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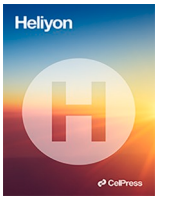

Research article

Revealing antimicrobial resistance profile and associated factors of *Vibrio vulnificus* isolated from clinical, environmental, and seafood samples across asia: A systematic review and meta-analysis

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ABSTRACT

The escalating antimicrobial resistance (AMR) in highly virulent *Vibrio vulnificus* poses a significant public health concern in Asia. Profiling the antibiogram of this pathogen is crucial for revealing its complex AMR patterns and guiding the selection of appropriate medications. Although previous studies have provided valuable insights regarding *V. vulnificus* AMR, they are constrained by limited sample diversity, inconsistent methodologies, and insufficient regional data. Moreover, no systematic attempt has been made to synthesize *V. vulnificus* AMR data across various sources and regions in Asia. A systematic review and meta-analysis are thus conducted in this study to assess the current AMR status of *V. vulnificus* isolated from clinical, environmental, and seafood samples. By synthesizing data from 32 articles across 13 Asian countries, a broader antibiogram has been provided, covering 13 major antimicrobial groups against *V. vulnificus*. Subgroup and regression analyses were also performed using study-level and country-specific covariates to explore the associated risk factors. The findings revealed low AMR rates for tetracyclines (4.89 %), quinolones (1.85 %), nitrofurans (0.86 %), and phenicols (0.61 %), highlighting their potential as primary treatment options. Conversely, high AMR rates were detected for lincosamides (80.32 %), polypeptides (64.42 %), and glycopeptides (56.14 %), necessitating careful consideration for their clinical use. For study-level covariates, subgroup and meta-regression analyses revealed that variations in the type of antimicrobial (R^2 = 26.5 %, $p < 0.0001$), country (R^2 = 18.33 %, $p < 0.0001$), and pathogen source (R^2 = 10.46 %, $p = 0.0007$) significantly contributed to between-study heterogeneity in the detected AMR rates across studies. Moreover, the analyses of country-specific covariates indicated that antimicrobial consumption (AMC) in healthcare systems (R^2 = 29.3, $p = 0.06$) and the country's gross domestic product (GDP) (R^2 = 28.59, $p = 0.06$) affected the variations in AMR rates across countries to some extent. Consideration of study-level and country-specific covariates is thus recommended for future research to effectively mitigate the threat of *V. vulnificus* AMR across Asia and reduce its pervasive impact on public health.

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1. Introduction

Vibrio vulnificus, a Gram-negative opportunistic pathogen that naturally inhabits marine and estuarine environments, is frequently found in various fish and shellfish species [1,2]. The consumption of raw or undercooked seafood and exposure of open wounds to seawater are the primary routes of transmission to humans, potentially leading to gastroenteritis, septicemia, or necrotizing fasciitis [3]. Asian countries, renowned for their extensive coastlines and flourishing aquatic ecosystems, are at high risk of *V. vulnificus* infection because of their substantial seafood consumption [4,5]. For instance, a survey among emergency medicine physicians in Japan estimated an annual occurrence of 425 cases of *V. vulnificus* sepsis [6]. Hsueh et al. (2004) reported a clinical case series of 84 patients with *V. vulnificus* infection from 1995 to 2000 in Taiwan [7]. The Korea Centers for Disease Control and Prevention reported 913 cases of *V. vulnificus* infection between 2001 and 2016 [8]. Considering the high risk of morbidity and mortality associated with this pathogen, particularly in Asia, early diagnosis and prompt administration of appropriate medications are thus imperative for the safety of public health.

Several broad-spectrum antimicrobials, such as trimethoprim-sulfamethoxazole, tetracyclines, fluoroquinolones, and 3rd-generation cephalosporins, are often prescribed as preliminary treatment options for *V. vulnificus* infections [9,10]. However, the excessive utilization of antimicrobial agents, particularly in the aquaculture sector, whether as feed additives or immersion baths for prophylaxis or therapy, has significantly contributed to the emergence of multidrug-resistant (MDR) strains of *Vibrio* species, which are prevalent seafood-borne pathogens in aquaculture environments [11]. In one study, 81 % of *Vibrio* isolates from fish farms were found to be MDR, with multiple antibiotic resistance (MAR) indices ranging from 0.42 to 0.86 [12]. This resistance complicates the treatment of their infections and presents a significant threat to public health [13,14]. Over the past few decades, *Vibrio* species have developed increasing resistance to various antimicrobials through genomic evolution and selective pressures, leading to the emergence and spread of antimicrobial-resistant genes (ARGs) [15,16]. These ARGs encode several biochemical and molecular mechanisms contributing to AMR, including enzymes that degrade antimicrobials, proteins that alter bacterial cell walls to prevent drug entry, efflux pumps that expel antimicrobials from the cell, and the formation of protective capsules or biofilms [17,18]. The ARGs can be transmitted to other bacteria via horizontal gene transfer, a process often facilitated by environments with high antibiotic usage, resulting in the dissemination of MDR traits within bacterial populations [19,20]. Moreover, the ARGs found in *Vibrio* species, such as $bla_{CTX\text{-}M\text{-}55}$, *qnrVC1, qnrVC5*, *strA*, *dfrA31*, *tetS*, *sul2*, and *ermB*, often co-exist with various virulence factors (VFs) including iron acquisition systems, cytotoxins, motility factors, capsular polysaccharides, adhesive factors, and others [21–24]. The co-occurrence of ARGs and VFs can enhance AMR and increase virulence, potentially leading to more severe infections and treatment challenges, thereby raising significant public health concerns [25]. Given the increasing prevalence of virulent and resistant *Vibrio* strains in Asia, a comprehensive study is thus essential to evaluate the current AMR profiles of a key species, *V. vulnificus*, across the region.

Despite increasing concerns regarding the emergence of AMR in *V. vulnificus* and its associated risks to public health, there is a lack of comprehensive research that systematically analyses and compares the available data on the prevalence of AMR in this pathogen across different sample sources and geographical regions, specifically within Asia. Considering this research gap, this study aimed to conduct a systematic review and meta-analysis to evaluate the pooled prevalence estimates (PPE) of AMR in *V. vulnificus* isolates obtained from various samples and regions of Asia. To analyze AMR in Asian countries guided by the One Health principles, the current analysis incorporates several potential covariates encompassing antimicrobial consumption (AMC) in healthcare and aquaculture, regulation of AMC, environmental quality, and the economic conditions of Asian countries, to monitor their influence on AMR. Such an approach would provide a comprehensive and region-specific understanding of the current prevalence of AMR and its driving factors in *V. vulnificus*. Moreover, it would fill a significant gap in the existing research and serve as a valuable guide for healthcare clinicians in selecting precise medications for more effective treatment.

Table 1
Eligibility criteria and search terms for assessing AMR patterns in *Vibrio vulnificus* across Asia.

Criteria	Inclusion	Exclusion
Study type	Cross-sectional studies Primary research	Cohort studies Case-control studies Ecological studies Non-primary research (reviews and meta-analysis)
Population	Clinical, environmental, and seafood samples	Marine algae, and other marine animals
Exposure	Antimicrobial resistance patterns of *V. vulnificus*	The antimicrobial resistance patterns of pathogens other than *V. vulnificus*
Outcomes	Proportion of resistant isolates	Outcomes other than antimicrobial resistance (e.g. genomic analysis)
Region	All subregions of Asia	Regions other than Asia

Search string: (Vibrio vulnificus) AND (Asia* OR China OR India OR Indonesia OR Pakistan OR Bangladesh OR Japan OR Philippines OR Vietnam OR Turkey OR Iran OR Thailand OR Myanmar OR South Korea OR Iraq OR Afghanistan OR Saudi Arab OR Uzbekistan OR Malaysia OR Yemen OR Nepal OR North Korea OR Sri Lanka OR Kazakhstan OR Syria OR Cambodia OR Jordan OR Azerbaijan OR United Arab Emirates OR Tajikistan OR Israel OR Laos OR Lebanon OR Kyrgyzstan OR Turkmenistan OR Singapore OR Oman OR Palestine OR Kuwait OR Georgia OR Mongolia OR Armenia OR Qatar OR Bahrain OR Timor-Leste OR Cyprus OR Bhutan OR Maldives OR Brunei) AND (antibiotic resistance OR drug resistance OR resistance against medication OR bacterial resistance OR antibiotic agents OR antibiotic susceptibility OR drug susceptibility).

2. Materials and methods

2.1. Study design

The systematic review and meta-analysis were conducted following the guidelines outlined in the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol" (PRISMA-P) [26] (Supplementary Table S1). The research question was structured in the "Population, Exposure, Comparator, and Outcome" (PECO) format [27]. In this study, "population of interest" refers to the clinical, environmental, and seafood samples, and "exposure" refers to the antimicrobial-resistant *V. vulnificus* isolates. As the concept of a "comparator" was not applicable to this study, it was disregarded. The AMR rate of *V. vulnificus* was considered the primary "outcome" in all eligible studies.

2.2. Search strategy

To ensure a comprehensive coverage of all relevant studies published until December 31, 2023, a systematic literature search was conducted across multiple electronic databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. This process involved the utilization of specific search terms along with Boolean operators (AND/OR), asterisks (*), and parentheses, in a meticulously selected manner to ensure the retrieval of relevant information [28,29]. A detailed search string has been provided in Table 1. The citations obtained from the initial search were then imported into EndNote software (version X9) to facilitate the removal of duplicate records and screening studies. Additionally, a manual search of the reference lists within the downloaded articles was performed to identify potential studies that may have been inadvertently overlooked during the initial search process.

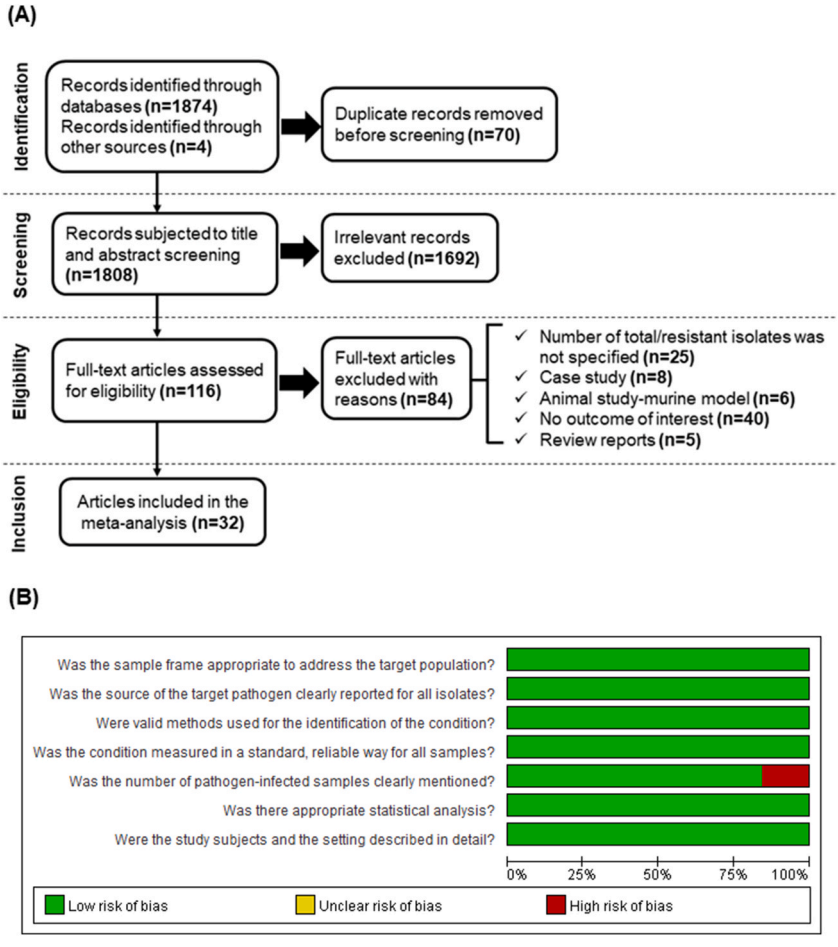

Fig. 1. (A) Selection of studies used in this systematic review and meta-analysis (PRISMA flow chart) to determine the antimicrobial resistance profile of *Vibrio vulnificus* isolated from different sample sources across Asia. **(B)** Risk-of-bias graph illustrating the validity of included studies.

2.3. Eligibility criteria and screening

To confirm the relevance of the studies included in the meta-analysis, three independent researchers rigorously assessed the eligibility of the retrieved articles using the predetermined inclusion and exclusion criteria [30]. Table 1 provides detailed inclusion and exclusion criteria for the meta-analysis. The screening process involved an initial evaluation of titles and abstracts, followed by a thorough assessment of the full texts [31,32]. Any discrepancies that arose during the screening process were resolved by consensus among independent reviewers. Following a two-level screening procedure, articles that met the inclusion criteria were considered eligible and subsequently selected for the meta-analysis (Fig. 1A).

2.4. Risk-of-bias (RoB) assessment

To evaluate the validity of the included studies, three independent researchers conducted a quality assessment using the critical appraisal checklist of the Joanna Briggs Institute for Prevalence Studies, with some modifications [33]. The checklist consisted of nine RoB guidelines that addressed the target population, sampling frame, sampling strategy, response rate, likelihood of non-response bias, diagnostic method, sample size, appropriate statistical analysis, and clear indications of sample types. Two RoB guidelines related to survey-type research were deemed inapplicable to this study and were excluded from the evaluation. Furthermore, considering the presence of three distinct sample types (clinical, environmental, and seafood) with diverse origins and characteristics, it was anticipated that imposing a single standardized sampling strategy or sample size requirement on such heterogeneous sample sources would be challenging and may not accurately reflect the true nature of the data. Therefore, these two criteria were disregarded in the RoB assessment to ensure a more realistic representation of the data. However, two supplementary inquiries concerning the origin of the target pathogen and the number of contaminated samples were considered suitable for inclusion in the RoB assessment checklist because of their relevance and were therefore incorporated into the evaluation process. Each study was rated as having a low, high, or unclear RoB based on the responses to these questions. Subsequently, a RoB graph illustrating the validity of the included studies was generated using Review Manager software RevMan 5.4.1 to provide a visual representation of the assessment (Fig. 1B).

2.5. Data extraction

Relevant information from the eligible studies was systematically collected and organized in a Microsoft Excel spreadsheet to facilitate data analysis [34]. The extracted data encompassed several key variables, including article title, authors, publication year, country of research, source of *V. vulnificus* isolates: clinical (blood or bullous fluid from infected patients), environmental (aquatic or sediment samples harboring *V. vulnificus*), or seafood (fish/shellfish) samples, type of antimicrobials tested, minimum inhibitory concentration (MIC) of antimicrobials, prevalence rate of *V. vulnificus* resistance (number of total and resistant isolates), and susceptibility testing method. Notably, because multiple antimicrobials were assessed in a single study, data for each antimicrobial agent were extracted separately.

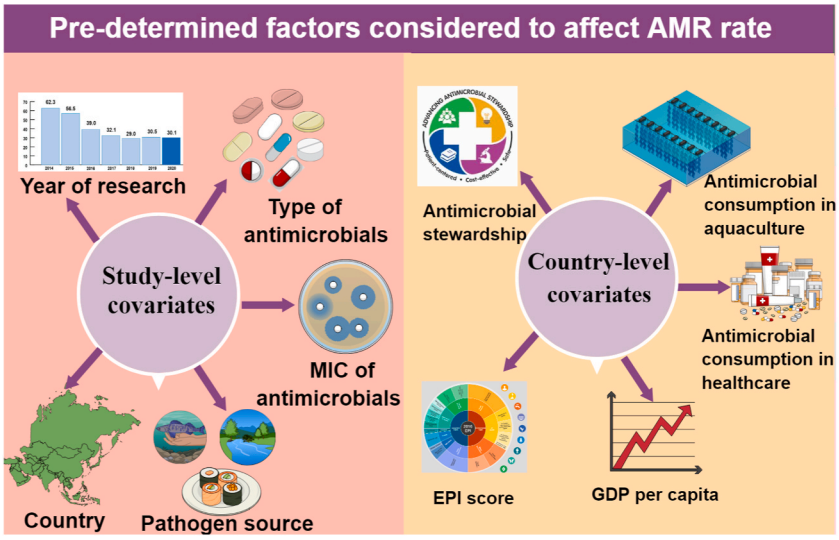

Fig. 2. Study-level and country-level covariates considered to affect the AMR rate of *Vibrio vulnificus*.

2.6. Statistical analysis and data synthesis

2.6.1. Meta-analysis and meta-regression

In this study, a random-effects meta-analysis was performed to determine the PPE of AMR in *V. vulnificus* isolates. This method was adapted to address both within-study and between-study variance owing to the likelihood of significant heterogeneity in AMR rates among primary studies [35]. The analysis was done by 'metafor' (*version 3.8-1*) and 'meta' (*version 5.5-0*) packages in the statistical program 'R' (*version 4.1.2*) along with R-studio (*version 1.4.1106*). To fulfill the assumption of normality and stabilize variances, the AMR rates from individual studies were subjected to a logit transformation. A Generalized Linear Mixed Model (GLMM) was then employed for pooling the data, and between-study variance (τ^2) was calculated by the Maximum Likelihood (ML) estimator [36]. The results, initially expressed in the logit model, were back-transformed to their original forms and represented as percentages. Between-study heterogeneity was assessed using Cochran's Q-statistic (χ^2 value) and I^2 statistic, representing the percentage of total variability in effect estimates caused by true heterogeneity rather than random error [37,38]. Heterogeneity was considered significantly high when the Q-test yielded a *p*-value of less than 0.05 and the I^2 statistic exceeded 50 %. The estimated AMR rates with corresponding 95 % confidence intervals (CIs) are visually presented in forest plots. Five *a priori*-determined covariates—type of antimicrobials, MIC of antimicrobials, publication year, country of research, and pathogen source—were presumed to be associated with variations in the AMR rate of *V. vulnificus* across studies (Fig. 2). Therefore, subgroup and meta-regression analyses were conducted using these variables to explore the potential sources of between-study heterogeneity. These analyses were performed using the R packages 'MuMIn' (*version 1.43.17*) and 'dmetar' (*version 0.0.9000*). To assess the robustness of the meta-analysis findings, a sensitivity analysis (using the leave-one-out method) was conducted to identify any outliers or influential studies that could potentially impact the pooled prevalence estimate [39]. To quantify the spread of multiple antimicrobial resistance (MAR) in *V. vulnificus* within clinical, environmental, and seafood samples, a quantitative metric known as the MAR index was employed. This was calculated using the formula $a/(b \times c)$, where a represents the cumulative count of resistant isolates, b is the number of antimicrobials, and c is the total number of isolates [40].

2.6.2. Assessment of socio-economic covariates

In addition to study-level covariates, variation in the AMR rates of *V. vulnificus* across countries was assumed to be influenced by certain country-specific socio-economic covariates, including the amount of AMC in healthcare and aquaculture systems, regulation of antimicrobial stewardship programs, environmental performance index (EPI) scores, and per capita Gross Domestic Product (GDP) (Fig. 2). Relevant data encompassing these variables were obtained from previously published literature and external databases, ensuring alignment with the corresponding study year and country. Any temporal inconsistencies among the AMR data and socio-economic covariates were resolved by employing the interpolation method using the R package "pracma" (*version 2.4.4*) [41]. For estimating the amount of AMC in healthcare systems, information regarding the Defined Daily Doses (DDDs) per 1000 individuals was gathered from the global repository of the One Health Trust [42]. The evaluation of AMC in aquaculture, measured in tons, was incorporated based on data provided by the Spatial Epidemiological Laboratory, Belgium [43]. To ensure proper access and stewardship, the World Health Organization (WHO) categorizes antimicrobials into three groups: Access (A), Watch (Wa), and Reserve (Re) [44]. Considering that the WHO recommends the consumption of 60 % of antimicrobials from the Access group in total AMC in the global effort against AMR, AMC regulation and stewardship in the countries were carefully evaluated by determining their Access-to-Watch (A/Wa) index ratio, which was calculated using the data reported by the Center for Disease Dynamics, Economics & Policy, USA [45]. The EPI scores were utilized to compare environmental quality among the countries based on data reported by the Yale Center for Environmental Law & Policy [46]. The economic status of the countries was determined by their per capita GDP in US Dollars, obtained from the World Integrated Trade Solution database [47]. Subsequently, the univariate and multivariate regression analyses were conducted to account for the role of the socio-economic covariates on the observed heterogeneity among the AMR rates of *V. vulnificus* across countries by employing the R packages 'MuMIn' (*version 1.43.17*).

2.6.3. Publication bias

Publication bias refers to the selective publication of studies based on the statistical significance, magnitude, and direction of findings. It can result in a skewed estimation of the effect size, underscoring the critical importance of thoughtful analysis when interpreting the results [48]. In this study, a meticulous assessment of publication bias in the studies on the patterns of AMR of *V. vulnificus* across Asia was carried out for each antimicrobial group. For this purpose, both visual inspection of the symmetry of contour-enhanced funnel plots and statistical estimation using Egger's regression test were employed. Following the confirmation of a likelihood of publication bias, the trim-and-fill method was used to generate an unbiased effect size by imputing the missing studies into the funnel plot [49,50].

3. Results

3.1. Literature search

An initial literature search of electronic databases and other sources yielded 1878 documents. After removing the duplicates, 1808 records remained. A further 1692 documents were eliminated after preliminary title and abstract screening, and another 84 were removed because of irrelevant content found during the full-text screening. Finally, 32 eligible articles were included in this meta-analysis (Fig. 1A).

3.2. RoB assessment

The eligible studies were then evaluated for RoB assessment. All of them exhibited a low RoB, meeting six of the seven criteria examined (C1, C2, C3, C4, C6, and C7) (Fig. 1B). According to the criterion for appropriateness of the sample type (C1), the intended target populations in all eligible studies aligned with the inclusion requirements (Table 1). Furthermore, each study precisely indicated the origin of *V. vulnificus* isolates, and any study with multiple sources provided a clear distinction in the number of isolates from each source, thus meeting the criterion pertaining to the target pathogen source (C2). Concerning the evaluation criterion for validating the detection methodologies (C3), the studies ensured that all *V. vulnificus* isolates were effectively utilized for detecting the rate of AMR. Additionally, the same methodology for assessing AMR prevalence (C4) was applied to all isolates. For appropriate statistical analysis (C6), a precise representation of the number of resistant isolates, total isolates, and/or the proportion of resistance to a specific antimicrobial (C7) was explicitly described in each study. According to the criterion related to the quantity of pathogen-infected samples (C5), a high RoB was observed in 16 % of the studies. This outcome could be attributed to the fact that 5 of the 32 studies included in the analysis [51–55] did not specify the number of infected samples from which *V. vulnificus* was isolated. Overall, the RoB assessment consistently indicated a low RoB for most of the studies, suggesting their reliability, robustness, and validity.

3.3. Descriptive characteristics of eligible studies

The relevant features of the 32 eligible studies included in this meta-analysis are summarized in Supplementary Table S2. The selected studies were conducted between 1992 and 2023 in 13 countries across West Asia (Iran and Saudi Arabia), South Asia (India), East Asia (China, Japan, Hong Kong, South Korea, and Taiwan), and Southeast Asia (Thailand, Malaysia, Singapore, Philippines, and Vietnam). Collectively, these studies investigated the AMR of 501 *V. vulnificus* isolates. Among these, 328 were sourced from seafood samples including fish and shellfish, 124 from environmental samples such as seawater and marine sediments, and 49 from clinical samples of human patients infected with *V. vulnificus*. The AMR of these isolates was tested against an extensive range of 54 antimicrobials encompassing 13 groups *viz.,* tetracyclines, *β*-lactams, aminoglycosides, sulphonamides, nitrofurans, diaminopyrimidines, quinolones, phenicols, polypeptides, macrolides, glycopeptides, lincosamides, and aminocoumarins. Notably, the MICs of certain antimicrobials varied across studies and have been appropriately documented (Supplementary Table S2). Furthermore, except for one study that utilized the direct spreading method, all other studies consistently employed the disk diffusion test to assess the AMR rate of *V. vulnificus* against different antimicrobial agents.

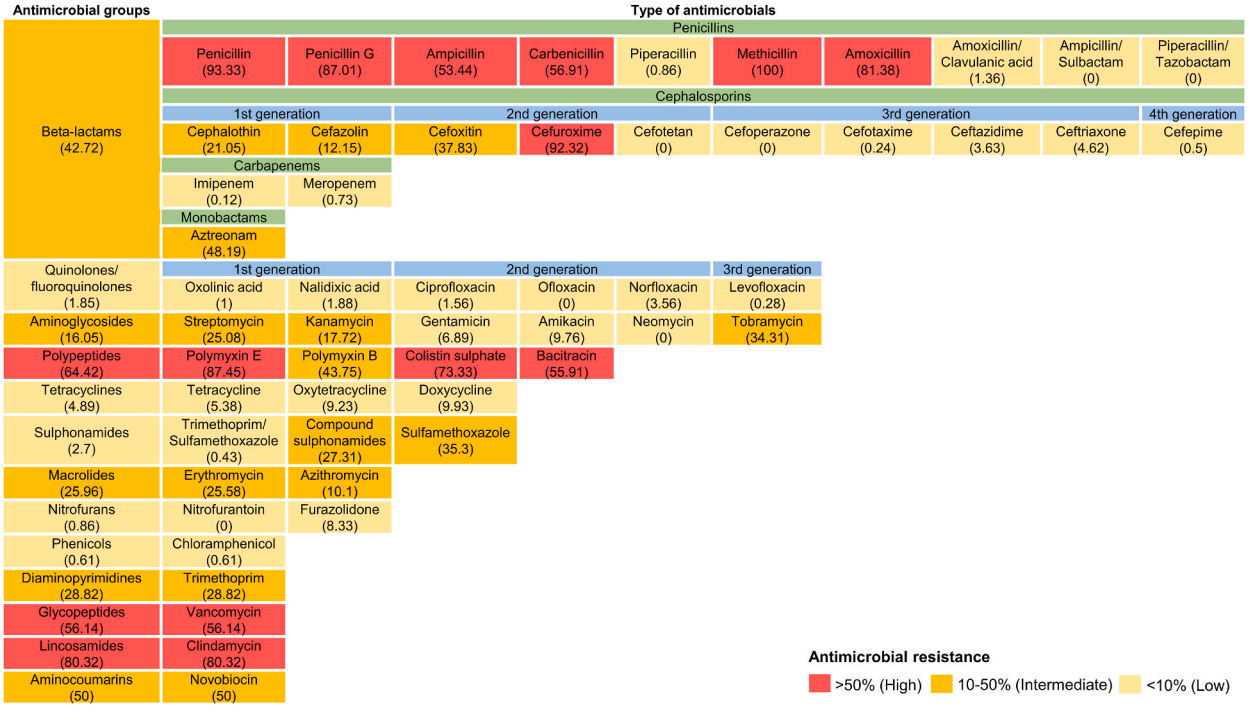

Fig. 3. Antimicrobial resistance patterns in *Vibrio vulnificus* against 13 antimicrobial groups and their 54 types. (The values in the brackets show the percentage of antimicrobial resistance calculated by meta-analysis and subgroup analyses based on the type of antimicrobials).

3.4. Statistical analysis and data synthesis

3.4.1. Meta-analysis and meta-regression

The AMR rates observed in *V. vulnificus* isolates against 13 antimicrobial groups and their corresponding 54 subgroups, derived from the meta-analysis and subgroup analyses were evaluated for interpretation (Fig. 3). Details regarding heterogeneity and *p*-values are summarized in Supplementary Tables S3 and S4. Notably, *V. vulnificus* exhibited elevated AMR rates against lincosamides (80.32 %, 95%CI: 60.8–91.48 %), followed by polypeptides (64.42 %, 95%CI: 43.81–80.79 %) and glycopeptides (56.14 %, 95%CI: 35.28–75.03 %). Conversely, AMR rates were low (<10 %) for tetracyclines, quinolones/fluoroquinolones, nitrofurans, phenicols, and penicillins in combination with β-lactamase inhibitors, 3rd/4th generation cephalosporins, and carbapenems. Intermediate resistance (10–50 %) was detected for 1st/2nd generation cephalosporins, monobactams, aminoglycosides, macrolides, diaminopyrimidines, and aminocoumarins. The between-study heterogeneity was significant for β-lactams ($I^2 = 93$ %), aminoglycosides ($I^2 = 86$ %), macrolides ($I^2 = 70$ %), glycopeptides ($I^2 = 60$ %), and lincosamides ($I^2 = 54$ %). Despite this high heterogeneity, the leave-one-out analysis demonstrated that no individual study substantially influenced the outcomes, suggesting that the results of the meta-analysis are robust and reliable (Supplementary Figs. 1–3). Other antimicrobial groups displayed low heterogeneity ($I^2 < 50$ %), indicating consistent effect sizes across the studies. Subgroup and meta-regression analyses for β-lactams identified four covariates that were significantly associated with the observed heterogeneity ($p < 0.05$): type of antimicrobials, MIC of antimicrobials, country, and pathogen source. The multiple meta-regression model, combining these four covariates and publication year, was also significant ($R^2 = 49.09$ %, $p < 0.0001$), explaining 49.09 % of the variance in AMR rates across the studies. In contrast, no potential covariates were identified for macrolides or aminoglycosides ($p > 0.05$) in the subgroup or meta-regression analyses, underscoring the need for further exploration beyond the considered variables. However, multiple meta-regression analyses revealed that the combination of selected covariates accounted for 40.92 % and 10.22 % of the variance in the AMR rates for macrolides and aminoglycosides, respectively (Supplementary Table S5). Owing to the limited number of studies, sensitivity or moderator analyses were not performed for the lincosamide and glycopeptide groups.

The MAR index of *V. vulnificus* was initially computed independently for each study and then aggregated using meta-analysis to obtain a pooled estimate. The findings revealed an overall MAR index of 0.29 (95%CI: 0.16–0.48), indicating that *V. vulnificus* isolates exhibit resistance to approximately 30 % of antimicrobial agents tested in this study. Subsequent subgroup analysis revealed MAR index values of 0.04, 0.31, and 0.30 for pathogens isolated from clinical, environmental, and seafood samples respectively. This indicates an increased possibility of the presence of multidrug-resistant (MDR) *V. vulnificus* in the latter two sources. Furthermore, the MAR index calculated for the period between 1992 and 2012 was 0.26, which elevated to 0.31 in the evaluation from 2013 to 2023, demonstrating a progressive increase in MDR *V. vulnificus* over time (Supplementary Figs. 4–6).

3.4.2. Impact of socio-economic covariates on AMR

The impact of socio-economic factors on *V. vulnificus* AMR was assessed by regression analyses. Table 2 presents the AMR rates of *V. vulnificus* in Asian countries as evaluated in this study, along with the corresponding values of socio-economic covariates derived from external sources. Univariate regression analyses highlighted that only the AMC in healthcare ($R^2 = 29.3$ %, $p = 0.06$) and per capita GDP ($R^2 = 28.59$ %, $p = 0.06$) exhibited a substantial relationship with the AMR rate (Table 3). Multivariate regression analysis, which included all covariates, yielded an R^2 value of 0.6957 ($p = 0.08$), indicating that 69.57 % of the variance in AMR rates across the countries could be explained by these covariates (Table 3). Data visualization further explained the detectable trends and multifaceted relationships between these covariates and AMR rates. Fig. 4A demonstrates that China and India exhibited the highest AMC in aquaculture (4633 and 1125 tons, respectively), with notable AMR rates of 13.13 % and 34.25 %, respectively, whereas Taiwan and the Philippines, with less than 50 tons of AMC in aquaculture, displayed AMR rates below 10 %. Fig. 4B shows that despite having a lower AMC in aquaculture, Saudi Arabia, Malaysia, Thailand, and India showed higher AMR rates than China, possibly influenced by elevated AMC in healthcare. Iran, with a low AMC in both aquaculture and healthcare, exhibited a considerable AMR rate of 43.23 %, probably due to a potential lack of AMC regulation in healthcare, as indicated by its low GDP per capita and low A/Wa ratio (Fig. 5A).

Table 2
The AMR rates across Asian countries, accompanied by the scores of various socioeconomic covariates.

Country	AMR (%)	AMC in healthcare (DID[a])	AMC in aquaculture (tons)	A/Wa index	GDP per capita (USD)	EPI score
India	34.25	5373	1124.72	0.3	1656	34.99
Malaysia	35.94	4180	137.79	1.2	8762	76.09
Taiwan	5.68	8631	30.85	4.2	23242	79.00
Iran	43.23	62	218.26	0.6	5241	54.43
Thailand	15.84	7748	189.69	1.7	6235	45.47
South Korea	4.01	9600	168.82	0.8	30974	60.88
Hong Kong	44.44	34	0.15	1.5	34458	67.65
Saudi Arabia	50	8890	34.00	1.6	17366	55.30
Japan	0.79	5288	113.83	0.16	32942	72.50
China	13.13	2880	4633.33	0.6	7056	51.22
Vietnam	0	10818	484.83	1.0	2741	58.50
Singapore	100	297	0.58	1.4	61277	64.23
Philippines	5.36	2002	23.67	2.1	1848	87.81

[a] Daily ingested dose (DID) = Defined Daily Dose (DDD)/1000 individuals.

Table 3
Univariate and multiple regression models, showing the relationship of AMR rates with the country-specific socioeconomic covariates.

Predictor	Estimate	SE	t value	*p*-value	R^2(%)
Univariate regression					
AMC (Healthcare)	−0.004	0.002	−2.135	0.06	29.30
AMC (Aquaculture)	−0.004	0.007	−0.582	0.57	2.99
A/Wa index	−2.025	8.239	−0.246	0.81	0.55
GDP per capita	0.001	0.000	2.099	0.06	28.59
EPI score	−0.327	0.583	−0.560	0.59	2.77
Multivariate regression					
Intercept	104.658	34.731	3.013	0.02	69.57
AMC (Healthcare)	−0.005	0.002	−2.620	0.03	
AMC (Aquaculture)	−0.006	0.005	−1.137	0.29	
A/Wa index	5.868	6.995	0.839	0.43	
GDP per capita	0.001	0.000	1.944	0.09	
EPI score	−1.154	0.524	−2.204	0.06	

p-value for multivariate regression model (p-value$_{model}$) = 0.08.

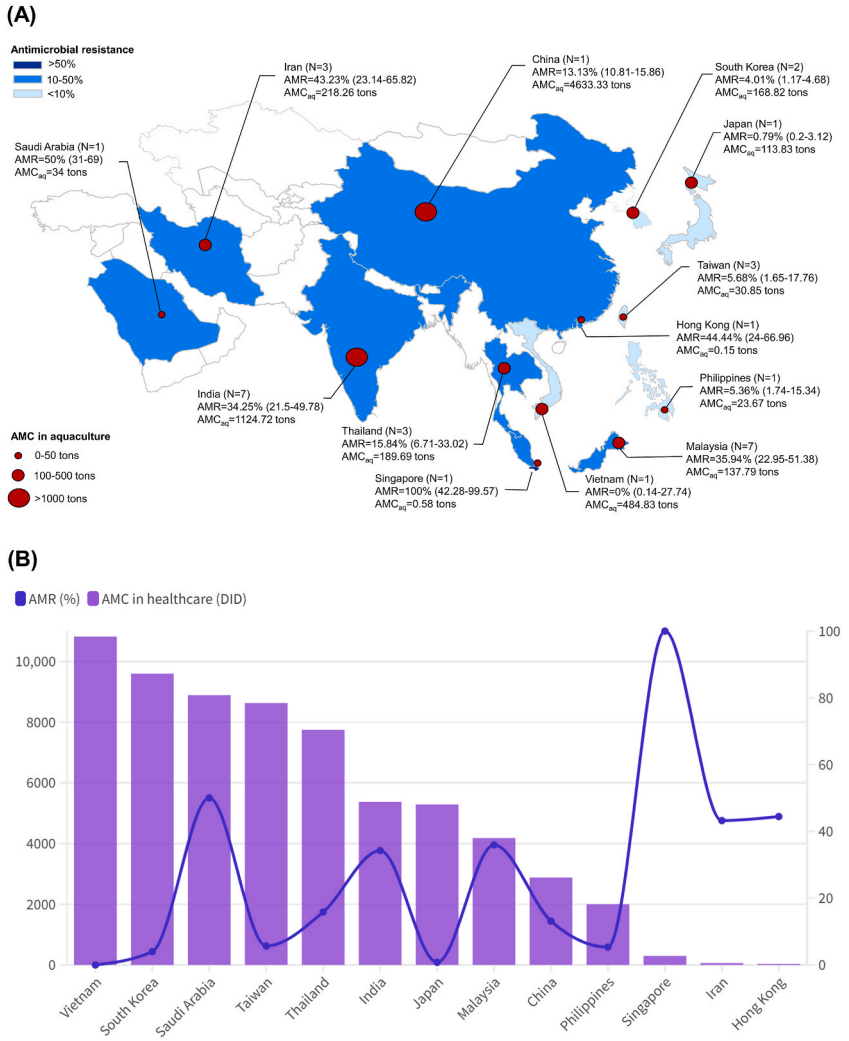

Fig. 4. **(A)** Comparison of *Vibrio vulnificus* antimicrobial resistance and antimicrobial consumption in aquaculture across Asian countries (N, AMR, and AMC_{aq} represent the number of studies, percentage antimicrobial resistance, and antimicrobial consumption in aquaculture calculated in tons). **(B)** Comparison of *Vibrio vulnificus* antimicrobial resistance and antimicrobial consumption in healthcare measured in DID (Daily ingested dose (DID) = Defined Daily Dose (DDD)/1000 individuals) (R^2 = 29.3 %, *p*-value = 0.06).

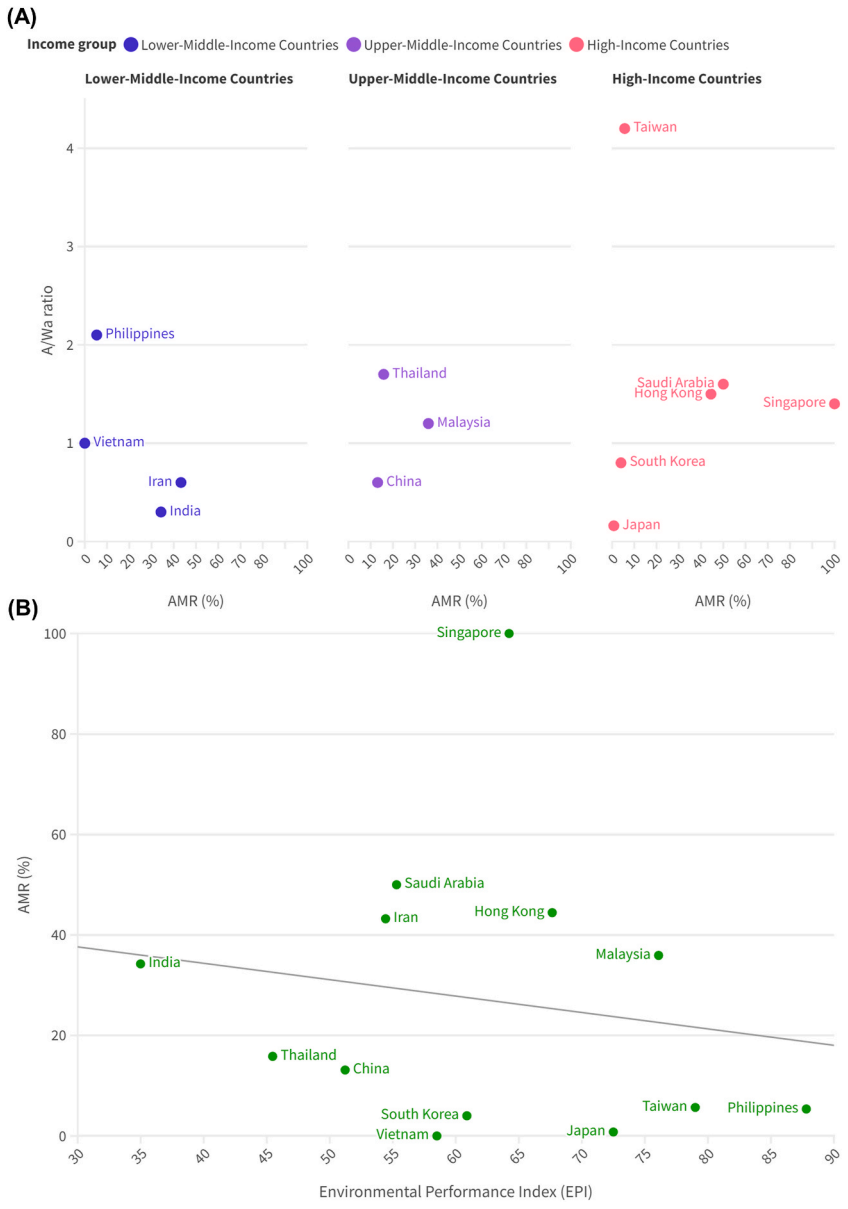

Fig. 5. **(A)** Comparison of *Vibrio vulnificus* antimicrobial resistance and Access-to-Watch index across Asian countries. The countries are categorized into lower-middle, upper-middle, and high-income countries based on their per capita GDP. **(B)** Comparison of Environmental Performance Index and antimicrobial resistance of *Vibrio vulnificus* across Asian countries.

Hong Kong and Singapore displayed low AMC in aquaculture and healthcare compared to Japan, Malaysia, Taiwan, and the Philippines. However, their AMR rates were higher than those reported in these countries. As shown in Fig. 5B, the EPI scores of Hong Kong and Singapore were lower than those of the aforementioned countries, which possibly influenced their heightened AMR.

3.4.3. Publication bias

To investigate publication bias concerning the prevalence of AMR in *V. vulnificus* across Asia, distinct contour-enhanced funnel plots were generated specifically for the antimicrobial groups with a minimum of 10 studies (Supplementary Figs. 7–14). These plots incorporated varying levels of statistical significance ($p < 0.1$, $p < 0.05$, and $p < 0.01$), and were constructed using logit-transformed proportions on the x-axis and the corresponding standard errors on the y-axis. Visual examination of the funnel plots revealed that studies on β-lactams, macrolides, aminoglycosides, polypeptides, and sulphonamides were symmetrically distributed on both sides of the mean effect, suggesting no publication bias. This was further confirmed using the Egger's regression test which yielded insignificant p-values ($p > 0.05$) (Table 4). In contrast, studies on tetracyclines, phenicols, and quinolones were asymmetrically distributed on both sides of the mean effect, indicating publication bias. The presence of funnel plot asymmetry was further confirmed using

Table 4
Publication bias on the patterns of antimicrobial resistance in *Vibrio vulnificus* isolated from clinical, environmental, and seafood samples across Asia.

Sr #	Group of antimicrobials	N	Egger's regression test			Trim-and-fill method		
			t-value	p-value	Funnel plot	n	K	Pooled prevalence (95%CI)
1	Beta-lactams	30	−0.386	0.7	symmetrical	0	30	39.47 (22.8–59.01)
2	Macrolides	15	−1.08	0.3	symmetrical	3	18	38.52 (24.55–54.69)
3	Aminoglycosides	27	−1.65	0.11	symmetrical	7	34	34.14 (21.43–49.62)
4	Tetracyclines	30	−3.389	0.002	asymmetrical	10	40	32.49 (18.95–49.77)
5	Diaminopyrimidines	6	−0.593	0.58	symmetrical	3	9	70.14 (31.83–92.2)
6	Phenicols	22	−2.259	0.035	asymmetrical	7	29	32.83 (16.17–55.33)
7	Polypeptides	11	0.505	0.63	symmetrical	0	11	58.07 (50.5–65.28)
8	Sulphonamides	20	−0.276	0.79	symmetrical	1	21	17.47 (8.5–32.55)
9	Nitrofurans	8	−3.931	0.008	asymmetrical	4	12	53.89 (17.66–86.43)
10	Quinolones	24	−4.967	<0.0001	asymmetrical	12	36	26.38 (14.69–42.7)
11	Aminocoumarins	4	0.024	0.98	symmetrical	0	4	49.66 (38.65–60.71)
12	Lincosamides	4	1.074	0.4	symmetrical	2	6	68.79 (45.1–85.54)
13	Glycopeptides	5	−0.344	0.75	symmetrical	0	5	59.52 (51.01–67.49)

N = Number of studies in meta-analysis, n = Number of studies added by trim-and-fill method, K = Number of studies combined (N + n).

Egger's regression test which yielded statistically significant *p*-values ($p < 0.05$). The trim-and-fill method identified 10, 7, and 12 missing studies for tetracyclines, phenicols, and quinolones, respectively, which led to a notable shift in their PPE of AMR (Table 4). However, it is crucial to emphasize that the shift in PPE did not result from the inclusion of the original data; therefore, it would not affect the validity of our findings. This underscores the importance of conducting additional studies to enhance our knowledge of the current AMR status of *V. vulnificus* in these antimicrobial groups.

4. Discussion

This study represents the first meta-analytical approach to provide valuable insights into the extent and distribution of *V. vulnificus* AMR across different sample sources and regions in Asia. High AMR levels (>50 %) against lincosamides, polypeptides, glycopeptides, and penicillins were observed, aligning with findings from the USA, Germany, Australia, Bulgaria, Canada, Italy, and France [56–61]. This widespread resistance signals a critical threat to the clinical effectiveness of these antibiotics, not only in Asia but also in Europe and Australia. Intermediate AMR rates (10–50 %) against aminoglycosides, erythromycin, and novobiocin were consistent with findings from the USA, Australia, and Denmark [62–64]. The elevated AMR rates in *V. vulnificus* are driven by several mechanisms, such as modifications in lipopolysaccharides (LPS), a key component of the bacterial cell wall, which reduce the interaction between antibiotics like polymyxins and bacterial cell membranes [65,66]. Furthermore, the genes *TolCV1* and *TolCV2* in *V. vulnificus* contribute to the efflux of erythromycin and novobiocin across the cell membrane [67]. Additionally, *V. vulnificus* employs various virulence and survival strategies, including protective capsule or biofilm formation, outer membrane reinforcement, point mutations in target genes, and structural protein variations that confer protection against both host defenses and specific antibiotics [18,68]. Careful consideration is thus required in the clinical use of these antimicrobials, as high AMR levels significantly compromise their therapeutic effectiveness.

Low AMR rates (<10 %) were observed in this study for tetracyclines, phenicols, nitrofurans, quinolones/fluoroquinolones, carbapenems, 3rd/4th-generation cephalosporins, and penicillins combined with β-lactamase inhibitors (ampicillin/sulbactam and piperacillin/tazobactam). Additionally, compared to the individual AMR rate of trimethoprim and sulfamethoxazole (~30 %), resistance to their combination (trimethoprim/sulfamethoxazole) was significantly lower (<1 %) (Fig. 3). These findings are consistent with previous reports from the USA, Germany, Italy, South Africa, Brazil, and Australia, where *V. vulnificus* strains from clinical, environmental, and seafood sources also showed low resistance to these antimicrobials [56,60,63,69–73]. This consistent efficacy across various regions and sample types indicates that these antibiotics remain effective in controlling *V. vulnificus* infections, making them primary therapeutic choices for clinical management [10,74]. The efficacy of these antimicrobials is also reflected in their global recognition as first- or second-line treatments for bacterial infections [9,10]. For instance, a case study in the USA demonstrated the ineffectiveness of vancomycin and clindamycin in treating a 53-year-old male with severe sepsis and soft tissue infections caused by *V. vulnificus*, however, the patient showed improvement when treated with 3rd/4th-generation cephalosporins, fluoroquinolones, and trimethoprim-sulfamethoxazole [75]. This underscores the importance of selecting antimicrobials with demonstrated effectiveness. The World Health Organization (WHO) categorizes many of these broad-spectrum agents under the Access and Watch groups, advocating their use as first or second-line therapies (Supplementary Fig. 15). The low AMR rates observed in this meta-analysis empirically support the continued use of these antimicrobials in treating *V. vulnificus* infections. However, continued vigilance and adherence to antimicrobial stewardship principles are crucial to preserve the effectiveness of these important antibiotics against *V. vulnificus* and other pathogens in the future.

Apart from the inherent mechanisms of *V. vulnificus* to escape the effect of antibiotics, the regression analysis and data visualization revealed the impact of country-specific socio-economic factors on *V. vulnificus* AMR in Asia. The results indicated that countries with aquaculture industries consuming over 100 tons of antimicrobials annually—such as China, India, Iran, Thailand, and Malaysia—showed notable AMR rates of 10–50 % (Fig. 4A). This is consistent with the findings of a previous meta-analysis that highlighted

the overuse of antimicrobials in aquaculture as a key driver of antimicrobial-resistant bacteria in aquatic environments and food animals, particularly in Asia [76]. As the primary contributor to global aquaculture output (77.8 %), Asia consumes substantial amounts of antimicrobials to maintain the health of farmed aquatic species and combat seafood-borne pathogens [77,78]. Owing to the persistent growth of the aquaculture industry in Asia driven by the increasing demand for seafood, the trend of AMC in aquaculture is expected to increase further in the future, which may elevate the dissemination of AMR [79]. This underscores the need for appropriate AMC practices in aquaculture systems to mitigate the escalating challenges of AMR in *V. vulnificus* in seafood and the surrounding ecosystems. The MAR index calculated in this study also revealed comparable values in both environmental and seafood samples, emphasizing the link between the development of MDR *V. vulnificus* in seafood and the surrounding environment (Supplementary Figure 5). Consequently, it is imperative to monitor the potential transfer of AMR from aquatic environments to seafood and, ultimately to seafood consumers, to maintain a healthy ecosystem.

The regression analysis indicated a notable influence of AMC in healthcare and per capita GDP on the variability in the AMR rate of *V. vulnificus* across countries (Table 3). Inappropriate AMC within healthcare systems, especially in low- and middle-income countries, reflects deficiencies in national antimicrobial stewardship programs. This is particularly concerning given that countries with higher AMC in healthcare are likely to experience elevated AMR rates, as seen with *V. vulnificus*. Adhering to WHO guidelines—such as the global action plan on AMR, which promotes reduced usage of Watch drugs relative to Access drugs—could significantly lower global AMC. This is crucial, especially during health crises like the pandemic, when AMC tends to surge [80]. The economic implications of unchecked AMR are also considerable. A synthesis of evidence suggests that by 2050, AMR could lead to a global GDP reduction of 2–3.5 %, translating to a loss of 60–100 trillion US dollars [81]. In the context of *V. vulnificus*, the rising resistance could exacerbate the economic burden, especially in countries where seafood is a major economic driver. To mitigate these risks, maintaining optimal AMC practices, even during crises, and implementing stringent antimicrobial stewardship in both healthcare and aquaculture sectors are essential. Fig. 5A shows that several Asian countries, including India, Iran, South Korea, Japan, Malaysia, and China, have low A/Wa index scores (<1.5), indicating a higher consumption of Watch group antibiotics than Access group antibiotics. This highlights a critical need for tighter national-level regulations on AMC in healthcare, specifically targeting *V. vulnificus*, to prevent further increases in AMR rates. The regression analyses also revealed a negative correlation coefficient between EPI scores and AMR, suggesting that improving environmental conditions could reduce AMR rates (Table 3). Although the EPI does not directly measure AMR, the environmental factors that are assessed by it such as antimicrobial residues in water bodies from inadequate waste treatment practices, may indirectly contribute to the emergence and spread of AMR in *V. vulnificus* [82]. Addressing environmental contamination through better waste management and water treatment practices could be a key strategy for controlling AMR in aquatic environments. Therefore, a balanced, multifactorial approach integrating socio-economic factors with environmental stewardship is crucial for managing AMR and protecting public health.

Although this study provides valuable insights into the AMR patterns of *V. vulnificus*, certain limitations should be acknowledged. The high heterogeneity observed in the AMR profiles of β-lactams, aminoglycosides, macrolides, glyopeptides, and lincosamides suggests a cautious interpretation and indicates the likely influence of unexplored covariates. The lack of studies from various Asian countries and the incomplete coverage of AMR data from all sources within each country underscore the need for further research. Future studies should investigate the influence of additional factors, such as genetic mutations, climate change, anthropogenic activities, and global health crises (e.g., pandemics), to enhance the understanding of *V. vulnificus* AMR. Owing to the dynamic nature of bacterial DNA, continuous monitoring and assessment of *V. vulnificus* AMR trends are essential. Future research should also explore the co-occurrence of ARGs and VFs in *V. vulnificus* that could provide key insights into how these interactions amplify resistance and virulence, posing significant public health risks, and help refine treatment strategies for resistant *V. vulnificus* infections. Moreover, the prevalent practice of prescribing antimicrobials without identifying the causative bacteria highlights the urgent need for rapid and cost-effective diagnostics at all healthcare levels to ensure precise treatment and infection management in the right fashion at the right time.

5. Conclusion

In conclusion, this systematic review and meta-analysis provide a comprehensive evaluation of the current AMR status of *V. vulnificus* in Asia. The results indicate a significant prevalence of *V. vulnificus* AMR across various antimicrobial classes, emphasizing the critical need for targeted antimicrobial selection and combination therapies to manage infections effectively. Given the influence of socio-economic factors on AMR trends, the findings emphasize the critical role of implementing antimicrobial stewardship programs in both the healthcare and aquaculture sectors. By reducing misuse and overuse of antimicrobials, these programs can help preserve the efficacy of existing treatments and prevent the emergence of resistant *V. vulnificus* strains, safeguarding public health and environmental sustainability.

CRediT authorship contribution statement

Maryum Tanveer: Writing – review & editing, Writing – original draft, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation. **Eurade Ntakiyisumba:** Writing – review & editing, Software, Resources, Investigation, Formal analysis. **Gayeon Won:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Data availability statement

The original contributions presented in the study are included in the article and supplementary material, further inquiries can be directed to the corresponding author.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Won Gayeon reports financial support was provided by National Research Foundation of Korea. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e40334.

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