Prevalence of Antibiotic Resistance in *Vibrio cholerae*: A Meta-analysis

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Research article

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Abstract

Background: Cholera could cause severe watery diarrhea and even death, but in patients diagnosed with severe dehydration, treatment with an appropriate antimicrobial agent could decrease the volume of diarrhea and shorten the duration of *V. cholerae* shedding. Unfortunately, due to the high antibiotic's consumption, antibiotic resistance in *V. cholerae* strains is progressively increasing worldwide. The present systematic review and meta-analysis study aimed to investigate the incidence of antibiotic resistance in *V. cholerae* strains worldwide.

Methods: The incidence of antibiotic resistance in *V. cholerae* strains was assessed by conducting a systematic review and searching international databases including PubMed and Google Scholar for articles published from Jan 1, 1990 to Sept 30, 2016 using related keywords. Studies were selected to be included in this systematic review according to a predefined eligibility criteria. International databases were searched for articles evaluating *V. cholerae* strains resistance rates to antibiotics. Pooled estimates of antibiotics resistance and 95% confidence intervals (CIs) were categorized based on WHO regions.

Results*:V. cholerae* was the most common bacterium showing high resistance rates to various antibiotics including furazolidone (83%), trimethoprim-sulfamethoxazole (67%), nitrofurantoin (66%), streptomycin (64%), and nalidixic acid (58%).

Conclusions: According to this meta-analysis results, the high resistance of *V. cholerae* strains to antibiotics could be considered as a global public health threat. Therefore, it is recommended to select appropriate antibiotic treatment regimens for each region based on antibiotic resistance patterns of local strains in that region.

Background

Cholera is an acute diarrheal disease caused by toxigenic strains of *V. cholerae* bacterium, belonging to O1 or O139 serogroups. So far, the world has witnessed seven cholera pandemics occurring during the 19th and 20th centuries. The first one occurred in 1817, and the next pandemics began in 1829, 1852, 1863, 1881,1889, and 1961, with the last continuing until now (1). In late 1992, an outbreak of *V. cholerae* O139 was reported in India and Southern Bangladesh. This epidemic continued until 1993. Since then, other outbreaks of *V. cholerae* O139 have been reported in Pakistan, Nepal, China, Thailand, Kazakhstan, Afghanistan, and Malaysia, and some imported cases have also been reported in the United Kingdom and the United States.

If the cholera outbreaks due to this new *V. cholerae* O139 serogroup are constantly recurred so that they could influence more countries around the world, this may be considered as the eighth pandemic (2).

The disease is currently considered as a primary public health concern in developing countries, and in some regions like Southern Asian, parts of African, and Latin American countries, the disease is in its endemic stage (1). It has the potential to be significantly disseminated among populations during epidemics or to affect endemic areas during regular seasons. In cholera-endemic areas, travelers could be infected by *V. cholerae* strains and act as carriers of this bacterium and spread it to non-endemic areas, although the risk is low (3). Cholera could cause severe watery diarrhea and even death, while those with mild to moderate symptoms could be treated successfully by taking fluids and salt orally or by injection. The early antibiotic therapies which were recommended for cholera patients during the 1940s and 1960s and used effectively included streptomycin and chloramphenicol. Antibiotics such as tetracycline and furazolidone are considered as suitable substitutes for tetracycline in the treatment of children. Sulfamethoxazole-trimethoprim (SXT) was recommended to be used for cholera patients' treatment during the 1970s. Azithromycin and ciprofloxacin are also recommended to be administered for cholera patients in order to decrease the duration of diarrhea, excretion of *V. cholera*, and the severity of the disease (4).

In cholera control strategies recommended by WHO, chemoprophylaxis along with antibiotics has not been suggested to be used for cholera treatment because in addition to not affecting the spread of the disease, it could induce adverse effects through contributing to the development of drug resistance. In regions where cholera is endemic, the Strategic Advisory Group of Experts (SAGE) on immunization suggests vaccination in combination with other prevention and control strategies (5). *V. cholerae* virulence and antimicrobial resistance grew during the seventh pandemic due to the emergence of a new variant cholera biotype called the atypical biotype (O1 El Tor). This atypical biotype diffuses mobile genetic elements, which are capable of self-transmission and integration into chromosomes, facilitating rapid spread and constant acquisition of resistance genes. It is also associated with more virulence and widespread drug resistance (6). Antimicrobial resistance (AMR) in *V. cholerae* strains is progressively increasing worldwide. Antimicrobial resistance is widespread in *V. cholerae* strains and currently threatens the effective treatment and control of cholera, especially in low and middle-income countries (6).

Recent studies have suggested that transposons, plasmids, mobile gene cassettes, and integrons are responsible for the emergence of MDR and XDR *V. cholerae* strains through inducing rapid and broad spread of genetic information between different species. Horizontal gene transfer (HGT) is a process that allows the pathogen to acquire exogenous DNA and develop drug resistance (7).

Studies have demonstrated that the prevalence rate of antibiotic-resistant *V. cholerae* strains is increasing worldwide. There is no general and accurate estimation about the prevalence rate of drug resistant *V. cholerae* strains. This systematic review and meta-analysis study aimed to investigate the incidence and pattern of antibiotic resistance in *V. cholerae* isolates worldwide, the results of which may be served as a yardstick for future control programs and interventions.

Methods

Search Strategy and Eligibility Criteria

Search engines in electronic databases, including PubMed and Google Scholar, were searched for articles assessing the incidence of antibiotic resistance in *V. cholerae* strains worldwide. No limitation was applied regarding the study type, time, or population. Only studies published in English were included.

Literature published was analytically searched using the following key terms: *Vibrio cholerae*, antibacterial, antimicrobial, antibiotic, drug, resistance, and resistant.

Data Extraction

At first, title and abstract screening process was performed to select relevant studies, then full texts of the eligible articles were reviewed for detailed evaluation. Duplicate articles were documented and deleted before selecting final eligible articles. Moreover, the present study was a meta-analysis; therefore, ethical approval was not required. Data were extracted from the included studies and classified based on author name, publication year, country, samples size (total number of tested samples), the number of resistant samples, sample type (clinical or environmental), methodology (antibiotic susceptibility test methodology), and resistance mechanism (refer the “Appendix 1”).

Data Analysis

A meta-analysis of proportions was conducted by pooling prevalence data using a random-effect model. Pooled estimates were classified according to study country or continent. Given the different geographic origins, it was assumed that there was a significant heterogeneity between the studies. Between-study variation was measured using the I2 statistic. An I2 value of more than 75% was considered as a significant heterogeneity. All statistical analyses were accomplished using R statistical software, Version 14.2 (StataCorp LLC, College Station, TX). The prevalence rate of antibiotic resistance in samples was reported by 95% confidence intervals (CIs). A p value of $< .05$ was considered as a statistically significant publication bias.

Results

In this study, a total of 5742 articles were screened based on their title and abstract, of which 84 studies were selected for full text evaluation and final analysis (Fig. 1) (. The selected articles were conducted from 1997 to 2019 in 32 countries, mainly in Asia. About 27182 samples (clinical and environmental) were included in the final analysis. Most of the studies used disc diffusion method to test antimicrobial sensitivity of the bacteria. The general characteristics of the studies reviewed are summarized in (Table 1).

Table 1
Study characteristics

Study characteristics	Number of studies %
Region of study	
Asia	65.6
Africa	23.8
America	5.9
Oceania	1.2
Europe	3.5
Type sample	
environmental	20
clinical	80
Method of antimicrobial susceptibility testing	
disc diffusion	85.7
E-test	5.9
agar dilution	2.4
microbroth dilution	4.7
microbroth dilution& disc diffusion	1.2
Strain	
Vibrio cholerae non-O1 non-O139	26.1
V. cholerae O1	44.9
V. cholerae O139	13
Mechanism reported	
reported	21.4
Not reported	78.6

The highest number of studies was accomplished in India (n = 20) compared to those conducted in Iran (n = 11), Thailand (n = 11), Nepal (n = 7), Ghana (n = 5), and Kenya (n = 3), as well as China, Haiti, Pakistan, Vietnam, Mozambique, and Indonesia (each n = 2), and Brazil, Austria, Slovakia, Uganda, Zambia, Guinea, German, Cote d'Ivoire, Sierra Leone, Ethiopia, Lima-Peru, Cameroon, Maryland, Senegal, and Namibia (each n = 1). Pooled antibiotic resistance prevalence rates by country and continent are shown in (Table 2, 3).

Table 2
Pooled Prevalence of antibiotic resistance, Stratified by continent, % (95% CI)

Country	Aminoglycosdes		Quinolones			Cephalosporins			Phenicols
	S	GM	CIP	NOR	NA	CTX	CXM	CRO	C
Austria	44 (33–55)	0 (0–1)	0 (0–1)	0 (0–1)	ND	0 (0–1)	ND	ND	0 (0–1)
Bangladesh	ND	0 (0–7)	0 (0–1)	ND	0	1 (0–2)	ND	0 (0–1)	ND
Brazil	75 (68–82)	0 (0–1)	0 (0–1)	ND	0 (0–1)	0 (0–1)	ND	7 (1–15)	0 (0–1)
Cameroon	ND	ND	0 (0–1)	ND	ND	ND	ND	ND	20 (16–25)
China	97 (95–99)	0 (0–1)	4 (2–7)	0.36 (0.04–1.3)	37 (0–93)	ND	0	0	20 (0–79)
Congo	ND	ND	0 (0–10)	ND	19 (8–36)	ND	ND	0 (0–10)	0 (0–10)
Cote d'Ivoire	24 (10–44)	ND	7 (1–23)	ND	14 (4–32)	7 (1–23)	ND	ND	14 (4–32)
Ethiopia	ND	ND	1 (0–7)	ND	ND	ND	ND	ND	94 (86–98)
German	1 (0–4)	ND	ND	ND	0 (0–1)	ND	ND	ND	ND
Ghana	90 (85–93)	0 (0–3)	8 (0–41)	ND	51 (42–69)	19 (6–38)	19 (10–30)	63 (51–75)	35 (6–71)

S-streptomycin; GM-gentamicin; CIP-ciprofloxacin; Nor- Norfloxacin; NA-nalidixic acid; CTX-Cefotaxime; CXM- cefuroxime; CRO- ceftriaxone; C-chloramphenicol; ND- Not determined.

Country	Aminoglycosdes		Quinolones			Cephalosporins			Phenicols
	S	GM	CIP	NOR	NA	CTX	CXM	CRO	C
Guinea	ND	ND	1 (0–2)	0 (0–1)	0 (0–1)	ND	ND	0 (0–3)	4 (2–6)
Haiti	8 (2–16)	ND	30 (12–54)	ND	13 (6–22)	ND	ND	ND	6 (1–17)
Iran	76 (19–100)	1 (0–4)	0 (0–10)	0.41 (3–11)	92 (71–100)	ND	ND	ND	31 (0–89)
Italy	1 (0–7)	3 (0–10)	0 (0–3)	ND	6 (0–16)	0 (0–3)	ND	ND	6 (0–16)
India	71 (56–85)	9 (5–13)	11 (5–17)	8 (4–13)	84 (72–93)	2 (0–8)	15 (12–18)	0 (0–2)	13 (7–22)
Indonesia	18 (4–43)	ND	0	0	ND	ND	ND	0	1 (0–2)
Ivory Coast	ND	ND	0 (0–12)	ND	100 (88–100)	ND	ND	0 (0–12)	11 (2–28)
Kenya	80 (34–100)	0 (0–2)	0 (0–1)	0 (0–1)	43 (0–97)	1 (0–7)	0 (0–2)	0 (0–8)	1 (0–4)
Nepal	100 (95–100)	0 (0–5)	0 (0–2)	ND	0	2 (0–24)	ND	ND	4 (0–13)
Lima-Peru	14 (5–26)	ND	ND	ND	7 (1–18)	ND	ND	ND	3 (0–11)

S-streptomycin; GM-gentamicin; CIP-ciprofloxacin; Nor- Norfloxacin; NA-nalidixic acid; CTX-Cefotaxime; CXM- cefuroxime; CRO- ceftriaxone; C-chloramphenicol; ND- Not determined.

Country	Aminoglycosdes		Quinolones			Cephalosporins			Phenicols
	S	GM	CIP	NOR	NA	CTX	CXM	CRO	C
Maryland	0 (0–1)	ND	0 (0–1)	ND	0 (0–1)	ND	ND	ND	0 (0–1)
Mozambique	ND	ND	0 (0–1)	ND	78 (1-100)	ND	ND	100 (87–100)	83 (58–98)
Namibia	100 (99–100)	ND	0 (0–1)	ND	0 (0–1)	ND	ND	0 (0–1)	0 (0–1)
Pakistan	ND	ND	ND	ND	ND	ND	ND	ND	2 (1–4)
Senegal	100 (93–100)	ND	ND	ND	0 (0–7)	ND	ND	ND	8 (2–19)
Sierra Leone	ND	ND	0 (0–22)	ND	7 (0–32)	ND	ND	ND	93 (68–100)
Slovakia	66 (43–85)	0 (0-0.16)	0 (0–16)	ND	ND	ND	ND	ND	0 (0–16)
Thailand	97 (88–100)	0	0	0 (0–1)	43 (32–55)	0 (0–2)	ND	ND	1 (0–3)
Togo	ND	ND	0 (0–8)	ND	90 (77–97)	ND	ND	0 (0–8)	0 (0–8)
Uganda	ND	0 (0–5)	6 (2–14)	ND	51 (38–63)	ND	ND	ND	12 (5–22)

S-streptomycin; GM-gentamicin; CIP-ciprofloxacin; Nor- Norfloxacin; NA-nalidixic acid; CTX-Cefotaxime; CXM- cefuroxime; CRO- ceftriaxone; C-chloramphenicol; ND- Not determined.

Country	Aminoglycosdes		Quinolones			Cephalosporins			Phenicols
	S	GM	CIP	NOR	NA	CTX	CXM	CRO	C
Vietnam	58 (41–74)	ND	0 (0–4)	ND	83 (76–89)	ND	ND	ND	0 (0–1)
Zambia	ND	0 (0–10)	26 (13–44)	20 (9–38)	100 (90–100)	0 (0–10)	ND	ND	9 (2–24)
Total	64 (50–76)	2 (1–4)	2 (1–3)	4 (1–7)	58 (44–72)	1 (0–3)	4 (0–18)	4 (1–8)	12 (7–17)

S-streptomycin; GM-gentamicin; CIP-ciprofloxacin; Nor- Norfloxacin; NA-nalidixic acid; CTX-Cefotaxime; CXM- cefuroxime; CRO- ceftriaxone; C-chloramphenicol; ND- Not determined.

Continued Table 2. Pooled Prevalence of antibiotic resistance, Stratified by continent, % (95% CI)

Country	Macrolides		Penicillins		Nitrofurans		Tetracycline		Sulfonamide
	AZ	E	AP	AMX	NF	F	T	DOX	SXT
Austria	ND	0 (0-1)	24 (15-34)	33 (7-70)	ND	ND	0 (0-1)	0 (0-1)	0 (0-1)
Bangladesh	0	12 (0-37)	0 (0-1)	ND	ND	51 (13-89)	37 (8-73)	0	90 (69-100)
Brazil	ND	ND	66 (39-89)	ND	ND	33 (23-45)	8 (1-20)	ND	0 (0-1)
Cameroon	ND	ND	92 (88-95)	88 (84-91)	ND	ND	68 (62-73)	12 (9-16)	64 (58-69)
China	12 (0-58)	95 (92-97)	37 (0-97)	ND	3 (2-4)	ND	33 (0-91)	3 (0-19)	45 (0-98)
Congo	ND	6 (1-19)	0 (0-10)	ND	72 (55-86)	ND	0 (0-10)	ND	97 (85-100)
Cote d'Ivoire	ND	ND	21 (8-40)	10 (2-27)	ND	ND	24 (10-44)	ND	79 (60-92)
Ethiopia	ND	15 (8-24)	89 (80-95)	ND	ND	ND	6 (2-14)	0 (0-4)	100 (96-100)
German	ND	ND	10 (5-16)	0 (0-1)	ND	ND	ND	ND	ND
Ghana	26 (0-82)	95 (92-98)	68 (34-94)	ND	ND	ND	8 (0-22)	8 (2-17)	87 (74-96)
Guinea	ND	22 (18-26)	1 (0-4)	76 (71-80)	60 (51-69)	ND	5 (3-8)	ND	27 (23-31)
Haiti	ND	2	25	ND	ND	ND	4	2	19

		(0-11)	(15-36)				(0-11)	(0-11)	(10-29)
Iran	1 (0-2)	12 (2-28)	21 (4-45)	27 (17-38)	23 (16-32)	90 (73-99)	24 (9-42)	9 (3-17)	70 (50-87)
Italy	ND	1 (0-7)	21 (10-37)	4 (0-13)	ND	ND	3 (0-10)	ND	3 (0-10)
India	6 (0-27)	56 (15-92)	79 (66-90)	34 (21-49)	72 (47-90)	94 (88-98)	14 (8-22)	10 (0-40)	62) 51- 72)
Indonesia	ND	ND	20 (1-50)	ND	ND	ND	6 (0-19)	ND	1 (0-2)
Ivory Coast	ND	0 (0-12)	0 (0-12)	ND	93 (76-99)	ND	0 (0-12)	ND	96 (82-100)
Kenya	0 (0-8)	ND	16 (0-53)	ND	ND	79 (18-100)	0 (0-3)	0 (0-8)	100 (99-100)
Nepal	0 (0-2)	21 (3-47)	46 (6-89)	ND	ND	98 (87-100)	0 (0-8)	0 (0-11)	100 (97-100)
Lima-Peru	ND	ND	5 (0-14)	ND	ND	5 (0-14)	14 (5-26)	ND	ND
Maryland	ND	0 (0-2)	7 (4-10)	ND	ND	ND	0 (0-1)	ND	0 (0-1)
Mozambique	13 (8-20)	100 (87-100)	82 (8-100)	ND	97 (93-99)	ND	70 (28-99)	56 (48-64)	93 (73-100)
Namibia	ND	ND	0 (0-1)	ND	ND	ND	0 (0-1)	ND	ND
Pakistan	ND	ND	3 (2-5)	ND	ND	ND	1 (0-2)	ND	82 (79-86)

Senegal	ND	ND	ND	2 (0-11)	ND	ND	0 (0-7)	ND	100 (93-100)
Sierra Leone	0 (0-22)	100 (78-100)	ND	ND	ND	100 (78-100)	0 (0-22)	0 (0-22)	93 (68-100)
Slovakia	14 (3-36)	29 (11-52)	71 (48-88)	ND	ND	ND	0 (0-16)	0 (0-16)	0 (0-0.16)
Thailand	5 (1-12)	26 (0-66)	7 (2-14)	ND	ND	ND	19 (4-39)	ND	46 (21-71)
Togo	ND	0 (0-8)	0 (0-8)	ND	71 (55-84)	ND	0 (0-8)	ND	100 (92-100)
Uganda	ND	ND	100 (95-100)	ND	ND	ND	51 (38-63)	ND	51 (38-63)
Vietnam	1 (0-5)	0 (0-10)	0 (0-1)	ND	ND	ND	18 (12-25)	0 (0-4)	92 (87-96)
Zambia	0 (0-10)	32 (17-51)	0 (0-10)	ND	100 (90-100)	ND	6 (1-20)	ND	100 (90-100)
Total	4 (1-11)	26 (17-36)	39 (28-50)	24 (8-43)	66 (32-94)	83 (67-94)	13 (8-19)	6 (2-10)	67 (58-75)

AZ-azithromycin; E-erythromycin; AP-ampicillin; AMX-amoxicillin; NF- Nitrofurantoin; F-furazolidone; T-tetracycline; DOX-doxycycline; SXT-trimethoprim/sulphamethoxazole or co-trimoxazole; ND- Not determined

Table 3
Pooled Prevalence of Antibiotic Resistance, Stratified by continent, % (95% CI)

continent	S	GM	CIP	NOR	NA	CTX	CXM	CRO	C
Asia	79 (68–88)	4 (2–7)	2 (1–4)	4 (2–8)	81 (64–94)	1 (0–3)	2 (0–24)	0	10 (5–16)
Africa	84 (62–98)	0 (0–1)	2 (0–5)	1 (0–8)	44 (22–67)	4 (0–13)	6 (0–22)	14 (0–40)	23 (10–38)
Americas	29 (3–65)	0 (0–1)	1 (0–7)	ND	4 (0–12)	ND	ND	7 (1–15)	0 (0–3)
Europe	8 (0–29)	1 (0–7)	0 (0–2)	ND	3 (0–14)	0 (0–3)	ND	ND	3 (0–11)
Oceania	44 (33–55)	0 (0–1)	0 (0–1)	0 (0–1)	ND	0 (0–1)	ND	ND	0 (0–1)
continent	**AZ**	**E**	**AP**	**AMX**	**NF**	**F**	**T**	**DOX**	**SXT**
Asia	2 (0–10)	24 (14–36)	41 (28–55)	33 (21–46)	24 (3–55)	9 (75–99)	16 (9–24)	6 (2–10)	69 (59–79)
Africa	8 (0–25)	49 (21–78)	36 (12–64)	42 (10–79)	87 (70–97)	86 (37–100)	11 (3–22)	7 (1–20)	90 (75–99)
Americas	ND	0 (0–1)	34 (9–64)	ND	ND	2 (6–37)	6 (1–15)	2 (0–11)	4 (0–14)
Europe	14 (3–36)	7 (0–29)	27 (7–53)	0 (0–6)	ND	ND	1 (0–7)	0 (0–16)	1 (0–7)

E-erythromycin; C-chloramphenicol; CIP-ciprofloxacin; NOR- Norfloxacin; T-tetracycline; SXT-trimethoprim/sulphamethoxazole or co-trimoxazole; NA-nalidixic acid; AP-ampicillin; S-streptomycin; AZ-azithromycin; CTX- Cefotaxime; CRO- ceftriaxone; DOX-doxycycline; NF- Nitrofurantoin; GM-gentamicin; CXM- cefuroxime ; F-furazolidone; AMX-amoxicilliN; ND- Not determined.

continent	S	GM	CIP	NOR	NA	CTX	CXM	CRO	C
Oceania	ND	0 (0–1)	24 (15–34)	33 (7–70)	ND	ND	0 (0–1)	ND	0 (0–1)

E-erythromycin; C-chloramphenicol; CIP-ciprofloxacin; NOR- Norfloxacin; T-tetracycline; SXT-trimethoprim/sulphamethoxazole or co-trimoxazole; NA-nalidixic acid; AP-ampicillin; S-streptomycin; AZ-azithromycin; CTX- Cefotaxime; CRO- ceftriaxone; DOX-doxycycline; NF- Nitrofurantoin; GM-gentamicin; CXM- cefuroxime ; F-furazolidone; AMX-amoxicilliN; ND- Not determined.

According to the present study results, resistance to furazolidone was identified as the most common antibiotic resistance pattern worldwide. The forest plot in (Fig. 2) displays odd ratio and weight for each study. The prevalence rate of furazolidone resistance has previously been reported to vary from 2% in America to 86% in Africa. The incidence of furazolidone resistance tended to be more in developing countries, such as Sierra Leone, Nepal, India, and Iran, than in other countries.

According to the present study results, resistance to trimethoprim-sulfamethoxazole was 67%, to nitrofurantoin was 66%, and to streptomycin was 64%, and the highest rates of resistance to these antibiotics were reported in Africa. The highest rate of nalidixic acid resistance was reported in Zambia and Ivory Coast; nalidixic acid resistance (81%) was the highest in Africa. In the current study, the prevalence rates of tetracyclines and doxycycline resistant *V. cholerae* strains were found to be 13 and 6%, respectively; high resistance rates were found against tetracyclines (70%) and doxycycline (34.5%) antibiotics in Mozambique.

In this study, the pooled prevalence rates of ciprofloxacin and norfloxacin-resistant *V. cholerae* strains were found to be 2 and 4% in most WHO regions with the highest rate in Haiti and Zambia. Also, the prevalence rate of azithromycin resistance was found to be 4% among *V. cholerae* strains. This meta-analysis study results showed that resistance rate of *V. cholerae* strains to other beta-lactam antibiotics was variable; and resistance rates to ampicillin (39%), amoxicillin (24%), ceftriaxone (4%), cefotaxime (1%), cefuroxime (4%), and other aminoglycosides such as gentamicin (2%) were found (8–10). Also *V. cholerae* resistance to chloramphenicol was found to be (12%) moderately high in Ethiopia (94%), Sierra Leone (93%), and Mozambique (83%).

This meta-analysis showed that *V. cholerae* resistance rates to other β-lactam antibiotics were variable and resistance rate to ampicillin (39%), amoxicillin (24%), ceftriaxone (4%), cefotaxime (1%) and cefuroxime (4%) and other aminoglycosides such as gentamicin (2%) was found. Our study showed that *V. cholerae* resistance to chloramphenicol was (12%) moderately high in Ethiopia (94%), Sierra Leone (93%) and Mozambique (83%).

Discussion

This study was a comprehensive systematic review and meta-analysis, investigating antibiotic resistance in *V. cholerae* strains. Unfortunately, *V. cholerae* strains antibiotic resistance patterns are not well

elucidated. Antibiotic therapy could not be used alone to treat the disease, to control and reduce the disease duration by approximately 50%, and to reduce bacterial excretion in the feces (11). Oral or intravenous administration of fluids comprising of sodium chloride, glucose, trisodium citrate, and potassium chloride is the primary option that could be used to treat cholera and protect a patient from dehydration (WHO, 2002). However, only patients with severe dehydration need an appropriate antibiotic therapy (WHO, 2017). The incidence of antibiotic resistance is considered as a serious challenge threatening the efficiency of almost all antimicrobial agents commonly administered to remedy or prevent this infectious disease (12).

The choice of an appropriate antibiotic should be made by taking into account drug resistance patterns of local strains of *V. cholerae* O1 or O139. Repeated antibiotic therapy also imposes destructive and harmful ecological effects on the community and further increases the global burden of antibiotic resistance, especially in low and lower-middle income countries. This negatively affects control programs and threatens active treatment of cholera (6).

Treatment of a whole community with an antibiotic is not recommended by WHO. To further complicate the epidemiology of antibiotic resistant cholera, it is sufficient to mention that there is a wide range of antibiotics to which *V. cholerae* could be resistant. If *V. cholerae* strain is thought to be sensitive, some antimicrobial agents may be effective in its treatment, including doxycycline, ciprofloxacin, and azithromycin (13). Currently, some *V. cholerae* strains have emerged in Haiti, which are sensitive to tetracycline (a proxy for doxycycline) and azithromycin, while resistant to nalidixic acid, sulfisoxazole, and trimethoprim–sulfamethoxazole (14).

In this study, the antibiotic resistance pattern of *V. cholerae* strains was comprehensively evaluated globally, and its high resistance to various antibiotics in several regions of the world was shown. This study results demonstrated that resistance to furazolidone, trimethoprim-sulfamethoxazole, nitrofurantoin, streptomycin, nalidixic acid, and ampicillin was the most common antibiotic resistance pattern worldwide (Table 2,3).

The use of doxycycline in combination with oral rehydration solutions is suggested in some cholera cases; also, tetracyclines are extensively used against *V. cholerae* infection. Erythromycin is another effective option used to reduce cholera symptoms in children and pregnant women (15). In the present study, *V. cholerae* resistance rate to erythromycin antibiotic was 26% in Africa and developing countries, such as Mozambique and Sierra Leone. Furthermore, due to low resistance rate of *V. cholerae* strains to macrolide antibiotics, especially azithromycin, they are considered as the drugs of choice for cholera treatment in children and adults.

Chloramphenicol is another effective option which acts through inhibiting protein synthesis and is commonly prescribed for cholera therapy. The use of chloramphenicol has been restricted in some country such as India in the past due to the availability of more effective antibiotics with less side effects (16). Significant increase in furazolidone resistance might be attributed to the increased consumption of this antibiotic in countries with lower level of socioeconomic development. Generally, the choice of an

appropriate antibiotic depends on drug resistance pattern of local strains. Inappropriate antibiotic prescription, over-the-counter availability of antibiotics without valid prescription, and consumption of inappropriate or partial antibiotic regimens could be the reasons for the emergence of antibiotic resistance crisis. In this regards, antimicrobials resistance is on the rise, and a recent concern is the development of antimicrobial resistance in *V. cholerae* strains in endemic areas (17).

This study showed that the pooled prevalence rates of *V. cholerae* strains which were resistant to trimethoprim–sulfamethoxazole, erythromycin, nalidixic acid, ampicillin, streptomycin, and ceftriaxone varied from 0% in countries such as Brazil, Austria, Slovakia, and Maryland (trimethoprim–sulfamethoxazole); Austria, Togo, Ivory Coast, Vietnam, and Maryland (erythromycin); Brazil, Bangladesh, Nepal, Guinea, German, Maryland, Senegal, and Namibia (nalidixic acid); Bangladesh, Zambia, Congo, Togo, Ivory Coast, Vietnam, and Namibia (ampicillin); Maryland (streptomycin); and India, China, Bangladesh, Guinea, Congo, Togo, Ivory Coast, Kenya, and Namibia (Ceftriaxone) to 100% in countries such as Zambia, Nepal, Togo, Kenya, Ethiopia, and Senegal (trimethoprim–sulfamethoxazole); Mozambique and Sierra Leone (erythromycin); Ivory Coast and Zambia (nalidixic acid); Uganda (ampicillin); Namibia, Senegal, and Nepal (streptomycin); and Mozambique (ceftriaxone). These differences in antibiotic resistance rates could be observed even within countries. It could be justified by taking into account that antibiotic resistance depends on multi factors in each geographical area (2).

Significant differences in antibiotic resistance rates from 0 to 100% in most WHO regions might be attributed to the lack of a uniform consumption pattern and access to the same antibiotics in different countries. The use of low-price antibiotics for treating this infection in developing countries, over-the-counter availability of these antibiotics, and their widespread consumption in these areas and countries might explain these outcomes. Furthermore, uncertainty about the effectiveness of simple rehydration solutions for mild and moderate dehydration could be considered as another cause of antibiotic resistance (18). Antibiotic resistance rate tended to be higher in African and Asian regions, especially in low and lower-middle income developing countries. More cholera outbreaks in these areas are the reasons for the increase in antibiotic resistance. Research results have displayed that susceptibility pattern of *V. cholerae* O1 strains to antimicrobials has altered over time, and that the spread of resistance to antibiotics commonly used for cholera treatment is on the rise in Africa and Asia (19). Resistance to azithromycin was higher in European countries, such as Slovakia, than in other countries. These findings collectively suggest that pattern of antibiotic consumption in these countries should be according to antibiotic resistance pattern.

V. cholerae is an environmental pathogen that could obtain resistance genes through direct contact with inherently resistant organisms carrying resistant genes on mobile genetic elements. This meta-analysis showed that 20% of samples studied were environmental. Antibiotic resistance mechanisms including efflux pumps, spontaneous chromosomal mutation or the development of genetic resistance via the exchange of conjugative plasmids, transposons, integrons, or self-transmissible chromosomally integrating SXT element could be accounted for the mechanisms of antibiotic resistance action in *V. cholerae* strains.

Antibiotic resistance genes could be exchanged between *V. cholerae* strains and other bacteria as well as commensals or enteric microorganisms in the human intestine, raising doubt about the reliability of several of these outcomes. The results showed that resistance patterns fluctuate may be induced via stable plasmids and plasmid-mediated mechanisms. Few studies investigated (21.4%) antibiotic resistance genes, but other studies did not investigate or discuss about the mechanisms of *V. cholerae* resistance or these alarming results (15). However, it is recommended that more investigations be carried out in order to determine the exact mechanisms of resistance action.

There are several limitations in this study. First, publications in some countries were very unusual. Between-study variation among the included studies was significant. Second, studies conducted on bacterial infections in few countries employed heterogeneous methodologies. A certain challenge was the lack of a standardized panel of antimicrobials against *V. cholerae* strains tested, thereby making it difficult to combine the results of these studies. The majority of studies performed only disc susceptibility testing without further MIC and ESBL testing or determination of MDR and XDR *V. cholerae* strains due to differences in patterns of economic development, antimicrobial consumption, and transmission of *V. cholerae* genotypes. High-quality antibiotic susceptibility testing is considered as a significant public health method; identifying AMR contributes to the update of local treatment guidelines and prevents the use of ineffective antibiotics. These issues are vital as our antimicrobial facilities are limited, especially in low-income epidemic areas.

Conclusions

This meta-analysis study provides an overview of the global incidence of antibiotic resistance in *V. cholerae* strains, exhibiting high resistance rates against various antibiotics. Therefore, to improve the efficacy of *V. cholerae* infection treatment, the following measures need to be taken, including exploring practical mechanisms of antibiotic resistance and dominant antibiotic-resistant elements, monitoring the incidence of antibiotic resistance in *V. cholerae* strains, implementing surveillance networks at the local and national levels, and designing new noninvasive methods suitable for clinical practice. Given the complexity of antibiotic-resistant *V. cholerae* epidemiology, strategies including antibiotic rotation, the use of previous clinical experiences, and modeling of studies to control antibiotic consumption pattern are recommended to be taken into account in future guidelines. However, given the threat imposed by antibiotic-resistant *V. cholerae* strains on public health, it seems more prudent to use vaccination as an alternative way to reduce antibiotic selection pressure.

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Not applicable

Availability of data and materials:

The datasets supporting the conclusions of this article are included within the article.

Competing interests:

The authors declare that they have no competing interests.

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SB-J, BB drafted the manuscript. SB-J, BB and MM contributed to data interpretation. All authors reviewed the manuscript. All authors read and approved the final manuscript.

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Figures

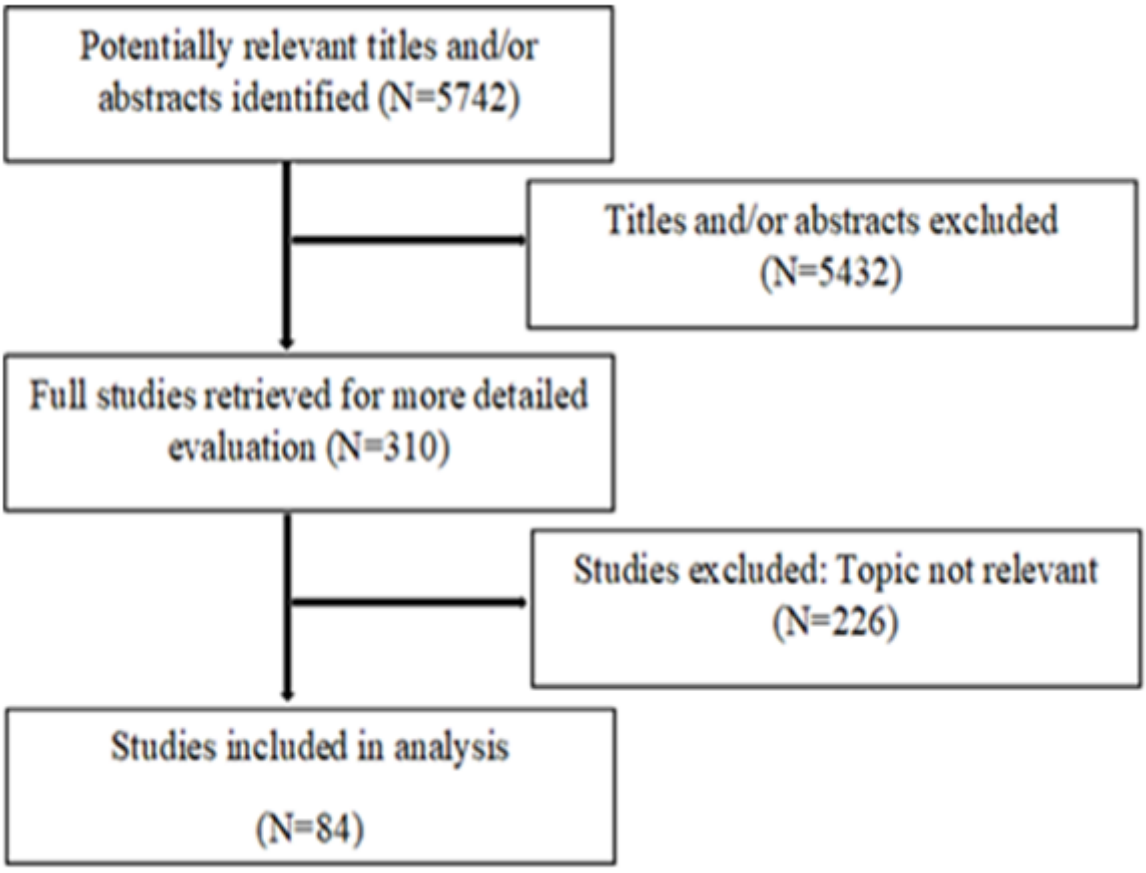

Figure 1

Study selection

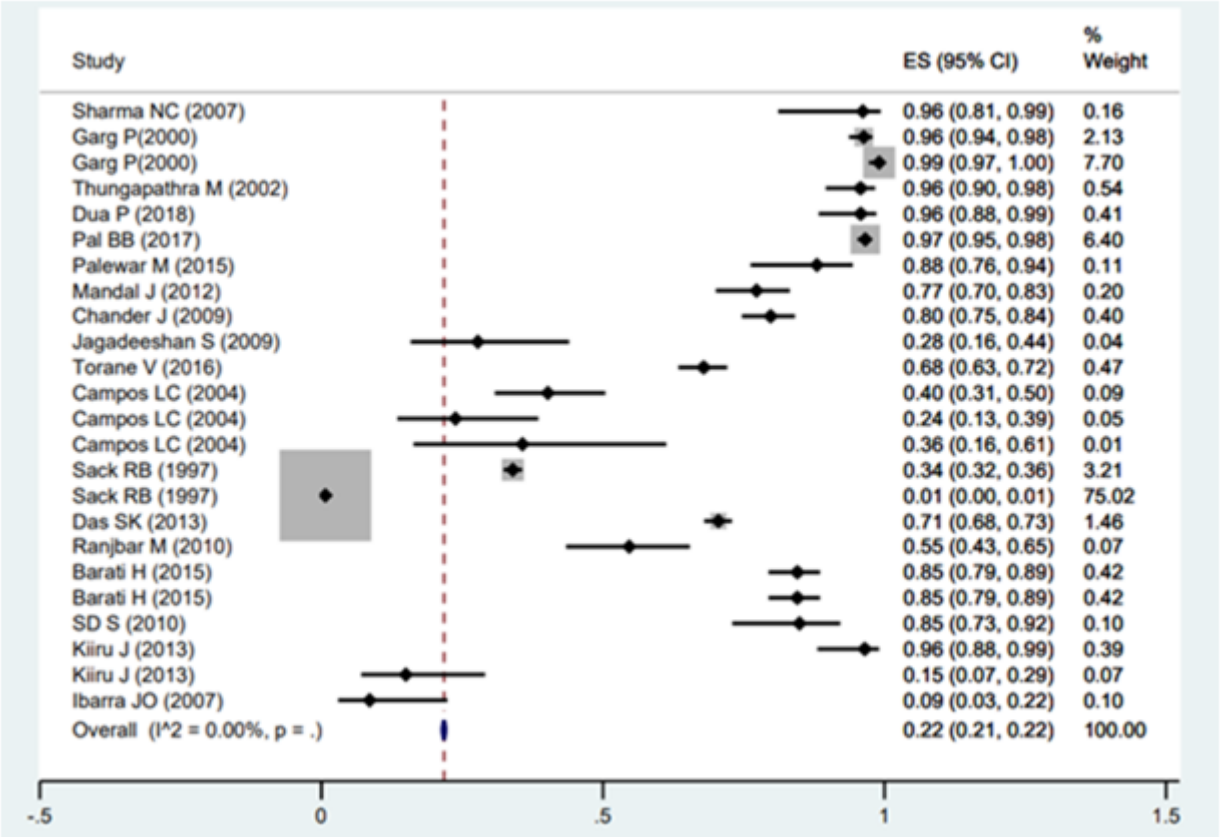

Figure 2

Summary forest plot of the odds ratios furazolidone resistance Vibrio cholerae.

Supplementary Files

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- APPENDIX.pdf
- PRISMA2009checklist1.doc