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Epidemiological Investigation and Assessment of HEVs in Shellfish Based on Meta-Analysis

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Abstract

Hepatitis E virus (HEV) is an acute zoonotic infectious disease that can cause hepatitis E and may even lead to death in severe cases. Porcine organisms are regarded as the natural hosts carrying hepatitis E virus, and it is also commonly found in other products. Meanwhile, shellfish are also one of the main hosts. The aim of this study was to estimate the global prevalence of hepatitis E virus in shellfish at different periods through meta-analysis. By searching three Chinese databases (CNKI.cn, Vipu, Wanfang) and two English databases (Science Direct and Web of Science), a total of 27 articles published between 2011–2024, from five databases were included. Using the random effects model for analysis, the overall prevalence of HEVs in shellfish was 3.7% (95% confidence interval: 3.3–4.1%). In terms of shellfish species, the prevalence of mussels was 4.7% (95% confidence interval: 3.9–5.5%), slightly higher than that of clams at 3.9% (95% confidence interval: 2.8–5.0%), and much higher than that of oysters at 1.7% (95% confidence interval: 1.0–2.5%). Due to the small sample size and no positive samples detected, other shellfish species do not have much reference significance. In terms of time periods, the prevalences in 2011–2012 at 15% (95% confidence interval: 11.2–19.3%) and in 2015–2016 at 16.7% (95% confidence interval: 12.0–22.1%) were much higher than those in other time periods. In terms of regions, the prevalence in Spain was the highest at 21.5% (95% confidence interval: 16.7–26.8%), while the prevalences in China and Italy had higher reliability. Regarding the genotypes of HEVs infecting humans through shellfish, HEV-3 is predominant in Europe, while HEV-4 is mainly found in Asian and African regions. By monitoring the prevalence of HEV in shellfish, the risk of people getting infected with HEV through consuming shellfish can be reduced, people's risk perception of HEV can be enhanced, and relevant suggestions for reducing the prevalence of HEV in shellfish can be provided for regulatory authorities and related aquaculture institutions. This study also has some limitations, such as the impacts of research methods, heterogeneity, and the differences between real situations and ideal conditions on the research results. However, it also provides a foundation for future studies on the distribution of HEV genotypes and the influence of different factors on hepatitis E virus in shellfish.

Keywords:
shellfish; HEVs; META analysis; prevalence; global; different time periods

1. Introduction

HEV is a member of the hepatitis virus family. Hepatitis E caused by it, is an acute zoonotic infectious disease, which is mainly transmitted through the fecal-oral route. After the infected animals excrete feces and the feces are not disposed of in a timely manner, they contaminate environmental media such as soil and water, and then directly or indirectly infect other animals and plants through the environmental media. HEVs is one of the important pathogens of viral hepatitis on a global scale. In some developing countries, about half of the acute viral hepatitis cases are related to HEV [1,2]. Usually, most of the patients are infected because they have consumed the infected plants, animals or their internal organs as well as water sources, etc. According to the investigation of the WHO, about

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20 million people are infected every year, 3.3 million people show clinical symptoms, and more than 70,000 people die from HEV infection [3]. According to the report of the Chinese Center for Disease Control and Prevention, it can be statistically concluded that about 20,000 to 30,000 people in China seek medical treatment every year due to infection with the HEVs. The report of China's notifiable infectious diseases shows that in the past decade, the reported number of cases of HEVs has exceeded that of hepatitis A virus, and its reported mortality rate has risen to the first place among the five major viral hepatitis [4]. Moreover, before 2012, about 30 people died of HEVs every year. After 2013, about 20 people die of HEV infection every year. Figures 1 and 2 show the number of people with HEV infection and the number of deaths in China from 2010 to 2023 every year.

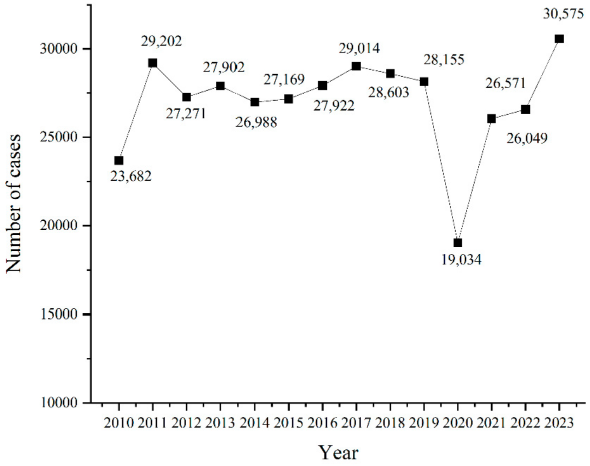


Figure 1: The number of cases of HEVs in China, 2010–2023.

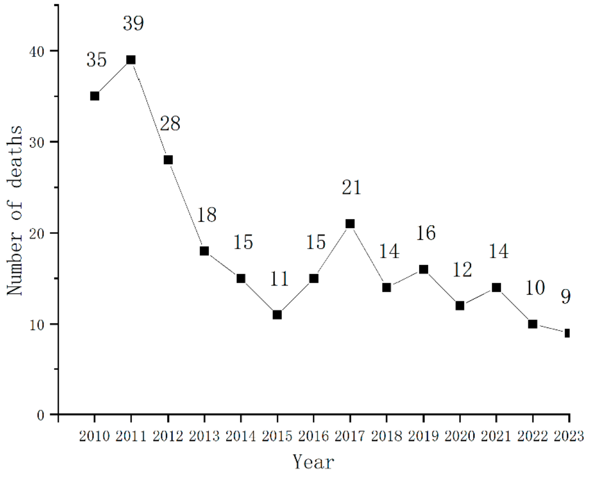


Figure 2: HEVs deaths in China, 2010–2023.

HEV has an extremely strong survival ability and can be transmitted through the most common environmental media. Nowadays, it can be detected in or on the surfaces of many animals and plants, and also in environmental water bodies.

Porcine organisms are regarded as the natural hosts carrying hepatitis E virus. A survey in the Netherlands in 2014 showed that the prevalence of anti-HEV antibodies was 89.0% in 417 organic pigs, 72% in 265 conventionally farmed pigs, and 76% in 164 free-range pigs [5]. In 2017, among 115 slaughtered pigs in Hebei, the prevalence of HEV antibody sera was 90.4% [6]. Crossan et al. collected shellfish near slaughterhouses and pork processing plants respectively and conducted tests. The detection rates of HEV RNA were 92% and 55% respectively. Gene sequence analysis showed that all samples belonged to HEV-3, similar to the HEV sequences isolated from local pigs and humans. This suggests that HEV-3 might be transmitted through water sources and shellfish contaminated by human excreta [7]. The runoff sewage from farms or slaughterhouses may cause HEV to contaminate river channels. Bivalve shellfish are filter-feeding organisms, and they can accumulate and concentrate pathogens in the environment within their tissues, which increases the risk of HEV transmission by aquatic animals such as bivalve shellfish [8]. After pigs are infected with HEV during the farming process, their untreated excreted feces will contaminate nearby water sources and the ocean, and then infect other animals and plants. Therefore, HEV mostly exists in the water sources, animals and plants around the infected pig farms. Shellfish, as one of the most common marine organisms, is known as the "marine purifier". It grows by filtering tiny organisms or influencing substances in the ocean, and inevitably filters contaminated water bodies during the process, thus getting infected with HEV. The latest research shows that hepatitis E has been recorded as a foodborne disease related to the consumption of shellfish [9,10]. In recent years, the catches and farming volumes of shellfish in countries around the world have been on the rise continuously. Just in China, in 2022, the total farming volume of domestic shellfish in China was as high as 1588.26 tons [11]. Shellfish has long become a delicacy on the dining table, and people in coastal areas take shellfish as one of the main consumer foods. Once people eat shellfish infected with HEV, it is likely to cause a series of diseases, and in severe cases, it may even lead to death.

The clinical manifestations of HEV infection are similar to those of hepatitis A and hepatitis B. It can cause great harm to pregnant women, with the risks of miscarriage, fetal or maternal death. The mortality rate in pregnant women is as high as 25% [12]. After the elderly are infected, it can cause fulminant liver failure and a series of hepatitis E complications, such as renal failure, acute pancreatitis, neurogenic muscular atrophy and encephalitic nerve syndromes [13]. This article collected, analyzed and integrated the data from the literatures on the infection of HEVs in shellfish in various countries. This article aims to evaluate the prevalence of hepatitis E virus (HEV) in shellfish in different countries and periods through meta-analysis. Through the investigation and analysis of the prevalence of hepatitis E virus in shellfish among different shellfish species, different periods and different geographical locations, it provides reference standards for relevant testing departments to control hepatitis E virus infection in shellfish. The research shows that in terms of species, the comprehensive prevalence rate of HEVs in clams and mussels is slightly higher than that in oysters and other shellfish of unknown species. In terms of time, the comprehensive prevalence rate during 2011–2012 and 2015–2016 is much higher than that in the remaining time periods. Further, in terms of geographical location, the infection situation of HEVs in shellfish in Vietnam, the UK and Spain is more serious than that in other countries.

2. Materials and Methods

2.1. Article Search Strategy, Eligibility and Inclusion

This study followed the PRISMA guidelines to search for and collect relevant literature for meta-analysis. The search scope included two English databases (ScienceDirect and Web of Science) and three Chinese databases: China National Knowledge Infrastructure (www.cnki.net, accessed on 15 October 2024), Wanfang Data Knowledge Service Platform (www.wanfangdate.net, accessed on 15 October 2024), and VIP Database (http://qikan.cqvip.com/, accessed on 15 October 2024). The time range included relevant articles from 2010 to 2024. The search keywords for the two English databases were: [(HEV) OR (HEVs)] AND [(shellfish) OR (oyster) OR (mussels) OR (clam)] AND (2010:2024). The search keywords for the three Chinese databases were: (HEV) AND [(shellfish) OR (oyster) OR (mussels) OR (clam)] AND (2010:2024).

The retrieved articles were read, and those with duplicate records were screened out. An article was considered to meet the requirements of this study, if it presented the following research: (I) Relevant investigations such as contamination rates and positive rates were included in the article; (II) There was qualitative or quantitative analysis related to HEV; (III) Different types of shellfish were clearly identified; (IV) The total number of samples exceeded 25; (V) Whether the sampling locations were random. The above principles should be strictly followed during the relevant search.

During the search process, it was found that the relevant literature on HEVs in shellfish was very scarce, resulting in a limited number of available studies. After reading this part of the literature, it was found that, except for a few review articles, most of the research articles had accurate qualitative or quantitative detection data. Therefore, the research data of most articles could be used. The whole search process is shown in Figure 3. After searching for relevant keywords in five databases, a total of 361 relevant records were displayed. After the first round of eliminating duplicate entries, only 77 records remained. Then, after reading the titles and abstracts of the literature, 146 irrelevant articles were excluded. After that, by reading the full texts, review articles, articles with incorrect/ambiguous results, articles with the number of samples not meeting the inclusion criteria, and articles without qualitative or quantitative detection were excluded, leaving only 43 records. Ultimately, 27 articles were selected for inclusion in this meta-analysis. A total of 5052 shellfish biological samples were extracted from these 27 research articles, and 186 positive samples were detected.

After extracting the data of the 27 included relevant studies, the following five aspects of relevant reviews were carried out on these 27 relevant research articles: (1) Whether the selected samples were completely random; (2) Whether the researchers were professional researchers; (3) Whether the relevant data in the articles were accurate; (4) Whether there was a situation of selectively reporting part of the data in the article; (5) Whether there were other influencing factors. On the basis of the research articles, the potential biases are summarized in Figure 4. The yellow items ? indicate uncertainty or unclearness, the green items + indicate low risk or affirmation, and the red items ● indicate high risk or negation. The data shown in the figure can indicate that the included literature is basically available. The data provided in the vast majority of articles are to a certain extent clear and accurate, avoiding large biases in the analysis process. The relevant researchers who participated in the publication of the articles also have relevant professional knowledge and sufficient research experience, making the data presented in the articles more credible. In terms of data, most of the literature provided specific data and had detailed relevant detection methods to prove their research and experimental methods. The above points greatly enhance the credibility of this study.

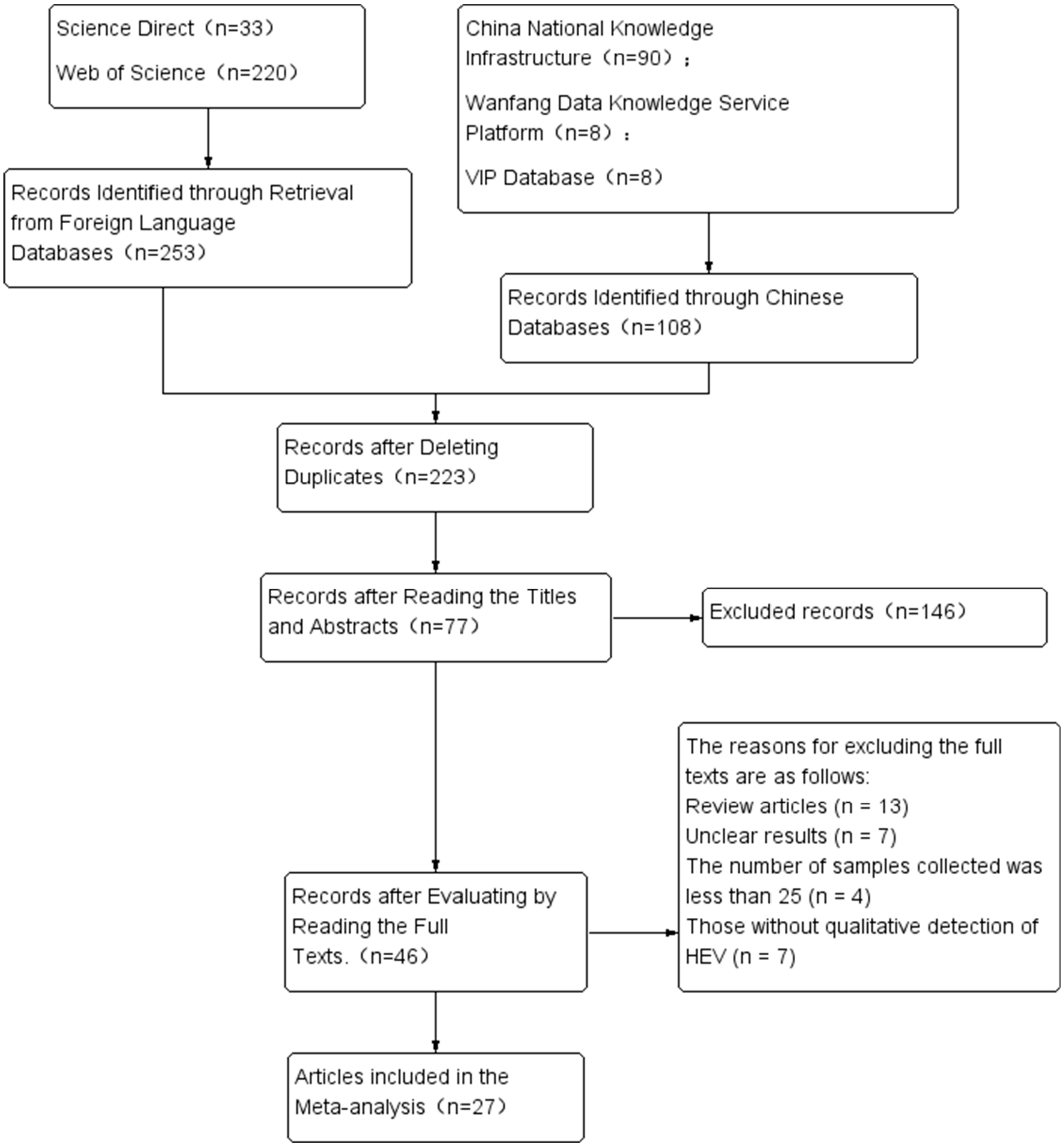


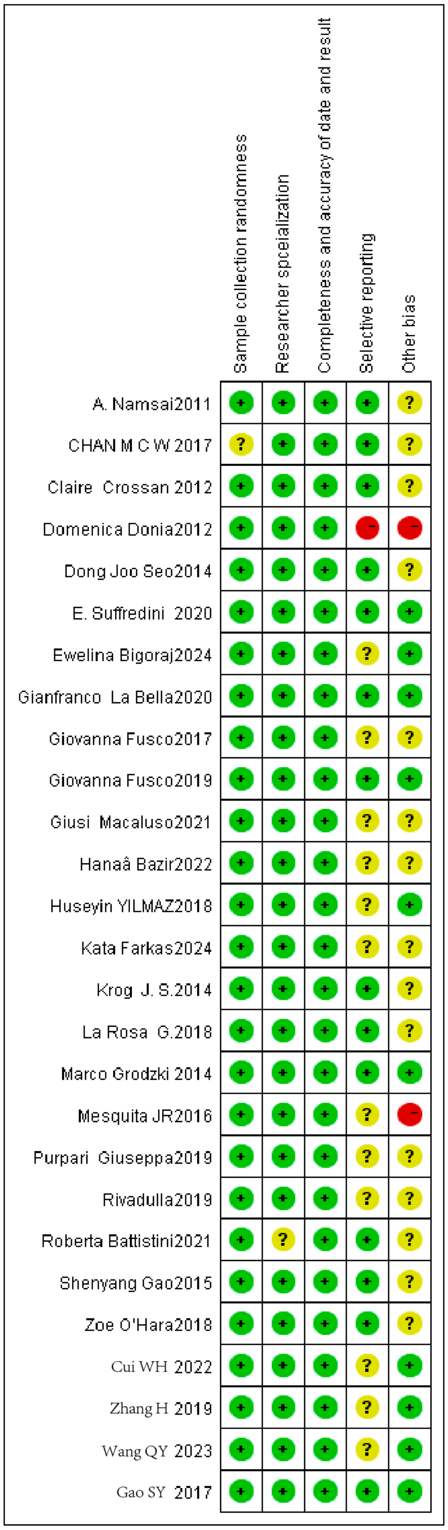
Figure 3: Prisma Flow Chart for Document collection and screening.

2.2. Data Extraction

After carefully reading and selecting the relevant literature, the following data were extracted from the articles: the species of shellfish samples, sampling methods, research years, the number of collected samples, the number of positive samples, and the geographical location of the sampling area. After extraction, the data were entered into Microsoft Excel and formatted in Microsoft Excel before further analysis was carried out.

2.3. Data Analysis

Commonly used Meta-analysis software includes R language, Stata and Review Manager. Compared with R language and Stata, Review Manager focuses more on systematic reviews and meta-analysis. Moreover, this software incorporates a large number of methods and effect models related to meta-analysis and systematic reviews, such as the fixed-effect model, random-effects model, and forest plot drawing. It can display research results and data characteristics in an intuitive manner. Additionally, this software is more user-friendly than R and Stata, making it particularly accessible for beginners and facilitating more convenient data calculations. Therefore, the Review Manager 5.4 version is chosen for relevant data analysis.



	Sample collection randomness	Researcher spceialization	Completeness and accuracy of date and result	Selective reporting	Other bias
A. Namsai2011	+	+	+	+	?
CHAN M C W 2017	?	+	+	+	?
Claire Crossan 2012	+	+	+	+	?
Domenica Donia2012	+	+	+	−	−
Dong Joo Seo2014	+	+	+	+	?
E. Suffredini 2020	+	+	+	+	+
Ewelina Bigoraj2024	+	+	+	?	+
Gianfranco La Bella2020	+	+	+	+	+
Giovanna Fusco2017	+	+	+	?	?
Giovanna Fusco2019	+	+	+	+	+
Giusi Macaluso2021	+	+	+	?	?
Hanaâ Bazir2022	+	+	+	?	?
Huseyin YILMAZ2018	+	+	+	?	+
Kata Farkas2024	+	+	+	?	?
Krog J. S.2014	+	+	+	+	?
La Rosa G.2018	+	+	+	+	?
Marco Grodzki 2014	+	+	+	+	+
Mesquita JR2016	+	+	+	?	−
Purpari Giuseppa2019	+	+	+	?	?
Rivadulla2019	+	+	+	?	?
Roberta Battistini2021	+	?	+	+	?
Shenyang Gao2015	+	+	+	+	?
Zoe O'Hara2018	+	+	+	+	?
Cui WH 2022	+	+	+	?	+
Zhang H 2019	+	+	+	?	+
Wang QY 2023	+	+	+	?	+
Gao SY 2017	+	+	+	+	+

Figure 4: Summary of risk bias in the included literature [7,10,14–38].

Meta-analysis was conducted on the included literature using Review Manager 5.4. Quantitative data were analyzed using the random effects model. Based on the sampling areas, sampling environments, positive rates, and years of research publication in various countries, the prevalence of HEVs in shellfish in different time periods or countries was analyzed by subgroups. Heterogeneity was evaluated by Cochran's Q test [39], and the level of inconsistency was evaluated by Higgins and Thompson's I^2 test [40]. Funnel plots and Egger's test were used to evaluate possible publication bias ($p < 0.05$ was considered an indication of statistically significant publication bias).

3. Results Analysis

3.1. Literature Selection and Data Characteristics

The development process of China's laws and regulations regarding HEVs is shown in Figure 5. In 1997, the diagnostic criteria for Hepatitis E were promulgated for the first time, which was the first diagnostic criteria related to Hepatitis E in China [41]. Then, in 2008, the first version of the diagnostic criteria was revised and improved, and the second version of the diagnostic criteria for Hepatitis E was promulgated [42]. In 2011, the RT-nPCR and ELISA detection methods for animal Hepatitis E were promulgated, which was the first formal promulgation of the method for detecting HEVs in animals [43]. In 2014, two methods for detecting hepatitis E virus (HEV) in domestic animals were promulgated: the RT-PCR method for the determination of HEVs in pigs, cattle, and sheep [44], and the nested reverse transcription polymerase chain reaction method for the detection of HEVs in domestic animals [45]. However, the relevant limit standard for HEVs in food promulgated by China has not been found. Therefore, the laws and regulations regarding the detection of HEVs still need to be improved.

3.2. Distribution of Different Genotypes of HEV

There are eight genotypes of HEV, among which HEV 1 to HEV 4 can infect humans. In developing countries with poor sanitary conditions, HEV is mainly transmitted through water sources, whereas, in industrialized countries, HEV is mostly transmitted through food sources [46]. Gao Shenyang et al. [47] found that 13 kinds of HEV gene sequences were isolated from shellfish samples collected in the estuary and coastal areas of China, all of which belonged to HEV 4 type. HEV 1 and HEV 2 can only infect humans, and these two genotypes mainly appear in

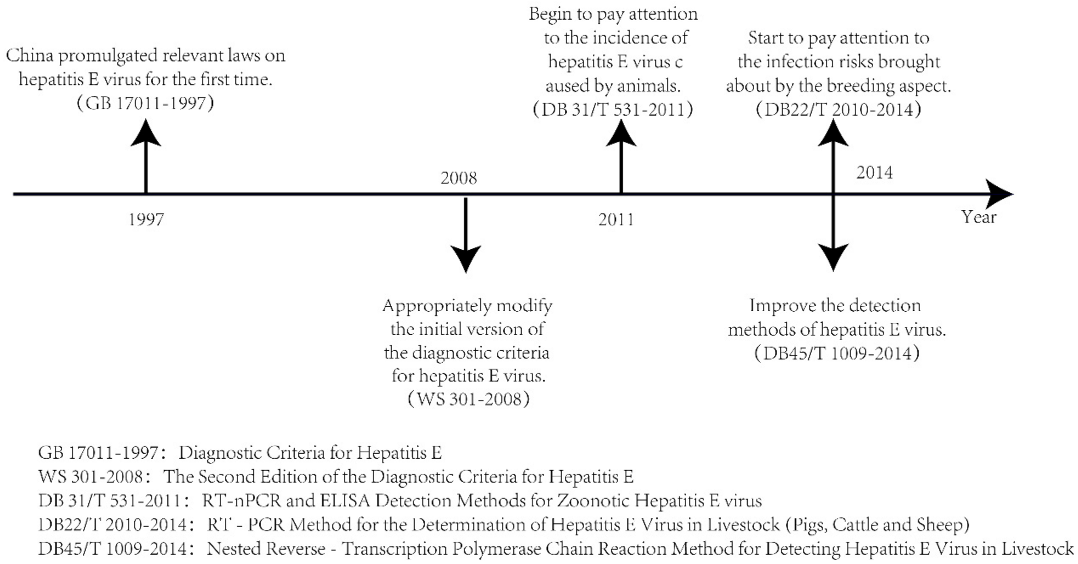


Figure 5: HEVs testing standards and development timeline in China.

some areas with poor sanitary conditions in the Middle East, Africa, and South America. At the same time, there will also be some cases of infection by HEV 4 type. In these areas, the most important reason for the outbreak of hepatitis E infectious diseases is water pollution, which will lead to occasional large-scale infection events. HEV 3 type and HEV 4 type are zoonotic types, mainly existing in industrialized countries [48]. The approximate distribution of different genotypes of HEVs around the world is shown in Figure 6.

3.3. Prevalence Probability of HEVs in Different Species of Shellfish

A total of 5052 shellfish samples were included in this study. All the samples included in the literature were divided into four major categories: oysters, mussels, clams, and others. Table 1 shows the total number of the four types of shellfish in the included literature as well as the comparison of positive rates and prevalences. The comprehensive prevalence in the table was calculated using the RiskBert function in @risk software. RiskBert is an optimized formula of the Bert function, mainly used for handling risk assessment and other tasks, and is more suitable for calculating prevalence problems than other functions. It can be seen from the table that the most mussel samples were used in the study, accounting for 52.4% of the total sample number. At the same time, the detected positive samples also accounted for 66.1% of the total positive samples, and the comprehensive prevalence was also the highest among the major types. After calculation, the comprehensive prevalence of oysters was relatively lower than that of other types of samples. The sample sizes of other types of shellfish were small, and the confidence intervals fluctuated greatly. The prevalence of HEV in the total shellfish was 3.7%, with a 95% confidence interval of (3.2–4.2%). Based on the content in the Table 2, it can be concluded that the order of the prevalence of HEV in the major shellfish is mussels > clams > oysters. The sample sizes of other types of shellfish are too small, and the calculated confidence intervals span a large range, so they are not suitable for relevant comparisons.

3.4. Prevalence Probability of HEVs in Shellfish at Different Time Periods

All the research literatures included in this study are within the range of 2011–2024. The period from 2011 to 2024 was divided into seven segments, with each segment covering a period of two years. The literatures within each time segment were summarized; for example, 2011–2012, 2013–2014, and so on. After summarization, the overall prevalence level of HEVs detected in shellfish within each time segment was calculated, resulting in Figure 7 and Table 3. As shown in Figure 7, the larger the arc occupied by a certain time segment in the figure, the more samples were used to study the HEVs-carrying situation in shellfish within that time segment, indicating a higher credibility of the detected prevalence rate. The farther the arc representing a certain time segment is from the center of the circle in the figure, the higher the prevalence rate of that time segment, and the greater the risk of being infected with HEVs by consuming shellfish during that period. Table 3 shows the total number of all research

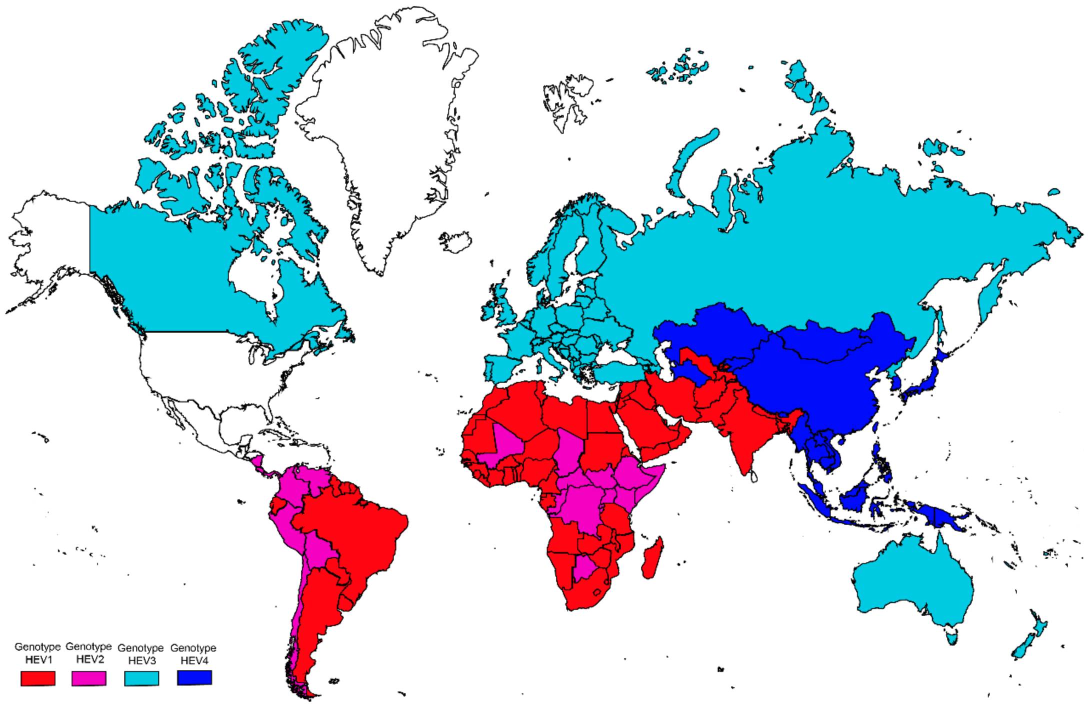


Figure 6: Global distribution of four HEV genotypes.

shellfish objects in the included literatures within that time segment, as well as the number of positives, comprehensive prevalence rate, and 95% confidence interval within that time segment. From the data in the figure and the table, it can be observed that the comprehensive prevalence rates of HEVs in the two-time segments of 2011–2012 and 2015–2016 are much higher than those in other time segments. Further, in the subsequent several time segments, the comprehensive prevalence rate of HEVs in shellfish has decreased significantly and stabilized at a relatively low level (around 1–5%).

3.5. Prevalence Probability of HEVs in Shellfish from Different Countries

The countries to which the included research literatures belong were classified, and Table 4 was summarized. Most of the included research literatures were from Southeast Asia and Europe, and a small part were from Africa or the Middle East. By observing the data in the table, it can be seen that the prevalence rate in Spain was much higher than that in other countries. Among the 27 included research literatures, 2 were from Spain, which were published in 2016 and 2019 respectively. Twelve and forty-one samples out of 81 and 168 shellfish samples were detected to carry HEVs. The sampling time of both literatures was as long as 18 months, and the long sampling time, on the other hand, reduced the possibility of errors caused by multiple or repeated samplings within a relatively short period of time. It can be indicated that the shellfish in Spain were seriously polluted by HEVs. Besides Spain, the pollution levels in the United Kingdom and Vietnam were also relatively high, reaching more than 10%. The pollution levels in other countries were relatively low. In certain countries, such as Denmark, Turkey, and Morocco, the limited number of samples included in the research diminishes their value as reliable references for estimating the prevalence of HEV in shellfish over extended periods within their territories. For some countries, such as China and Italy, the number of research objects included was sufficient and the sampling and research times were different, so the prevalence rates calculated basically could represent the prevalence rate of HEVs in shellfish in these countries in recent years. Although the detection rate of HEV in shellfish is usually low at present, it has been confirmed by previous research that HEV has biological accumulation in shellfish [28].

Based on the research data of the literatures included in this study, it can be seen that the prevalence rate of HEVs in shellfish in most Asian countries is lower than that in most European countries. The main reason may be that most European countries started the development and utilization of the ocean earlier than Asian countries, which led to the pollution of the water sources near the

Table 1: The types and quantities of samples included in each article as well as the countries where they are located.

	Oyster	Mussel	Clam	Others	Total	Sampling Position
A. Namsai 2011	52	92	69	0	213	Thailand
CHAN M C W 2017	479	0	0	0	479	China
Claire Crossan 2012	0	48	0	0	48	Britain
Domenica Donia 2012	0	37	0	0	37	Italy
Dong Joo Seo 2014	51	50	51	0	152	Korea
E. Suffredini 2020	63	0	58	0	121	Vietnam
Ewelina Bigoraj 2024	0	246	0	0	246	Poland
Gianfranco La Bella 2020	32	182	0	11	225	Italy
Giovanna Fusco 2017	0	108	0	0	108	Italy
Giovanna Fusco 2019	0	280	9	0	289	Italy
Giusi Macaluso 2021	14	124	0	24	162	Italy
Hanaâ Bazir 2022	0	52	0	0	52	Morocco
Huseyin YILMAZ 2018	0	92	0	0	92	Turkey
Kata Farkas 2024	150	114	0	0	264	Britain
Krog J. S. 2014	0	29	0	0	29	Denmark
La Rosa Contact G. 2018	0	384	0	0	384	Italy
Marco Grodzki 2014	73	94	119	0	286	France
Mesquita JR 2016	0	81	0	0	81	Spain
Purpari Giuseppa 2019	2	90	2	14	108	Italy
Rivadulla 2019	0	105	63	0	168	Spain
Roberta Battistini 2021	0	20	0	0	20	Italy
Shenyang Gao 2015	0	0	126	0	126	China
Zoe O'Hara 2018	40	270	0	0	310	Britain
WH C 2022	11	48	87	5	151	China
SH Gao 2017	0	0	315	0	315	China
QY Wang 2023	120	0	0	0	120	China
H Zhang 2019	103	101	262	0	466	China

Table 2: Analysis of the comprehensive prevalence of HEVs in different types of shellfish organisms.

	The Total Number of Research Objects Included in the Study	Number of Positives	Comprehensive Prevalence Rate (95%CI)
shellfish	1190	19	1.7% (1.0–2.5%)
oyster	2647	123	4.7% (3.9–5.5%)
mussels	1161	44	3.9% (2.8–5.0%)
Others	54	0	1.8% (0–6.5%)

Table 3: The total number of studies, positives and prevalence of the included literature in each time period from 2011 to 2024.

Time Period	The Total Number of Research Objects Included in the Study	Number of Positives	Comprehensive Prevalence Rate (95%CI)
2011–2012	298	44	15% (11.2–19.3%)
2013–2014	467	0	0.2% (0–0.9%)
2015–2016	207	34	16.7% (12.0–22.1%)
2017–2018	1,688	25	1.5% (1–2.3%)
2019–2020	1,377	63	4.6% (3.6–5.9%)
2021–2022	385	6	1.8% (0.7–3.5%)
2023–2024	630	14	2.4% (1.3–3.8%)

ocean and, in turn, the pollution of the shellfish living in the ocean.

A funnel plot is a graphical tool commonly used in meta-analyses to assess the potential risk of bias. The points in the plot are asymmetrically distributed, as shown in Figure 8. Each circle in the figure represents a study in the meta-analysis. The dotted line represents the 95% confidence interval. The X-axis represents the prevalence rate of positive samples calculated in the research literature, and the Y-axis represents the standard error of the article. In the absence of publication bias, the closer the point is to the top, the larger the sample size it selects, and the more accurate the research result is. On the contrary, the lower the research is, the greater the deviation from the overall experimental result, thus forming an inverted funnel shape. The studies should be approximately symmetrically distributed in the entire funnel area. From the funnel plot of this study, it can be seen that there is a certain asymmetry, and most of the points can be verified by the Egger test result ($p < 0.000001$). Combined with the Egger test result, it is known that this study has some publication bias. This may be closely related to the scale of the samples included in the study and the study years, resulting in differences in sample data and impacting the study. In order to avoid the mutual influence of publication bias caused by the mixture of non-Chinese and non-English articles, these two types of studies were differentiated and discussed independently. However, due to the fact that too few non-English articles were included, it was impossible to conduct an assessment of publication bias. Only the publication bias of non-Chinese articles could be evaluated, and Figure 9 was obtained. Compared with Figure 8, the pooled effect size represented by the central blue dotted line shifted slightly to the right along the X-axis, indicating that the degree of association among the various studies was strengthened.

All the included literatures were integrated and analyzed in detail to construct a forest plot, as shown in were adopted to facilitate the statistical characterization of each data. The forest plot is used to describe the effect size and confidence interval of each included study [40]. In the Cartesian coordinate system, with a vertical null line (the abscissa scale is 0 or 1) as the center, multiple line segments parallel to the horizontal axis are used to represent multiple research objects, and a rhombus (or other figure) is used to depict the combined effect size and confidence interval of multiple studies [49]. The point in the center of the line segment represents the weight of this literature among all the literatures. The larger the point, the greater the contribution of this article to the whole META analysis. In this study, the Risk Ratio (RR) under the random effects model was adopted. The rhombus representing the total effect size did not intersect with the null line (the abscissa scale is 1). RR < 1 indicates that under certain intervention conditions, the prevalence level of hepatitis E in shellfish can be reduced. By comparing Figure 10 with

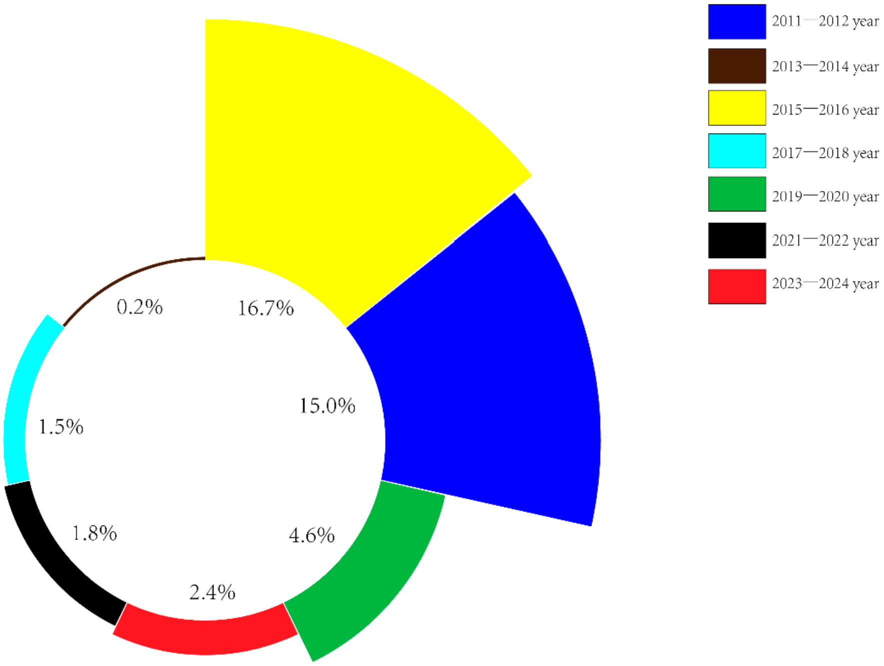


Figure 7: Prevalence of HEVs in shellfish, 2011–2024.

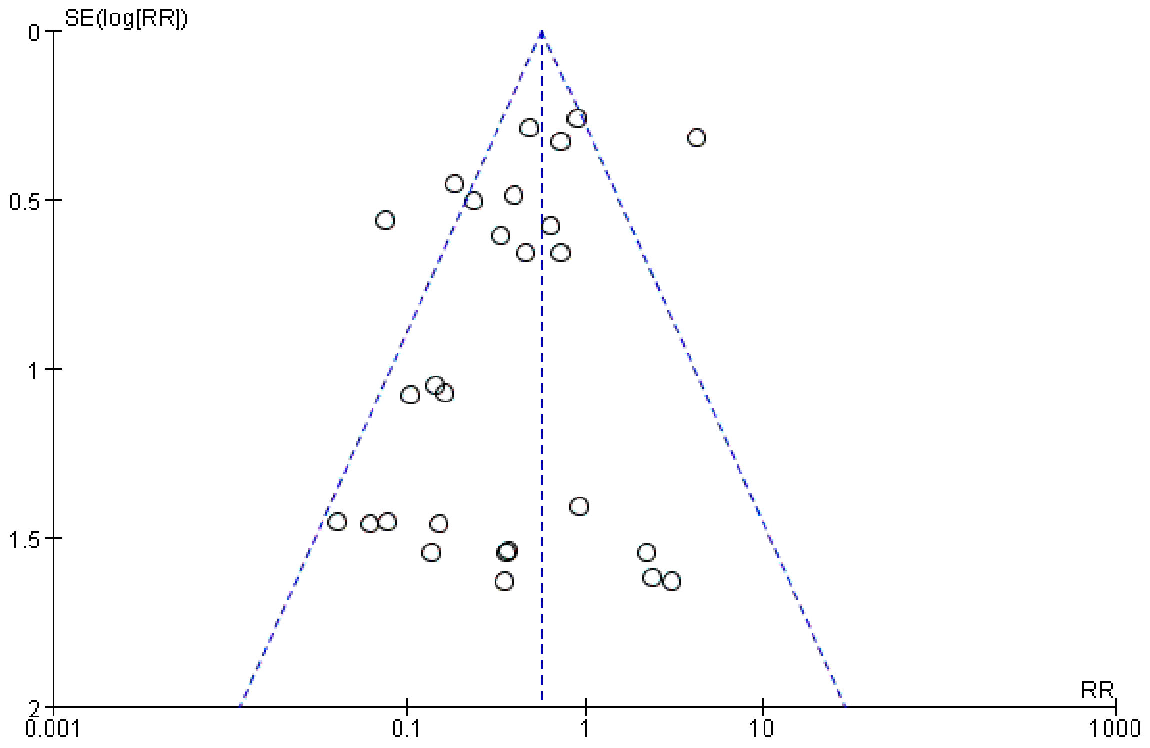


Figure 8: Publication biased funnel plot of HEVs prevalence in shellfish in all studies

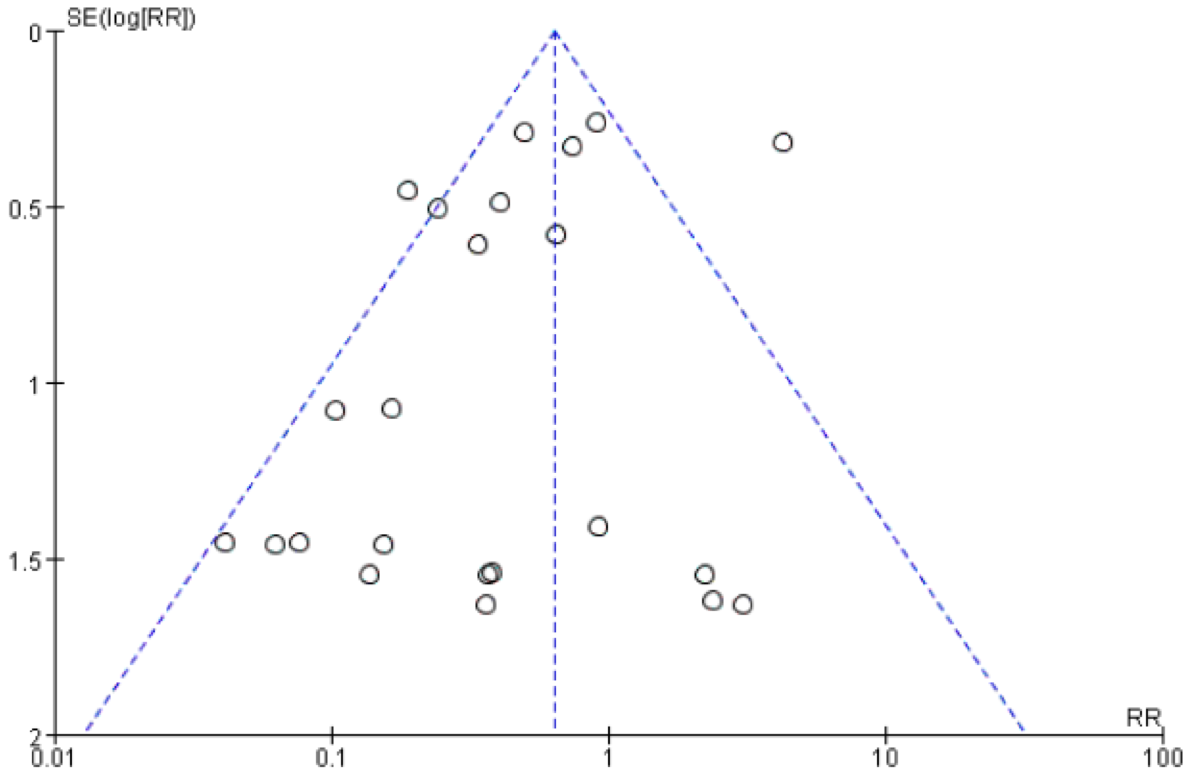


Figure 9: Funnel plot for publication bias of the prevalence of hepatitis E virus in shellfish in non-Chinese studies. **Note: SE (log (RR)):** Standard Error of the Logarithm of the Relative Risk. **RR:** Relative Risk.

Table 4: Prevalence of HEVs in shellfish by country worldwide.

	The Total Number of Research Objects Included in the Study	Number of Positives	Comprehensive Prevalence Rate (95%CI)	Continent of Affiliation
Thailand	213	0	0.5% (0–1.7%)	Asia
China	1,657	39	2.4% (1.7–3.2%)	Asia
Vietnam	121	14	12.2% (7.0–18.5%)	Asia
United Kingdom	622	62	10.1% (7.9–12.6%)	Europe
Italy	1,333	17	1.3% (0.8–2.0%)	Europe
Spain	249	53	21.5% (16.7–26.8%)	Europe
Turkey	92	0	1.0% (0–3.9%)	Asia
Morocco	52	0	1.9% (0–6.7%)	Africa
South Korea	152	0	0.6% (0–2.4%)	Asia
France	286	0	0.3% (0–1.3%)	Europe
Denmark	29	0	3.2% (0–11.6%)	Europe
Poland	246	1	0.8% (0.1–2.2%)	Europe

Figure 11, it was found that the heterogeneity among the various studies had decreased to a certain extent, but there was still some publication bias.

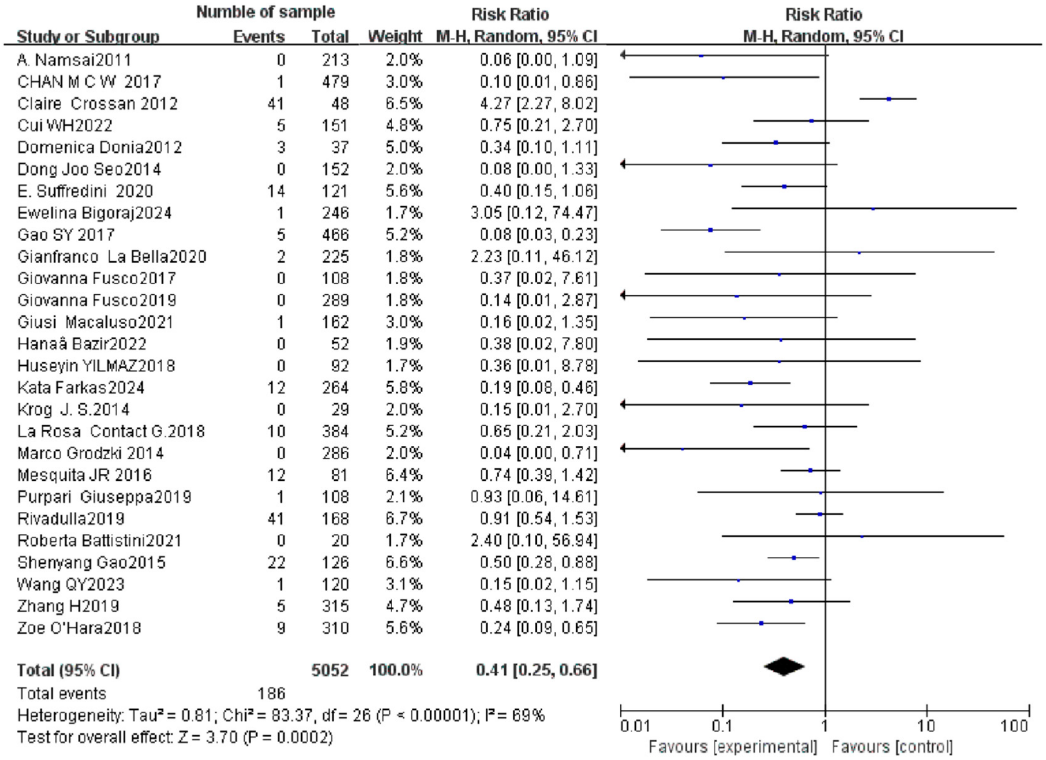
4. Discussion & Conclusions

The main reason for shellfish being infected with HEV is that during the process of absorbing substances from the surrounding environment, they take in water sources or nutrients carrying HEV into their bodies and become infected with HEV after digestion and absorption. However, no research has shown that HEV has a special impact on shellfish. Therefore, it can be considered that shellfish only play the role of a transmitter or transporter in the whole transmission process. In nature, there are many kinds of shellfish, and the common shellfish mainly include oysters, clams, mussels, etc. Therefore, the research objects of relevant studies are also mainly these common shellfish. Due to the lack of research on relatively rare shellfish species, such as giant clams and hairy clams, relevant literature is unavailable. Consequently, these species are not included in this analysis.

Shellfish is one of the most common marine products for daily consumption. It is rich in protein, vitamins, and various fatty acids, which can enhance the immune function of the human body and this makes it very popular among people. In recent years, its consumption and cultivation have been in a state of rapid growth. Along with this comes the safety issue of shellfish. Research has shown that in 2013, a follow-up survey of 122 cases of acute hepatitis E was completed to investigate the suspected risk factors exposed during the incubation period of hepatitis E. It was found that the consumption of marine products accounted for 50% [50]. At present, there have been no large-scale hepatitis E infection events caused by the consumption of infected shellfish. This is also closely related to the detection standards formulated by the World Health Organization and various countries, which can prevent the polluted shellfish from entering the market in advance. This study mainly focuses on the prevalence rate of shellfish in various countries and conducts subgroup and meta-analyses. This is beneficial for each country to evaluate the pollution situation of shellfish within its own country, discover the relevant hazard risks as early as possible, and prepare in advance to face the risks. However, it is far from enough to only investigate the prevalence rate of each country. Each country should attach importance to the research and investigation of shellfish, subdivide the pollution situation of various shellfish product types and cultivation locations, so as to provide more detailed information for exposure risk assessment.

As early as 2014, Grodzki M et al. [10] compared the accumulation efficiencies of four different species of shellfish in France with regard to hepatitis E virus (HEV), demonstrating that shellfish can accumulate HEV in the environment. They also analyzed the possibility of shellfish being affected by the feces of porcine organisms and conducted sampling and testing in contaminated areas as much as possible. However, they did not find any shellfish samples infected with HEV. Nevertheless, shellfish with HEV antibody vaccines were found in other regions of Europe, which provided a certain foundation for subsequent studies on the enrichment and transmission of hepatitis E virus in shellfish.

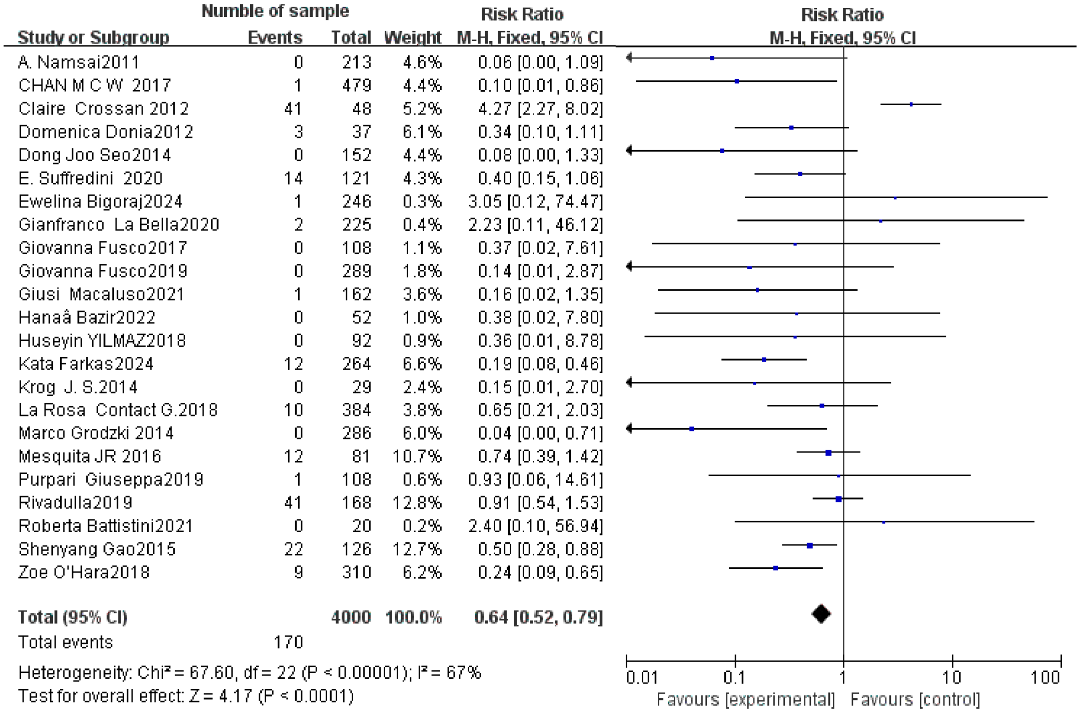
In this study, subgroup analysis was conducted by using the random effects model and RR, and meta-analysis was carried out with Review Manager version 5.4. The comprehensive prevalence rate of HEVs (HEV) in shell-



Study or Subgroup	Numble of sample Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
A. Namsai2011	0	213	2.0%	0.06 [0.00, 1.09]
CHAN M C W 2017	1	479	3.0%	0.10 [0.01, 0.86]
Claire Crossan 2012	41	48	6.5%	4.27 [2.27, 8.02]
Cui WH2022	5	151	4.8%	0.75 [0.21, 2.70]
Domenica Donia2012	3	37	5.0%	0.34 [0.10, 1.11]
Dong Joo Seo2014	0	152	2.0%	0.08 [0.00, 1.33]
E. Suffredini 2020	14	121	5.6%	0.40 [0.15, 1.06]
Ewelina Bigoraj2024	1	246	1.7%	3.05 [0.12, 74.47]
Gao SY 2017	5	466	5.2%	0.08 [0.03, 0.23]
Gianfranco La Bella2020	2	225	1.8%	2.23 [0.11, 46.12]
Giovanna Fusco2017	0	108	1.8%	0.37 [0.02, 7.61]
Giovanna Fusco2019	0	289	1.8%	0.14 [0.01, 2.87]
Giusi Macaluso2021	1	162	3.0%	0.16 [0.02, 1.35]
Hanaâ Bazir2022	0	52	1.9%	0.38 [0.02, 7.80]
Huseyin YILMAZ2018	0	92	1.7%	0.36 [0.01, 8.78]
Kata Farkas2024	12	264	5.8%	0.19 [0.08, 0.46]
Krog J. S.2014	0	29	2.0%	0.15 [0.01, 2.70]
La Rosa Contact G.2018	10	384	5.2%	0.65 [0.21, 2.03]
Marco Grodzki 2014	0	286	2.0%	0.04 [0.00, 0.71]
Mesquita JR 2016	12	81	6.4%	0.74 [0.39, 1.42]
Purpari Giuseppa2019	1	108	2.1%	0.93 [0.06, 14.61]
Rivadulla2019	41	168	6.7%	0.91 [0.54, 1.53]
Roberta Battistini2021	0	20	1.7%	2.40 [0.10, 56.94]
Shenyang Gao2015	22	126	6.6%	0.50 [0.28, 0.88]
Wang QY2023	1	120	3.1%	0.15 [0.02, 1.15]
Zhang H2019	5	315	4.7%	0.48 [0.13, 1.74]
Zoe O'Hara2018	9	310	5.6%	0.24 [0.09, 0.65]
Total (95% CI)		**5052**	**100.0%**	**0.41 [0.25, 0.66]**
Total events	186			

Heterogeneity: Tau² = 0.81; Chi² = 83.37, df = 26 (P < 0.00001); I² = 69%
Test for overall effect: Z = 3.70 (P = 0.0002)

Figure 10: Forest map of HEVs prevalence in shellfish in all studies



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Shenyang Gao2015	22	126	12.7%	0.50 [0.28, 0.88]
Zoe O'Hara2018	9	310	6.2%	0.24 [0.09, 0.65]
Total (95% CI)		**4000**	**100.0%**	**0.64 [0.52, 0.79]**
Total events	170			

Heterogeneity: Chi² = 67.60, df = 22 (P < 0.00001); I² = 67%
Test for overall effect: Z = 4.17 (P < 0.0001)

Figure 11: Forest map of HEVs prevalence in shellfish in non-Chinese studies. **Note: Tau^2**: The degree of dispersion of the effect sizes of different studies around the overall average effect size. **Chi^2**: Determine whether there is significant heterogeneity among different studies. **df**: The number of variables that can be freely valued when calculating statistics. **I^2**: Statistical measures for assessing the degree of heterogeneity among studies.

fish from 2011 to 2024 was obtained as 3.7% (95%CI: 3.3–4.1%). Between 2011–2012 and 2015–2016, the prevalence of Hepatitis E was notably higher compared to other periods, followed by a steady decline. This pattern suggests that specific factors during those peak years may have contributed to the intensified spread of the Hepatitis E virus (HEV). Subsequently, the observed decrease in prevalence could be attributed to the implementation of effective prevention and control measures or other influencing factors. From the perspective of countries, the pollution level of shellfish in Spain was the most serious, and the pollution levels of shellfish in China and Italy were more credible compared to those in other countries. The main genotype of HEV in the European region is HEV 3 type, the main genotype in the Middle East and Africa regions is HEV 1 type, while in Southeast Asia and East Asia regions it is HEV 4 type. This indicates that the genotypes of hepatitis E virus (HEV) are closely related to geographical factors and are affected by multiple conditions, such as the aquaculture environment, local climate conditions, and the distribution of virus hosts. From the perspective of shellfish species, the prevalence of HEV in several major shellfish species is ranked as mussels > clams > oysters, which may be related to their living habits, feeding patterns and biological characteristics. The prevalence rate of HEVs in shellfish has been on a downward level since 2015, which may be related to the ISO/TS 15216-2:2013 promulgated by the WHO in 2013, or the detection standards for HEVs or other similar viruses promulgated in various countries. It cannot be ruled out that data from certain studies may have significantly impacted the overall prevalence during 2015–2016, resulting in higher rates compared to other periods. Although the prevalence rate of HEVs in shellfish in this study has remained at a relatively low level in recent years, and it can be determined that the prevalence rate of HEVs in the samples obtained after 2016 has slightly declined, there is still a risk of threatening the health of consumers. Therefore, strict control must be exerted on the links of shellfish cultivation, fishing, storage, and sales to reduce the probability of shellfish being infected with HEVs from all aspects. Especially in the cultivation link, this link is most likely to cause large-scale infections of shellfish. In addition, foodborne viruses are important causes of global waterborne transmission and outbreaks of shellfish-related diseases. The detection of foodborne viruses in susceptible foods such as shellfish cannot be ignored. The actual number of safety incidents caused by them is higher than the reported number, and the important reasons are that the viruses are not detected and confirmed or are not detected due to low content [51]. This study aims to establish a reference standard for evaluating global HEV contamination in shellfish, thereby raising awareness among industry professionals and governmental agencies worldwide to promptly and proactively address potential consumer health risks. Therefore, it is recommended that regulatory agencies in various countries conduct regular sampling inspections to investigate the contamination of cultured shellfish by hepatitis E virus in the water bodies, individual shellfish during cultivation, and in the market, so as to prevent large-scale outbreaks. At the same time, improve the detection methods of hepatitis E virus and strengthen the requirements for the detection process. It is also recommended that shellfish farming institutions ensure the cleanliness of the aquaculture water during the farming process and promptly handle possible sources of pollution (such as animal feces, untreated sewage, and sediment in the farming area) in the farming environment. This can reduce the prevalence of HEV in shellfish from the source and ensure the safety of human consumption.

This study also has certain limitations. Firstly, there are limitations in the research method. The results of the Meta-analysis rely more on the quality of the published articles. The quality of the articles directly affects the results of the Meta-analysis. Articles are more inclined to publish positive results, thus, affecting the publication bias of this study. Secondly, the heterogeneity of the included articles has an impact on the study. Differences among articles in research methods, sampling objects (types of shellfish, cultured/wild shellfish), intervention measures (storage environment, testing environment, etc.), time (sampling time, testing time, etc.), environment (survival environment of shellfish, collection environment), and sample size will directly affect the results of the study. Although statistical methods can be used to reduce the impact of heterogeneity, it is impossible to eliminate this impact. Moreover, the Meta-analysis is based on certain statistical models, and all statistical models have assumed conditions, while the actual situation cannot perfectly meet these assumed conditions.

All in all, this study has provided an important basis for understanding the prevalence of hepatitis E virus in shellfish in different periods and locations around the world, formulating targeted prevention and control strategies, and safeguarding public health. This study also lays a solid foundation for future investigations into the global distribution of different HEV genotypes and the factors influencing HEV prevalence in shellfish across various geographical locations and environments.

Abbreviations

HEV	Hepatitis E virus
WHO	World Health Organization
RT-nPCR	Reverse Transcription-nested Polymerase Chain Reaction
ELISA	Enzyme-Linked Immunosorbent Assay
RR	Risk Ratio or Relative Risk

Author Contributions

Q.X.: Investigation, Resources, Supervision, Funding acquisition, Writing—review & editing. Y.L.: Methodology, Data curation, Visualization, Formal analysis, Writing—original draft. Z.Z.: Writing—review & editing, Sample collection. F.S.: Sample collection. H.Z.: Supervision. J.X. and J.W.: Resources. Y.Z.: Funding acquisition, Writing—review & editing. All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author.

Consent for Publication

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest regarding this manuscript.

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Standards of Reporting

This study followed the PRISMA guidelines and methodology to search for and collect relevant literature for meta-analysis.

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