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Vibriosis in South Asia: A systematic review and meta-analysis ☆

Basilua Andre Muzembo [1,*], Kei Kitahara [1,2], Ayumu Ohno [1,2], Januka Khatiwada [3], Shanta Dutta [4], Shin-Ichi Miyoshi [1]

[1] Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan
[2] Collaborative Research Centre of Okayama University for Infectious Diseases in India at ICMR-NICED, Kolkata, India
[3] Social Work Institute, Lalitpur-4, Nakhu, Nepal
[4] Division of Bacteriology, ICMR-National Institute of Cholera and Enteric Diseases, Kolkata, India

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ABSTRACT

Objectives: South Asia remains home to foodborne diseases caused by the *Vibrio* species. We aimed to compile and update information on the epidemiology of vibriosis in South Asia.
Methods: For this systematic review and meta-analysis, we searched PubMed, Web of Science, EMBASE, and Google Scholar for studies related to vibriosis in South Asia published up to May 2023. A random-effects meta-analysis was used to estimate the pooled isolation rate of non–cholera-causing *Vibrio* species.
Results: In total, 38 studies were included. Seven of these were case reports and 22 were included in the meta-analysis. The reported vibriosis cases were caused by non-O1/non-O139 *V. cholerae, V. parahaemolyticus, V. fluvialis*, and *V. vulnificus*. The overall pooled isolation rate was 4.0% (95% confidence interval [CI] 3.0-5.0%) in patients with diarrhea. Heterogeneity was high (I^2 = 98.0%). The isolation rate of non-O1/non-O139 *V. cholerae, V. parahaemolyticus*, and *V. fluvialis* were 9.0 (95% CI 7.0-10.0%), 1.0 (95% CI 1.0-2.0%), and 2.0 (95% CI: 1.0-3.0%), respectively. Regarding *V. parahaemolyticus*, O3:K6 was the most frequently isolated serotype. Cases peaked during summer. Several studies reported antibiotic-resistant strains and those harboring extended-spectrum beta-lactamases genes.
Conclusions: This study demonstrates a high burden of infections caused by non–cholera-causing *Vibrio* species in South Asia.

Introduction

Despite efforts to control vibriosis, reported cases are on the rise [1,2]. Vibriosis is a bacterial ailment caused by pathogenic strains of non-cholera *Vibrio* species [2,3]. The species most known to cause vibriosis include non-O1/non-O139 *V. cholerae, V. vulnificus, V. parahaemolyticus, V. fluvialis, V. mimicus*, and *V. alginolyticus* [3,4]. Of these, *V. vulnificus* and *V. parahaemolyticus* are the most common *Vibrio* species that are known to cause seafood-related food poisoning [5]. Research has demonstrated that the majority of vibriosis cases are associated with tropical or subtropical locations [6] and have spread worldwide. These bacteria have been associated with sporadic foodborne illnesses worldwide, including areas where they have not previously been reported [1,7]. The ailment is a serious public health threat in several countries, such as in European [8] and Asian countries [9], and in the United States [10]. For instance, in the United States, the incidence of vibriosis increased from 1996 to 2010 (0.09-0.28 per 100 000 habitants) [10]. Non-cholera *Vibrio* species cause about 80,000 illnesses each year in the United States, of which in approximately 52,000 cases, contaminated food is hypothesized to be the cause of the illness [7,11]. In the United States, vibriosis related to seafood is estimated to cost upwards of $350 million [12].

Depending on the etiologic agents, the most typical symptoms of vibriosis generally include symptoms of gastroenteritis (e.g., diarrhea), wound infections, and septicemia in severe cases [2,6,13–15]. Specifically, non-O1/non-O139 *V. cholerae, V. parahaemolyticus, V. fluvialis*, and *V. mimicus* often cause gastroenteritis, whereas *V. vulnificus* causes wound infections or even septicemia [2,16].

South Asian countries, such as India, are considered hotspots for *Vibrio* species transmission and an attractive destination for tourism. To date, there have been no systematic review on vibriosis in South Asia. Therefore, we conducted a systematic review to provide updates of vibriosis in South Asia and understand its cur-

☆ This systematic review is registered with PROSPERO: number CRD42023432160.

* Corresponding author.
E-mail addresses: andersonbasilua@yahoo.fr, muzembo_andre@okayama-u.ac.jp (B.A. Muzembo).

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rent epidemiology because it is vital for surveillance efforts and in guiding preventive measures.

Material and methods

Study design

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for a Systematic review and Meta-analysis (PRISMA) guidelines [17]. This systematic review is registered with PROSPERO: number CRD42023432160.

Definitions

We defined non-cholera *Vibrio* strains as *Vibrio* strains that exclude *V. cholerae* O1 and O139 strains. In addition, we defined "isolation rate" of non-cholera *Vibrio* strains as the number of participants testing positive for non-cholerae *Vibrio* strains divided by the total number of participants.

South Asian countries include Afghanistan, Bangladesh, Bhutan, India, the Maldives, Nepal, Pakistan, and Sri Lanka [18].

Search strategy and data sources

For this systematic review, we performed searches (up to May 2023) for relevant studies in four electronic databases (PubMed, EMBASE, Web of Science, and Google Scholar). The search terms are listed in Box 1. Language restrictions were not applied. Our search was supplemented by manually searching the reference lists of selected studies to identify additional relevant studies. The retrieved studies were exported to ENDNOTE software X9 (Clarivate, Philadelphia, PA, USA), and duplicates were removed.

Study selection

Population, exposure, comparison, outcomes, and study design were used to determine study eligibility. Cohort, case-control, cross-sectional, or case reports published in peer-reviewed journals were eligible for inclusion. Two authors (MBA and KK) reviewed all titles and abstracts retrieved from the search. Subsequently, the two authors reviewed the full texts of relevant articles based on the inclusion and exclusion criteria (Box 2). The full texts of all potentially relevant articles were shortlisted and reviewed, and a second screening was conducted. We used a blind review process, which ensured that each reviewer was unaware of the other's selections. The reasons for exclusion were recorded, and disagreements were resolved through discussion and review of the full text. Whenever a consensus was not reached, a third reviewer (JK) was consulted.

Extraction of data and methodological assessment

The data from all included studies were extracted by BAM and KK and entered into a structured data extraction sheet using Microsoft Excel 2019 (Version 2204, Microsoft Corp., Albuquerque, NM, USA). The extracted data included study characteristics, laboratory methods of *Vibrio* species confirmation, exposure source, information regarding antibiotic resistance, evidence of co-pathogens, number of participants testing positive for non-cholerae *Vibrio* species and the total number of participants that were tested, and serotypes (where applicable).

Two reviewers (BAM and KK) independently assessed the methodological quality of each included study using a modified Joanna Briggs Institute prevalence critical appraisal tool [19] (for cross-sectional studies), and a tool designed to evaluate the methodological quality of case reports and case series [20] (for case reports). Disagreements were addressed through consensus.

Data analysis and synthesis

Considering the potential sources of heterogeneity, random-effects models were used in the meta-analyses. When there were little data to conduct meta-analyses, the results were synthesized narratively. The case series results are presented descriptively. Heterogeneity was assessed using the I^2 statistics [21,22]. I^2 values greater than 50% were considered to indicate substantial heterogeneity [22]. We used a funnel plot to determine whether there was a potential publication bias and Egger linear regression test to determine whether there was evidence of small-study effects [23]. All statistical analyses were conducted using Stata software (version 18, StataCorp LP, College Station, TX, USA) using the metaprop command [24].

Box 1
Keywords and search terms used to identify studies on vibriosis in South Asia.

For vibriosis, we used the following keywords: "Vibriosis" [MeSH Terms] OR "Vibrioses" [MeSH Terms].
We combined these keywords with the names of the eight South Asian countries: ("Vibriosis or vibrioses" and "South Asia" and ("Afghanistan" and "Bangladesh" and "Bhutan" and "India" and "Maldives" and "Nepal" and "Pakistan" and "Sri Lanka")).
We further narrowed searches by including the following names for most common non-cholera *Vibrio* species that can cause illness in humans: ("Vibriosis" [MeSH] OR "Vibrioses" [MeSH] OR "Vibrio parahaemolyticus" [MeSH]) OR "Vibrio vulnificus" [MeSH]) OR "Vibrio mimicus" [MeSH]) OR "Vibrio fluvialis" [MeSH]) OR "non-O1/non-O139 Vibrio cholerae" [MeSH] OR "nonagglutinating vibrios" [MeSH] AND ("South Asia" [MeSH] OR "Afghanistan" [MeSH] OR "Bangladesh" [MeSH] OR "Bhutan" [MeSH] OR "India" [MeSH] OR "Maldives" [MeSH] OR "Nepal" [MeSH] OR "Pakistan" [MeSH] OR "Sri Lanka" [MeSH]). Limit: Humans

Box 2
Inclusion and exclusion criteria used to identify studies on vibriosis in South Asia.

Inclusion criteria:

- Population: individuals infected with non-cholera *Vibrio* spp. and residing in South Asia;
- Exposure: detection of non-cholera *Vibrio* spp. in blood, tissue, or stool using culture or polymerase chain lreaction (PCR), or both culture and PCR;
- Comparison: the study was conducted without a mandatory comparison group;
- Outcomes: the study provides information on the number of participants who tested positive for non-cholera *Vibrio* spp. or on the non-cholera *Vibrio* spp. serotype.

Exclusion criteria:

- Studies not performed in South Asia;
- Studies including only cholera patients;
- Non-clinical studies (studies consisting only of water samples, fish, and shellfish, to name a few);
- Studies that were only available as abstracts, reviews, commentaries, and editorials.

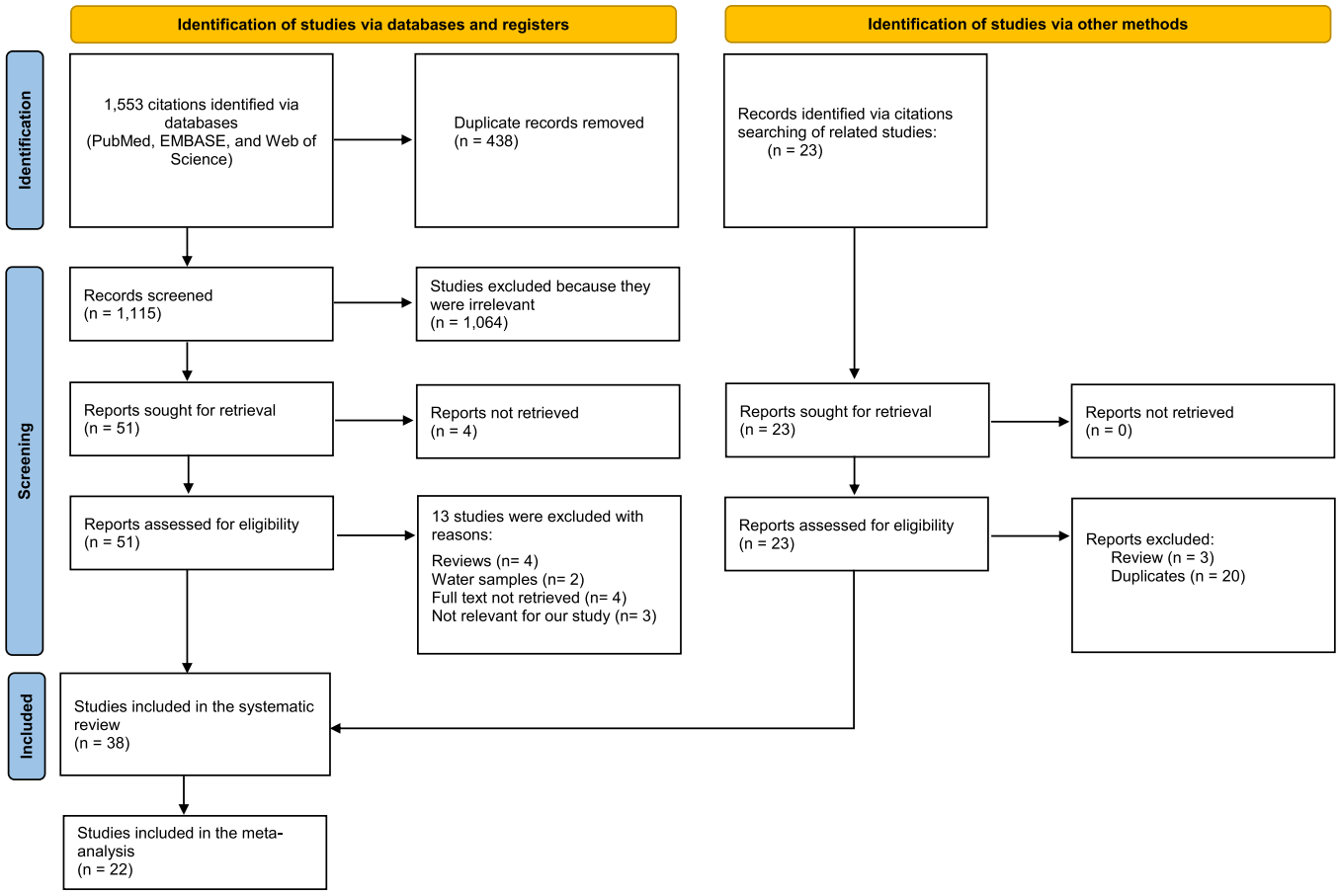

Figure 1. Study selection process.

Results

Search results

Our search of electronic databases and manual searches yielded a total of 1576 citations (Figure 1). After scanning the citations for duplicates, 438 studies were removed. Then, the remaining 1138 studies were screened based on the titles and abstracts. We additionally removed 1087 studies because we deemed that they were not relevant based on the titles and abstracts, leaving 51 articles for full article review. After scrutinizing the full texts of the 51 remaining studies, we removed 13 studies for reasons listed in Supplementary Table S1. Thus, 38 studies with 2609 vibriosis cases from four South Asian countries met the inclusion criteria and were used in this systematic review. Of these, 22 were used in the meta-analysis.

Study characteristics

The characteristics of the included studies are summarized in Tables 1 and 2. Supplementary Tables 2 and 3 provide further details regarding the included studies. Regarding study design, there were 31 cross-sectional studies [25–55] (Table 1); however, one study used data from a randomized controlled trial [44] and four studies were outbreak or epidemic investigations [25,31,46,48]. In addition, seven studies were case reports [56–62] (Table 2). Of the included studies, 27 were conducted in India, three in Bangladesh, and one in Pakistan (Figure 2). Furthermore, case reports were from two countries: six from India and one from Sri Lanka. No study from Afghanistan, Bhutan, the Maldives, and Nepal met the eligibility criteria. The included studies were published between 1989 and 2023. Most case reports (6 of 7, 85.7%) were published between 2011 and 2023.

In cross-sectional studies, the sample sizes ranged from 11 to 29,196. In five studies (5 of 31, 16.1%), only the number of patients with vibriosis were reported [26,29,32,51,53].

Regarding participants' ages in cross-sectional studies, most studies (18 of 31, 58.0%) evaluated mixed groups of adults and children (without separating the data). However, in two studies (2 of 31, 6.5%), only children were included, whereas eleven (11 of 31, 35.5%) did not disclose the age of the study participants. Particularly, in India, young children were reported to be the age group most affected by *V. cholerae* non-O1/O139 serogroups [34].

For vibriosis case reports, all patients (n = 8) were from India, of whom six were adults, whereas two were children. Of the patients from case reports with reported residential areas (7 of 8, 87.5.0%), all were from the coastal or fisherfolk community [56–60]. In terms of setting (in cross-sectional studies), the majority (23 of 31, 74.2.0%) of the studies were conducted in areas close to coastal regions [25–33,36–41,43,44,46–50,54,55].

As for peak season, vibriosis cases were more prevalent during summer than other seasons [40,52,54,56]. Some vibriosis outbreaks particularly arose after natural disasters. For instance, in India, *V. fluvialis* epidemic [25], and vibriosis cases caused by non-O1/O139 *V. cholerae* were reported after a cyclone [46].

The most reported non-cholera *Vibrio* species causing illnesses in South Asia are *V. fluvialis, V. parahaemolyticus*, non-O1/non-O139 *V. cholerae* (Table 1), and *V. vulnificus* (Table 2). Most patients from case reports had underlying medical conditions, such as diabetes [56,57], liver disease [56,62], and malnutrition [58,60]. The

Table 1
Characteristics of reviewed studies (n = 31).

Author (year) [Reference]	Years of data collection	Study design	Species	Age of patients	Other pathogens	Prevalence or number of cases
India						
Bhattacharjee et al. [25]	2009	Cross-sectional	*V. fluvialis*	All ages	*E. coli*; *V. cholerae* O1	5/100 (0.05%)
Chakraborty et al. [26]	1998 to 2000	Cross-sectional	*V. fluvialis*	Children	Mixed infection with *V. cholerae* or *V. parahaemolyticus*	11 cases
Chandrasekhar et al. [27]	2000 to 2004	Cross-sectional	Non-O1/non-O139 *V. cholerae*	All ages	Mixed infection with *V. cholerae* O1 (11/66; 16.7%)	66/256 (26%)
Chatterjee et al. [28]	2003	Cross-sectional	Non-O1/non-O139 *V. cholerae*	All ages	Mixed infection with *V. cholerae* O1 and O139 (137/197; 69.5%)	54/197 (27.4%) of *V. cholerae*
Chowdhury et al. [29]	2009	Cross-sectional	*V. fluvialis*	NR	NR	12 cases
Chowdhury et al. [30]	2002 to 2009	Cross-sectional	*V. fluvialis*	All ages	88/131 (67.2%) were mixed infection (with *V. cholerae; V. parahaemolyticus*; E. coli; *Shigella* spp.; parasites; or enteric viruses). 269 strains were *V. cholerae* strains.	131/11909 (1.1%)
Chowdhury et al. [31]	2011	Cross-sectional	*V. parahaemolyticus*	All ages	NR	3/44 (6.8%)
Chowdhury et al. [32]	2009 to 2013	Cross-sectional	*V. fluvialis*	NR	14/27 (52.0%) were mixed infections (with *Shigella* spp.; diarrheagenic *E. coli*; *Salmonella* spp.; rotavirus; Giardia lamblia; and *Campylobacter* spp.)	115 cases
Chowdhury et al. [33]	2014 to 2015	Cross-sectional	*V. fluvialis*	All ages	Mixed infection in 46% (13/28)	48/2308 (2.0%)
Cruz et al. [34]	1992 to 2014	Cross-sectional	Non-O1/non-O139 *V. cholerae*	All ages	NR	114/1401 (8.1%)
Das and Gupta [35]	1992 to 2000	Cross-sectional	Non-O1/non-O139 *V. cholerae*	All ages	NR	696/29196 (2.4%)
Dua et al. [36]	2013	Cross-sectional	Non-O1/non-O139 *V. cholerae*	NR	NR	78/147 (53.0%)
Dutta et al. [37]	2002 to 2010	Cross-sectional	Non-O1/non-O139 *V. cholerae*	All ages	Mixed infection in 0.8% (106/12719)	281/12719 (2.2%)
Garg et al. [38]	1992 to 1997	Cross-sectional	Non-O1/non-O139 *V. cholerae*	All ages	NR	200/840 (23.8) of *V. cholerae* strains.
Guin et al. [39]	2008 to 2011	Cross-sectional	*V. parahaemolyticus*	NR	NR	29/2603 (1.1%)
Kanungo et al. [40]	2007 to 2010	Cross-sectional	*V. parahaemolyticus*	All ages	*V. cholerae*	137/18087 (0.8%)
Matsumoto et al. [41]	1994 to 1996	Cross-sectional	*V. parahaemolyticus*	NR	NR	NR
Mohanty et al. [42]	1998 to 2002	Cross-sectional	Non-O1/non-O139 *V. cholerae*	NR	NR	6/3213 (0.2%)
Nair et al. [43]	2007 to 2009	Cross-sectional	Non-O1/non-O139 *V. cholerae*	All ages	Mixed infection in 29.2%. At least 2 pathogens in 72%	55/2519 (2.2%)
			V. fluvialis	All ages	Mixed infection in 29.2%. At least 2 pathogens in 72%	55/2519 (2.2%)
			V. parahaemolyticus	All ages	Mixed infection in 29.2%. At least 2 pathogens in 72%	74/2519 (2.9%)
Nair et al. [44]	2007 to 2008	Randomized controlled trial	*V. mimicus*	Children	*Campylobacter* spp. (38/133; 54.3%)	70/133 (52.6%) of *V. cholerae /mimicus*
Narang et al. [45]	1990 to 2005	Cross-sectional	Non-O1/non-O139 *V. cholerae*	All ages	NR	22/10406 (0.21%)
Panda et al. [46]	2009	Cross-sectional	Non-O1/non-O139 *V. cholerae*	All ages	*V. cholerae* O1 in 21/39 (54%) patients	4/39 (10.2%) of *V. cholerae* cases
Pazhani et al. [55]	2001 to 2012	Cross-sectional	*V. parahaemolyticus*	All ages	NR	178/13607 (1.3%)
Ramamurthy et al. [47]	1989 to 1991	Cross-sectional	Non-O1 *V. cholerae*	All ages	*V. cholerae* O1 in 10/28 (36%)	28/591 (4.7%)
Sen et al. [48]	2003	Cross-sectional	*V. parahaemolyticus*	NR	*E. coli* (non-pathogenic strain)	5/21 (24.0%)
Sinha et al. [49]	NR	Cross-sectional (archived stool samples were used)	*V. parahaemolyticus*	NR	*V. cholerae; campylobacter* spp.; *Shigella* spp.; and diarrhoeagenic *E. coli*	Using culture: 9/68 (13.2%) for single infection and 2/68 (2.9%) for mixed infection. Using PCR: 3/68 (4.4%) for single infection and 27/68 (39.7%) for mixed infection

(*continued on next page*)

Table 1 (*continued*)

Author (year) [Reference]	Years of data collection	Study design	Species	Age of patients	Other pathogens	Prevalence or number of cases
Srinivasan et al. [50]	1998 to 2002	Cross-sectional	*V. fluvialis*	NR	NR	19 strains
Bangladesh						
Bhuiyan et al. [51]	1998 to 2000	Cross-sectional	*V. parahaemolyticus*	NR	NR	66 cases
Klontz et al. [52]	1996 to 2001	Cross-sectional	*V. parahaemolyticus*	All ages	NR	126/13970 (0.9%)
Matsumoto et al. [41]	1977 to 1998	Cross-sectional	*V. parahaemolyticus*	NR	NR	NR
Qadri et al. [53]	2000 to 2001	Cross-sectional	*V. parahaemolyticus*	All ages	Two patients had *Ascaris lumbricoides*, and one patient had both *Giardia* and *Entamoeba histolytica*.	28 cases
Pakistan						
Irfan et al. [54]	1999 to 2012	Cross-sectional	Non-O1/non-O139 *V. cholerae*	All ages	NC	233/20124 (1.2%)

NR = not reported; NC = not clear; M = male; V = *Vibrio; E = Escherichia;* PCR = polymerase chain reaction; icddr,b = International Centre for Diarrheal Disease Research, Bangladesh.

Table 2
Characteristics of reviewed case reports (n= 7).

Author (year) [reference]	Years of data collection	Study design	Species	Age of patient (year) and gender	Route of exposure	Other diagnosis	Underlying medical condition	Outcome
India								
Bhat et al. [56]	2017	Case report	*V. vulnificus*	52; M	Not explored	Necrotizing fasciitis	Diabetes and alcoholic liver disease	Died from septic shock
D'Souza et al. [57]	2017	Case report	*V. vulnificus*	67; F	No history of seafood intake or exposure to seawater	Increased erythrocyte sedimentation rate (84 mm/h)	Diabetes	Discharged after recovery
D'Souza et al. [57]	2017	Case report	*V. vulnificus*	63; M	No history of seafood intake or exposure to seawater	NR	Diabetes	Not available (ambulatory care)
De and Mathur [58]	2007	Case report	*V. vulnificus*	1.5; M	No history of seafood intake. The source of infection could not be traced.	*Klebsiella pneumoniae* and *Acinetobacter* from endotracheal secretions	Malnutrition	Discharged after recovery
Madiyal et al. [62]	NR	Case report	*V. vulnificus*	52; M	No history of seafood intake or exposure to seawater. But he lived in the coastal area.	Necrotizing fasciitis	Alcoholic liver disease	Discharged without complete recovery
Narendrakumar et al. [59]	NR	Case report	*V. vulnificus*	55; M	No history of seafood intake or exposure to seawater. The source of infection could not be traced	Lower limb Necrotizing fasciitis progressing to cellulitis and septicemia	None except dyslipidemia	Died from septic shock and multi-organ failure on the day of admission
Saraswathi et al. [60]	NR	Case report	*V. vulnificus*	6; M	History of contact with sea water	Septicemia	Malnutrition	Discharged after recovery
Sri Lanka								
Abeyagunawardena and Priyankara [61]	NR	Case report	*V. vulnificus*	46; M	Occupational exposure to seawater and seafood	Consolidation of the lung	The patient was not immunocom-promised	Discharged after full recovery

NR = not reported; M = male; F = female; V = *Vibrio*.

outcomes for the eight case reports were as follows: half (4 of 8, 50.0%) were discharged after complete recovery [57,58,60,61], two died from septic shock (2 of 8, 25.0%) [56,59], one (1 of 8, 12.5%) was discharged without complete recovery [62], and one (1 of 8, 12.5%) was on ambulatory care without a recorded outcome [57].

Only eight cross-sectional studies (8 of 31, 26.0%) reported the exposure routes, namely, contaminated water [25,30,39,40,46,54], consumption of contaminated fish [39], ingestion of contaminated food [31,48], contaminated fish at a fish market, and contaminated food in the kitchen [40]. In the case reports, history of contact with sea water [60] and occupational exposure to seawater and seafood [61] were reported to be exposure routes, along with living close to coastal regions [56–60].

Several reviewed studies reported the presence of non-cholera *Vibrio* species that were multidrug-resistant (MDR) against first-

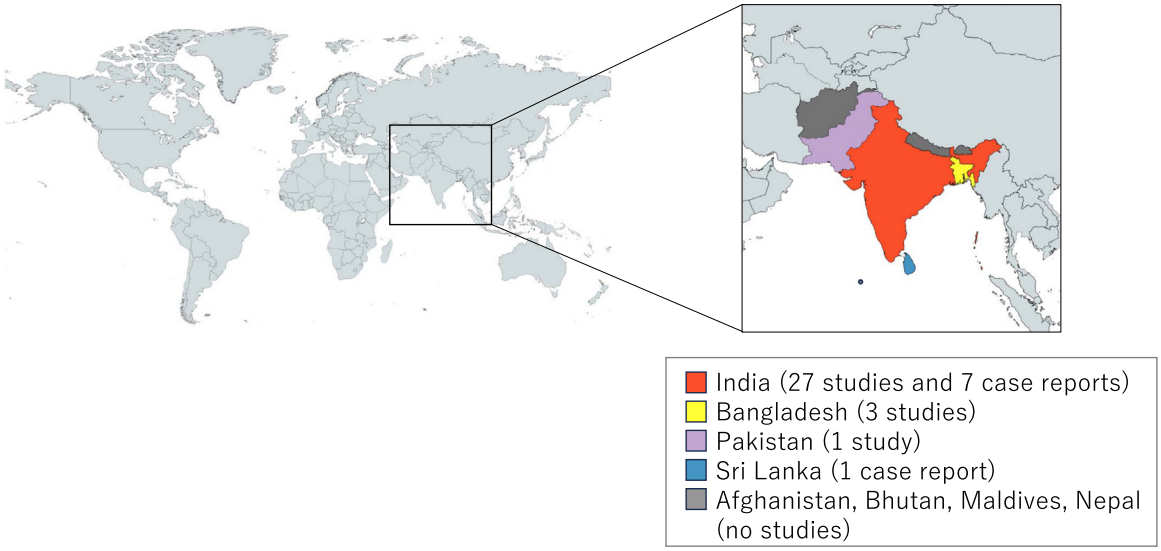

Figure 2. Number of studies conducted in each country.

and second-line antibiotics [25–30,32,33,36,38,42,47,50,53–55], including strains harboring extended-spectrum beta-lactamase genes [29,33], New Delhi metallo-beta-lactamase-1 genes [32], or genes encoding hemolysin and metalloprotease [30].

One study performed in an urban slum in Kolkata (India) reported the existence of asymptomatic carriers of *V. cholerae* and *V. mimicus* (70 of 133, 52.6%) in healthy children aged 1 to 5 years old [44]. In these asymptomatic carriers, *V. mimicus* could not be distinguished from non-O1/non-O139 *V. cholerae* [44].

A total of 16 studies (16 of 31, 51.6%) reported mixed infections with enteric pathogens in the stool samples of the participants. The most reported pattern of mixed enteric pathogens was the co-occurrence of non-O1/non-O139 *V. cholerae* with *V. cholerae* O1 [25–28,30,40,46,47,49]. In addition, *V. parahaemolyticus* was mixed with *V. fluvialis* [26,30]. Other enteric pathogens that were mixed with non-cholera *Vibrio* spp. included *Campylobacter* spp. [32,44,49], rotavirus [44], *Escherichia coli* [25,48], Enterotoxigenic *Escherichia coli* [32,44,49], Enterohemorrhagic *Escherichia coli* [44], *V. parahaemolyticus* mixed with *V. fluvialis* [26,30], *Shigella* spp. [30,32,49], *Salmonella* spp. [32], rotavirus [32], and *Giardia lamblia* [32,53].

Of note, the majority of *V. parahaemolyticus* strains belonged to serotype O3:K6 [39,41,48,51,53,55]. The other *V. parahaemolyticus* serotypes were the O4:K8 serotype [31,41,55], O4:K68 serotype [41,51], O3:KUT serotype [39,55], O1:K25 and O2:K3 serotypes [55], O2:K4 and O8:K21 serotypes [39], O1:KUT serotype [41,51], O1:K25 serotype [53], and multiple non-classified serotypes from multiple Asian countries [41].

Methodological assessment

The results of the quality assessments (graphic and tabular summaries) are available in the supplementary materials (Supplementary Figure 1 and Supplementary Table 4). Of the 31 studies that were evaluated using the Joanna Briggs Institute assessments, the scores for individual studies ranged from 3 to 9. We did not exclude studies because of the methodological flaws in the quality of their reporting.

Meta-analysis

A total of 22 studies (with 24 data points and a sample size of 117,986) reported data on the isolation rates of non-cholerae *Vibrio* species and were included in the meta-analysis of prevalence of vibriosis in South Asia. Table 3 shows the random-effect model estimates for the pooled isolation rates of non-cholerae *Vibrio* species. The overall pooled isolation rate was 4.0% (95% confidence interval [CI] 3.0-5.0%) with high heterogeneity (I^2 = 98.0%).

Subgroup analysis

Subgroup analyses showed that the isolation rate of non-O1/non-O139 *V. cholerae, V. parahaemolyticus*, and *V. fluvialis* were 9.0 (95% CI 7.0-10.0%), 1.0 (95% CI 1.0-2.0%), and 2.0 (95% CI 1.0-3.0%), respectively (Table 3).

Removing outliers

The sensitivity analysis did not affect the robustness of the overall pooled estimate (4.0%): after removing one study outlier that reported an isolation rate of 53.0% [36], we found that the overall pooled isolation rate remained unchanged (4.0%, 95% CI 3.0-4.0%). Furthermore, we excluded five studies that reported an isolation rate higher than 20.0% [27,28,36,38,48] and found that the overall pooled isolation rate slightly dropped to 3.0% (95% CI 3.0-4.0%).

The funnel plot (Supplementary Figure 2) was evidently asymmetric (with less precise studies reporting higher isolation rates), indicating that publication bias may exist. The Egger linear regression test was 2.72, with a slope beta1 of 3.54 (with a standard error of 1.29), and a *P*-value of 0.007, meaning that there was some evidence of small-study effects.

Discussion

Herein, we document vibriosis in South Asia. We compiled 38 studies that described vibriosis in South Asia. Seven of these studies were case reports. The reported vibriosis cases were caused by non-O1/non-O139 *V. cholerae, V. parahaemolyticus, V. fluvialis*, and *V. vulnificus*. In contrast to the United States, where *V. alginolyticus* has been identified as one of the species contributing to an increase in reported infections, *V. alginolyticus* was not reported in the reviewed studies. In addition, *V. fluvialis* is not among the species driving the increase in vibriosis in the United States [10]. Similarly, *V. fluvialis* and *V. alginolyticus* were not in the list of the drivers of vibriosis in Europe [8]. Compared with the data from

Table 3
Meta-analysis of isolation rate for non-cholera vibrio species in South Asia.

Group and study	Data points (Number of studies)	Sample size	Pooled isolation rate, % (95% confidence interval)	Heterogeneity
All studies [25,27,28,30,31,34–40,42,43,45–49,52,54,55]	24 (22)	117,986	4.0 (3.0-5.0)	I^2 = 98.0%; Z = 12.8; and *P* <0.001
***Vibrio* species**				
Vibrio cholerae non-O1/non-O139 [27,28,34–38,42,43,45–47,54]	13 (13)	52,539	9.0 (7.0–10.0)	I^2 = 98.2%; Z = 11.3 and *P* <0.001
Vibrio parahaemolyticus [31,39,40,43,49,52,55]	8 (8)	50,919	1.0 (1.0–2.0)	I^2 = 89.9%; Z = 6.7 and *P* <0.001
Vibrio fluvialis [25,30,43]	3 (3)	14,528	2.0 (1.0–3.0)	I^2 = 87.1%; Z = 3.23 and *P* <0.001
Other				
Removing 1 outlier study[a] [25,30,31,34,35,37,39,40,42,43,45–47,49,52,54,55]	23 (21)	117,839	4.0 (3.0–4.0)	I^2 = 97.8%; Z = 12.3; and *P* <0.001
Removing five outlier studies[b] [25,30,31,34,35,37,39,40,42,43,45–47,49,52,54,55]	19 (17)	116,525	3.0 (2.0–3.0)	I^2 = 97.0%; Z = 10.3; and *P* <0.001
Vibrio cholerae non-O1/non-O139 (using all patients with diarrhea as the denominator) [27,34–37,43,47]	7 (7)	46829	6.0 (5.0–8.0)	I^2 = 97.8%; Z = 8.5; and *P* <0.001
Vibrio cholerae non-O1/non-O139 (using only the total number of patients infected with *Vibrio cholerae* species as the denominator) [28,38,42,45,46,54]	6 (6)	519	12.0 (6.0–17.0)	I^2 = 98.1%; Z = 4.4; and *P* <0.001

[a] We excluded one study that reported an isolation rate of 53.0% [36]
[b] We excluded five studies that reported isolation rate above 20% [27,28,36,38,48].

African countries, non-O1/non-O139 *V. cholerae, V. parahaemolyticus, V. fluvialis*, and *V. vulnificus* are present in water bodies [63,64]. In other Asian countries, such as in Malaysia, *V. parahaemolyticus* has been reported to be the main species driving vibriosis [65].

Worldwide, vibriosis cases seem to be on the rise [1,66]. Consistent with this observation, overall, the data from the reviewed studies are unequivocal, indicating that vibriosis is an emerging public health problem of serious concern in South Asia that requires increased attention because exposure to *Vibrio* species can have severe health consequences for individuals and the public and threatens food security. Health authorities should be aware of these emerging human pathogens to design control measures, support new research on vibriosis, and educate the local community and visitors to coastal areas because the reviewed studies showed that most of the infections occurred in people living close to coastal areas. Travelers to South Asia should also be aware of these emerging human pathogens for better preparedness, such as avoiding consuming undercooked or raw seafood (e.g., oysters, clams, mussels, crabs, shrimp, and prawns) or potentially contaminated seafood such as ready-to-eat foods [67]. This is because the following reasons: first, vibriosis can be acquired through the consumption of contaminated raw or insufficiently cooked seafood, and contamination of sea food occurs frequently in Asia [68–70]; raw seafood consumption in Asia is on the rise [68], and Asia is a setting where aquaculture production demand is rising [1]. Second, vibriosis is generally self-limited and short-lived; however, the disease can be fatal for young children, people with underlying conditions such as diabetes and liver or renal diseases, and those with impaired immune functions. Prompt diagnosis and treatment are vital to reduce the risk of death in these high-risk groups. Third, vibriosis caused by *V. vulnificus* may require intensive care or amputation of the affected limb because the outcome can be fatal [3]. For instance, it is projected that deaths due to *V. vulnificus* will cost billions of dollars in the United States [5].

The reviewed studies showed that vibriosis cases peaked throughout the summer months, as seen for infectious diseases showing seasonal dynamics such as shigellosis [18,71] and cholera outbreaks in India [72]. One plausible explanation is that most bacteria, including the *Vibrio* species, multiply and grow faster during hot seasons [66,73]. For instance, *V. parahaemolyticus* and *V. vulnificus* grow extremely well above 15°C [1]. Indeed, in the summer, when the water is warmer, individuals are more likely to visit coastal areas for recreation, which increase the risk of being in contact with the *Vibrio* species. It has also been reported that hot temperatures provide a better environment for *Vibrio* species to colonize hosts, such as crustaceans and fish [74], and increase the risk of disease in humans.

Moreover, some reviewed studies reported the possible emergence of MDR strains of non–cholera-causing *Vibrio* species. Although this may be of interest, it is worthwhile considering the overall clinical implications of MDR strains, given that mild vibriosis cases may not require hospitalization or antibiotic treatment. The misuse of antibiotics could be one of the reasons for the possible emergence of MDR strains. This observation suggests that continuous monitoring is necessary, including enforcement of regulations for the misuse of antibiotics. This is because antimicrobial resistance can lead to difficult-to-treat infections, prolonged hospital stay, increased health care costs, and increased risk of death [75]. In our review, most strains reported as MDR originated from India, a country where the use of antibiotics is widespread but unregulated [33]. Environmental MDR *Vibrio* strains that are potentially harmful to human health have also been reported in various regions of the world [76], including Africa [77], Europe [78], the Americas [79], and other parts of Asia [80–84].

The overall isolation rate of *Vibrio* species (non-O1/non-O139 *V. cholerae, V. parahaemolyticus*, and *V. fluvialis*) in South Asian countries is estimated to be 4% in symptomatic patients. This pooled prevalence is underestimated because vibriosis is often underdiagnosed, underreported, and understudied [2]. This is evidenced by the fact that only four South Asian countries had studies that were eligible for inclusion in this review. The lack of laboratory diagnos-

tic resources in low-resource settings and lack of constraints on reporting vibriosis cases, as well as poor surveillance may explain, at least in part, this underreporting. For instance, access to various diagnostic tests may not always be available in remote settings. As a result, vibriosis cases may be underdiagnosed and treatment may be incorrect, particularly, when health professionals are not expecting vibriosis to occur. Furthermore, the studies were heterogenous. Several factors could account for this heterogeneity, including the variability in the study designs and data analysis methods. For instance, the studies that used the total number of patients with *Vibrio* infection as a denominator reported a higher isolation rate than those that used all patients with diarrhea as a denominator (Table 3).

When considering the *V. parahaemolyticus* serotypes, we observed that the O3:K6 serotype was predominant. Our observation is in line with findings from other countries. For instance, a study showed that V. parahaemolyticus serotype O3:K6 was predominant in Shenzen Province in China between 2007 and 2012 [85]. In another study conducted in China in 2019, O3:K6 was also found to be predominant [86]. The serotype O3:K6 has also caused vibriosis in several countries, including France [87], Mozambique [88], and in the Americas [89]. Thus, this O3:K6 serotype has been identified as a pandemic serotype that has been associated with foodborne outbreaks as well as sporadic cases in almost all continents [2,14]. Of note, *V. parahaemolyticus* pandemic serotype O3:K6 is believed to have originated from the Bay of Bengal in Asia before spreading to other part of Asia and the world [2,89]. Shellfish transport and ballast water dumping (which displace organisms and hence alter marine microbial ecosystems), movement of marine waters, and seawater temperature and salinity have been hypothesized to contribute to the international spread of *V. parahaemolyticus* O3:K6 serotype [2,90,91]. Other environmental factors associated with international spread of O3:K6 remain elusive. Because most pandemic *V. parahaemolyticus* belong to the O3:K6 serotype, a potential future vaccine against *V. parahaemolyticus* infection should include at least the pandemic serotype O3:K6. It is important to note that recently, *V. parahaemolyticus* serotype O10:K4 (which might be a clone of O3:K6 [92]) has been reported in China [70,86,92,93] and Thailand [94].

Although, to the best of our knowledge, this is the first meta-analysis on vibriosis in South Asia that might provide insights for policymakers in planning surveillance efforts for *Vibrio* species, our study has limitations.

First, we were limited by the lack of studies conducted in Afghanistan, Bhutan, the Maldives, and Nepal. Therefore, our pooled estimates may potentially be biased and may not necessarily be applicable to other South Asian countries. However, the lack of studies in these countries should not be interpreted to mean that exposure to *Vibrio* species is not an issue. Vibriosis in the Maldives and Nepal might also be an underdiagnosed and underreported health issue because of the potential contamination of seafood and global warming owing to climate change. For instance, *V. parahaemolyticus* has been isolated at Osaka Airport from patients with traveler's diarrhea who had visited the Maldives [95]. In addition, *V. parahaemolyticus, V. fluvialis*, and *V. vulnificus* had been isolated in the sewage in Nepal [96].

Second, despite a thorough literature search, it is possible that some studies could not be retrieved. We were unable to identify publications in languages other than English or unpublished articles that could have met our inclusion criteria. This highlights the problem of publication bias toward studies that yield negative outcomes. Indeed, there was some evidence of publication bias. Nevertheless, this limitation is partially tempered by the large sample size of 117,986 participants that was used in the meta-analysis. Thus, our pooled estimate of a 4% isolation rate helps to obtain an overview of vibriosis in South Asia.

Conclusion

In conclusion, we conducted this study to provide an overview of the epidemiology of vibriosis in South Asia, an area in which the *Vibrio* species have been identified as the leading cause of foodborne diseases. Our analysis confirms that infections caused by non–cholera-causing *Vibrio* species are prevalent in South Asia and are significant diarrheal pathogens. Therefore, we highlight the importance of these species in the differential diagnosis of gastroenteritis in endemic regions, such as South Asia.

Declaration of competing interest

The authors have no competing interest to declare.

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Institutional review board statement

No ethical approval was necessary for this study because it is a review.

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Author contributions

All authors contributed significantly to this study. BAM, KK, and SIM: study conception and its design; BAM and KK: literature search, data collection, analysis, and interpretation; BAM: wrote the first draft of the manuscript; KK and JK: commented on the early version of the manuscript; KK, AO, JK, SD, and SIM: revised the manuscript for important academic content; and SIM: supervised the study.

Informed consent statement

Not applicable for this study because this study is a review.

Data availability statement

All relevant data are included in the manuscript and its supporting information files.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.01.022.

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