-event studies may lead to instability in standard error–based estimates. Studies reporting zero anti-HEV IgM events were retained in the pooled prevalence analysis and displayed in the forest plot (fig. 3); however, they were excluded from heterogeneity testing and funnel plot–based publication bias assessment, including Egger's regression, to ensure the stability of standard error–based diagnostics. This analytical distinction is explicitly reflected in the reported degrees of freedom for heterogeneity analyses and does not affect the pooled prevalence estimates. Confidence intervals for zero-event studies were not displayed in descriptive tables because they are typically extremely wide and uninformative; nevertheless, these studies were appropriately incorporated into the pooled estimates through the applied variance-stabilizing transformation.

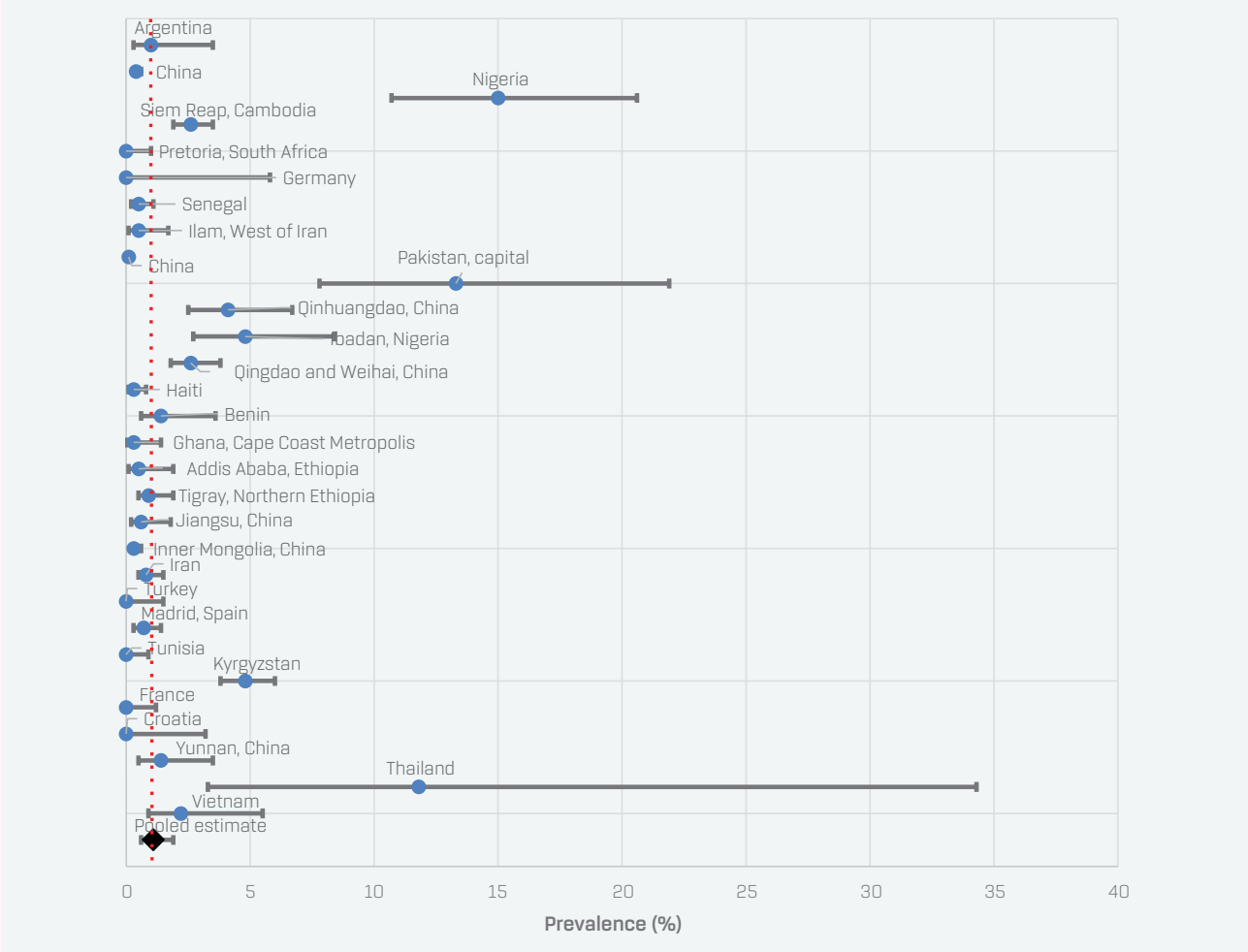

Figure 3. Forest plot of anti-HEV IgM seroprevalence among pregnant women. Individual study estimates and 95% confidence intervals are shown. Zero-event studies were included in the meta-analysis and displayed in the forest plot. The pooled seroprevalence estimate was calculated using a random-effects model with Freeman–Tukey double arcsine transformation.

All extracted prevalence data were cross-checked against the original publications to ensure consistency between reported sample sizes, numbers of seropositive cases, and calculated prevalence estimates.

Publication Bias

Visual inspection of the funnel plots did not reveal marked asymmetry for either anti-HEV IgG or anti-HEV IgM seroprevalence (fig. 4 and 5). Egger's regression test did not indicate statistically significant small-study effects for anti-HEV IgG (intercept = 2.27, p = 0.19).

For anti-HEV IgM, Egger's regression test was also non-significant (intercept = 2.94, p = 0.58). This finding should be interpreted cautiously because IgM positivity was rare and several included studies reported zero events. Consistent with the analytical approach described in the Methods, zero-event IgM studies were retained in the pooled prevalence meta-analysis and forest plot but were excluded from funnel plot visualization and Egger's regression to avoid instability in standard error–based diagnostics. Egger's test was performed using Freeman–Tukey transformed proportions and corresponding standard errors.

Given the extremely high heterogeneity observed (I^2 > 95%) and the methodological limitations of funnel plot asymmetry and Egger's regression in meta-analyses of prevalence – particularly when outcomes are rare and zero-event studies are frequent – the lack of statistically significant small-study effects in this analysis should be interpreted cautiously and cannot be considered definitive evidence against the presence of publication bias.

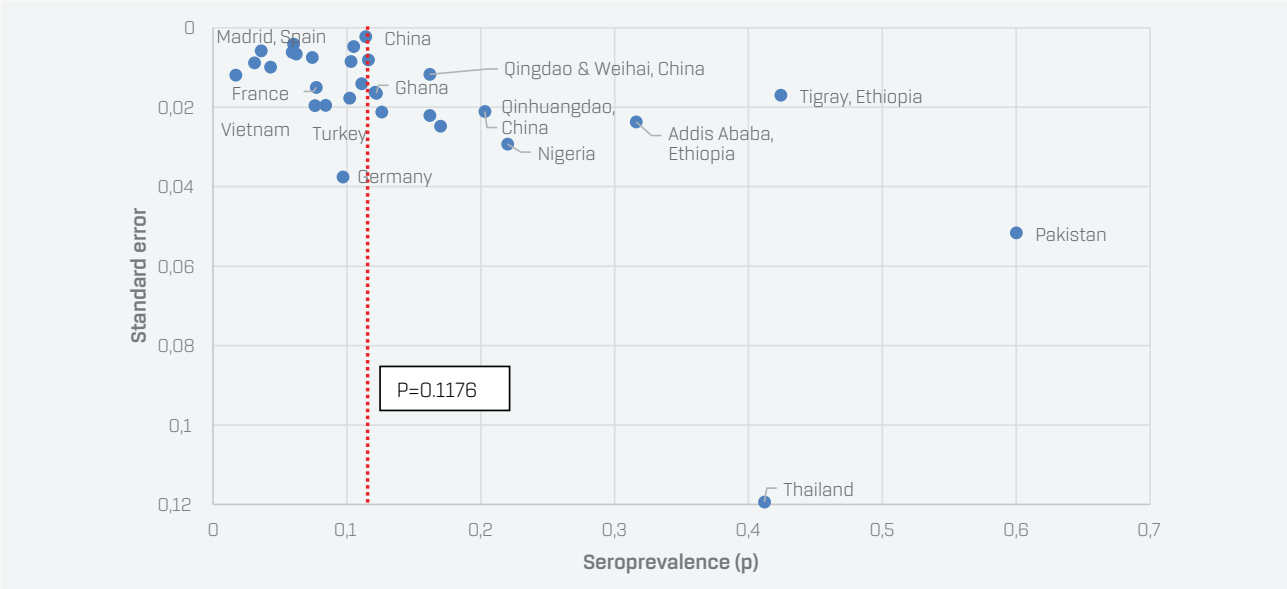

Figure 4. Funnel plot of anti-HEV IgG seroprevalence among pregnant women. Each point represents an individual study. The x-axis shows seroprevalence estimates expressed as proportions, while the y-axis represents standard errors, with smaller standard errors displayed at the top of the plot. The vertical dashed line indicates the pooled seroprevalence estimate (p = 0.1176). The distribution of studies does not suggest marked asymmetry.

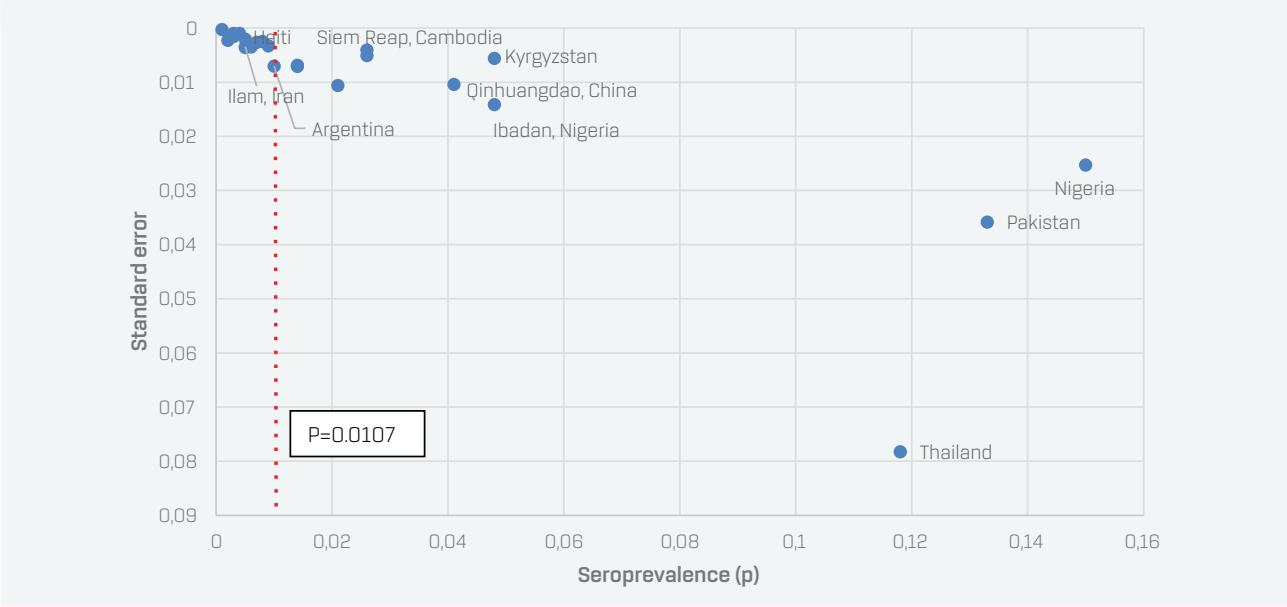

Figure 5. Funnel plot of anti-HEV IgM seroprevalence among pregnant women. Each point represents an individual study reporting non-zero IgM prevalence. The x-axis shows seroprevalence estimates expressed as proportions, while the y-axis represents standard errors, with smaller standard errors displayed at the top of the plot. The vertical dashed line indicates the pooled seroprevalence estimate (p = 0.0107). Studies reporting zero IgM events were excluded from the funnel plot to ensure the stability of standard error–based diagnostics.

DISCUSSION

In this meta-analysis, we estimated a pooled global seroprevalence of anti-HEV IgG of 11.76% and anti-HEV IgM of 1.07% among pregnant women using a random-effects model. These findings suggest that previous exposure to HEV is relatively common worldwide, whereas recent or acute infection during pregnancy is uncommon at the global level. Nevertheless, the substantial heterogeneity observed for both markers indicates pronounced regional and contextual differences in HEV epidemiology.

Comparison with Previous Evidence

Our results are broadly consistent with previous meta-analyses demonstrating wide geographic variability in HEV seroprevalence among pregnant women. For example, Ahmad et al. reported an overall IgG seroprevalence of 16.51%, with marked regional differences, ranging from low prevalence in Europe to substantially higher levels in parts of Africa and Asia (35). Similarly, Dagnew et al. reported high pooled seroprevalence among pregnant women in Africa, accompanied by considerable intra-regional heterogeneity (36). Bigna et al. further highlighted important differences between asymptomatic and symptomatic women, with substantially higher seroprevalence in clinically affected populations (37).

Compared with these earlier reports, the slightly lower pooled IgG estimate observed in our analysis may reflect methodological differences, including broader geographic coverage, stricter inclusion criteria, and exclusive use of a random-effects model. Differences in study populations, time periods, and diagnostic approaches are also likely to contribute to variability across meta-analyses (35-37).

Interpretation of Heterogeneity

The very high heterogeneity observed reflects the complex and multifactorial nature of HEV epidemiology across different settings. Variations in socioeconomic conditions, access to safe drinking water, sanitation infrastructure, dietary practices, and exposure to zoonotic reservoirs differ substantially across regions and are known determinants of HEV transmission (36,37). In addition, disparities in healthcare access and diagnostic capacity may lead to underestimation of HEV exposure in settings with limited serological screening.

Methodological factors may further contribute to heterogeneity. Differences in ELISA kits, assay sensitivity and specificity, and potential cross-reactivity with other endemic infections, such as hepatitis A virus, have been shown to influence reported seroprevalence. Dagnew et al. demonstrated that the choice of diagnostic assay alone can result in large differences in estimated HEV prevalence (36), highlighting the importance of diagnostic standardization.

Although subgroup analyses or meta-regression were considered to further explore sources of heterogeneity, these analyses were not performed due to limited and inconsistently reported covariate data across studies, as well as the risk of generating spurious or unstable findings in the context of highly heterogeneous prevalence estimates.

Clinical and Public Health Implications

Although global anti-HEV IgM seroprevalence was low in this analysis, higher IgM prevalence in specific regions suggests ongoing transmission and potential risk for adverse maternal and fetal outcomes. Previous studies have consistently shown that HEV infection during pregnancy, particularly in the second and third trimesters, is associated with severe maternal disease and poor pregnancy outcomes, including increased risks of fetal loss and maternal mortality (35-37).

The regional disparities observed in our study support the need for context-specific public health strategies, particularly in endemic and high-prevalence settings. Strengthening water, sanitation, and hygiene infrastructure, improving access to safe drinking water, and increasing awareness of HEV transmission routes may substantially reduce disease burden. In high-risk areas, integration of HEV testing into routine prenatal care may facilitate earlier detection and improve maternal management (36, 37).

Methodological Considerations and Limitations

Several limitations should be considered. First, the high heterogeneity across studies limits the interpretability of pooled prevalence estimates and reflects genuine epidemiological diversity rather than a uniform global pattern. Second, incomplete reporting and variability in diagnostic assays may have influenced seroprevalence estimates. Third, restriction to English-language publications may have led to the exclusion of relevant studies from certain regions. Finally, assessment of publication bias for IgM seroprevalence remains limited due to the rarity of the outcome and the presence of multiple zero-event studies (36, 37).

Although exploratory subgroup assessment indicated differences by geographic region and diagnostic assay, formal subgroup meta-analyses and meta-regression were not undertaken. This decision was based on incomplete reporting of key covariates, heterogeneity in study design, and small numbers of studies within several potential subgroups, which could have resulted in unstable or misleading estimates. Consequently, pooled prevalence values should be interpreted as global summaries that encompass substantial regional and methodological variation.

CONCLUSIONS

1. HEV exposure among pregnant women is widespread globally, with substantial regional variability in anti-HEV IgG seroprevalence.
2. Recent or acute HEV infection during pregnancy, reflected by anti-HEV IgM positivity, is relatively rare at the global level but remains elevated in specific high-risk regions.
3. The very high heterogeneity observed across studies highlights the influence of geographic, socioeconomic, and methodological factors on reported HEV seroprevalence estimates.
4. These findings underscore the need for region-specific surveillance strategies, improved diagnostic standardization, and targeted preventive measures to reduce HEV-related risks during pregnancy.

CONFLICT OF INTEREST

No conflict of interest to declare.

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ETHICAL APPROVAL

Ethical approval was not required for this systematic review and meta-analysis, as it was based exclusively on previously published aggregate data and did not involve the collection or analysis of individual-level patient information.

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