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NARRATIVE REVIEW

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Cholera rages in Africa and the Middle East: A narrative review on challenges and solutions

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Abstract

Background and Aim: Cholera is a life-threatening infectious disease that is still one of the most common acute watery diarrheal diseases in the world today. Acute diarrhea and severe dehydration brought on by cholera can cause hypovolemic shock, which can be fatal in minutes. Without competent clinical therapy, the rate of case fatality surpasses 50%. The purpose of this review was to highlight cholera challenges in Africa and the Middle East and explain the reasons for why this region is currently a fertile environment for cholera. We investigated cholera serology, epidemiology, and the geographical distribution of cholera in Africa and the Middle East in 2022 and 2023. We reviewed detection methods, such as rapid diagnostic tests (RDTs), and treatments, such as antibiotics and phage therapy. Finally, this review explored oral cholera vaccines (OCVs), and the vaccine shortage crisis.

Methods: We carried out a systematic search in multiple databases, including PubMed, Web of Science, Google Scholar, Scopus, MEDLINE, and Embase, for studies on cholera using the following keywords: ((Cholera) OR (Vibrio cholera) and (Coronavirus) OR (COVID-19) OR (SARS-CoV2) OR (The Middle East) OR (Africa)).

Results and Conclusions: Cholera outbreaks have increased dramatically, mainly in Africa and many Middle Eastern countries. The COVID-19 pandemic has reduced the attention devoted to cholera and disrupted diagnosis and treatment services, as well as vaccination initiatives. Most of the cholera cases in Africa and the Middle East were reported in Malawi and Syria, respectively, in 2022. RDTs are effective in the early detection of cholera epidemics, especially with limited advanced resources, which is the case in much of Africa. By offering both direct and indirect protection, expanding the use of OCV will significantly reduce the burden of current cholera outbreaks in Africa and the Middle East.

KEYWORDS

Africa, COVID-19, cholera, oral cholera vaccination (OCV), The Middle East, *Vibrio cholerae*

1 | INTRODUCTION

The comma-shaped bacteria *Vibrio cholerae* is the cause of cholera, an acute diarrheal disease.[1] *V. cholerae* is a water-borne pathogen and can be transferred through vector and reservoir organisms such as flies, algae, and some crustaceans.[2,3] In coastal regions and estuaries, *V. cholerae* grows best in salt water.[4–6] Fecal samples of human cholera carriers can also carry high concentrations of *V. cholerae*.[7] Through such mechanisms, *V. cholerae* can contaminate water sources and food. Once ingested through the fecal–oral route, the disease can lead to symptoms such as diarrhea and dehydration.[8] In 1817, cholera appeared in the Ganges Delta and expanded to seven pandemics that killed millions of people across the world.[4–6] *V. cholerae* is constantly evolving, with novel phenotypes and genotypes arising as a consequence of outbreaks and growing drug resistance.[9] In Africa, cholera occurs in two different ways: as an endemic condition that recurs every 2–3 years during specific seasons, or as acute epidemics that start suddenly, endanger thousands of lives, and strain the healthcare infrastructure.[10] Cholera outbreaks are difficult to predict and therefore can occur in both endemic and nonendemic areas based on environmental changes, with refugee camps being especially vulnerable.[11]

Globalization and travel increase the spread of cholera, as was the case in Haiti following the 2010 earthquake, where imported cases from Nepal were the source of the infection. Cholera was brought to Haiti from a single source and then rapidly, widely, and continuously spread.[12,13] The spreading of cholera across countries' borders has been proposed between Iraq-Iran and Cameroon-Nigeria.[14,15] Since 2019, the COVID-19 pandemic has greatly increased mortality rates and put a burden on medical facilities all around the world. In Africa and the Middle East, COVID-19 has hindered the fight against infectious diseases that can be fatal, such as cholera, tuberculosis, HIV/AIDS, and several tropical diseases.[16–18] Numerous nations in Asia, Africa, and Europe experienced cholera outbreaks during the pandemic,[19–22] whereas no cases were recorded in the Americas in 2022. Due to inadequate monitoring and surveillance, it is anticipated that the actual number of cholera cases may be greater than those that have been released.[19–22] In 2022, isolated cholera cases were associated with damage to the sewage and water systems due to the fighting in Mariupol, Ukraine, which resulted in several health issues.[23–25]

This study reviews recent cholera outbreaks in Africa and the Middle East, the geographical distribution of cholera cases in 2022 and 2023, the different serogroups and biotypes of *V. cholerae* causing pandemics and outbreaks, and the causes of cholera outbreaks raging in Africa and the Middle East. We also describe different manifestations and complications of cholera, methods of diagnosis, available oral cholera vaccines (OCVs), and antimicrobial drug resistance. Finally, we discuss management strategies and promising cholera treatments. We carried out a systematic search in multiple databases, including PubMed, Web of Science, Google Scholar, Scopus, MEDLINE, and Embase, for studies on cholera using the following keywords: ((Cholera) OR (Vibrio cholera) and (Coronavirus) OR (COVID-19) OR (SARS-CoV2) OR (The Middle East) OR (Africa)).

2 | EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION OF CHOLERA IN AFRICA AND THE MIDDLE EAST IN 2022 AND 2023

Since 2021, there has been an upsurge in cholera cases in Africa (e.g., Cameroon, the Democratic Republic of the Congo, Ethiopia, Kenya, Malawi, Mozambique, Nigeria, South Sudan, the United Republic of Tanzania, Zimbabwe, Niger, Burundi, and Somalia), as well as the Middle East (e.g., Syria, Lebanon, Yamen, and Iraq).[26] Some countries fail to report cholera cases or deaths because of inadequate or nonexistent monitoring systems. Others delay reporting cholera outbreaks to reduce losses in commerce and tourism as well as societal hysteria. However, early detection of cholera outbreaks may lead to shorter epidemic durations and terminate any potential epidemics.[27] Figure 1 shows the geographical distribution of cholera in Africa and the Middle East in 2022.

In Table 1, we collected the recently reported numbers of cholera cases, deaths, and case fatality ratios (CFRs) in Africa and the Middle East in 2022. According to our research, Malawi had the largest number of cholera cases reported in Africa in 2022, with 28,132 confirmed cases, 916 fatalities, and a CFR of 3.3%. While in the Middle East, Syria had the largest number of cases, with 77,561 suspected cases, 1893 confirmed cases, 100 deaths, and a CFR of 0.13%.

3 | CHOLERA SEROLOGY

V. cholerae strains are defined by the structure of their O antigen, which has been classified into more than 200 O serogroups.[36–39] Despite this large number of serogroups, only the *V. cholerae* serogroups O1 and O139 are toxin-producing and have been reported as the cause of disease in epidemics.[39,40] The O1 serogroup has three serotypes based on the antigenic factors A, B, and C: Inaba, Ogawa, and Hikojima, and two biotypes, classical and E1 Tor.[39] 99% of the worldwide cases are caused by O1 serogroup.[41] Stool samples in the current outbreak in Yemen were positive for the O1 serogroup, Ogawa serotype.[42,43] In early October 2022, there was a rapid spread of cholera caused by Serotype O1 El-Tor Ogawa in Syria and Lebanon.[44,45]

Usually, *V. cholerae* strains have a prophage, CTXΦ, where the gene encoding *V. cholerae* toxins is present, the most important factor in its virulence. Atypical El Tor strains have the ctxB allele, which is a characteristic allele of the classical CTXΦ strain ($CTX^{Class}\Phi$).[46] In the 2004 Mozambique outbreak, there were two types of prophages nearly identical to $CTX^{Class}\Phi$, but they had the El Tor phenotype and were otherwise genotypically El Tor, so they were named Mozambique El Tor.[46–48] Other atypical El Tor strains are called hybrid El Tor because they have classical ctxB and rstR genes. All of these variations are caused by the transfer of mobile genetic elements.[46]

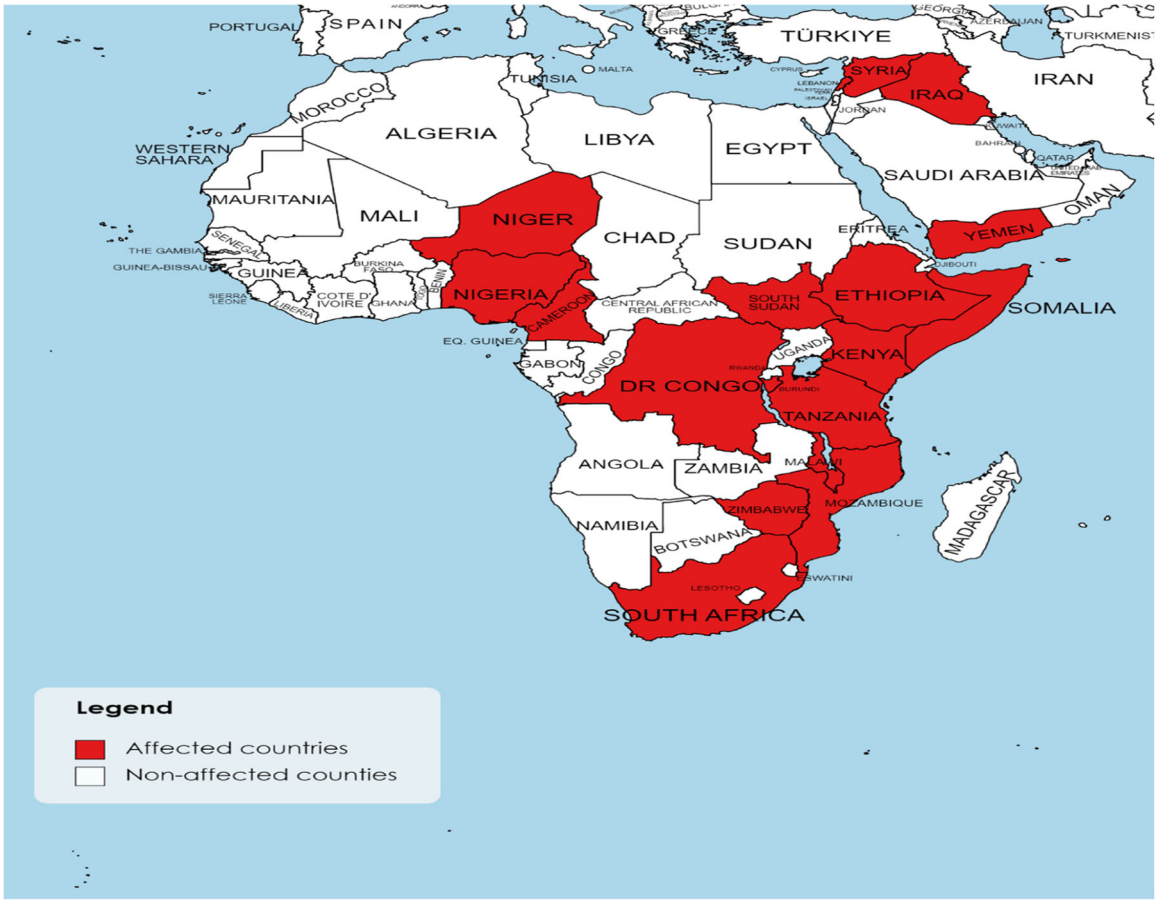

FIGURE 1 Geographical Distribution of documented cholera outbreaks in Africa and the Middle East in 2022 and 2023.

Serogroups other than O1 and O139 arise less frequently and are likely under-reported due to the lack of diagnosis. Currently, 1%–3.4% of cases of acute diarrhea cases are due to the non-O1/non-O139 serogroup (NOVC).[49] In a study of 58 hospitalized patients with acute diarrhea in Italy, 3.4% of the cases were due to NOVC.[50] 27.4% of hospitalized cholera patients with acute diarrhea at a hospital in India carried non-O1/non-O139 serogroup bacteria.[51] The O5 serogroup was responsible for cases of cholera in Czechoslovakia in the 1960s; the O37 serogroup caused cholera infections in Sudan in 1968.[52–54] After July 2015, there was a reported case of NOVC cholangitis and septicemia in Beirut, which was the third reported case of NOVC bacteremia in Lebanon and the first after the 2015 Lebanese waste crisis.[55]

Six pandemics caused by the O1 serogroup arising from India have spread worldwide from 1817 to 1923.[56,57] A seventh pandemic, which arose in Indonesia in 1961 due to the El Tor biotype, spread into Asia, Africa, and Latin America, including the devastating epidemic that occurred in Haiti in 2010. Other El Tor biotype outbreaks occurred in several African countries from 1997 to 1999, from 2012 to 2014 in Mozambique, and 2010 in Cameroon.[39,58–60] O139 epidemics have occurred less frequently but were responsible for infections among the elderly in Pakistan between 1995 and 2010,[61] in Thailand,[62] and sporadically in China[63] and Bangladesh.[64] Serotype O139 may be responsible for the probable eighth cholera pandemic, which emerged successfully between 1992 and 2015 before dying out, according to a study by Ramamurthy et al.[65] They included 330 O139 isolates in their study and reported that two key genomic evolutionary changes are responsible for the eventual epidemiological decline of O139. First, there was a transformation from the homogenous toxin genotype in wave-A to heterogeneous genotypes, followed by gradual loss of antimicrobial resistance due to the progression of waves.[65]

Table 2 depicts the classification of *V. cholerae* into serogroups and biotypes, as well as major pandemics and outbreaks over the years.[46,54] Pulsed-field gel electrophoresis (PFGE), polymerase chain reaction (PCR)-based methods, ribotyping, and sequencing-based methods such as multi-locus sequence typing (MLST), variable number of tandem repeats (VNTR) analysis, and multi-locus variable tandem repeat analysis (MLVA) are molecular tools for studying *V. cholerae*.[54]

4 | WHY ARE AFRICA AND THE MIDDLE EAST FERTILE ENVIRONMENTS FOR CHOLERA?

The key factors contributing to Africa's ongoing and repeated cholera outbreaks include poverty, inadequate sanitation, poor water supply, and overpopulation. The situation is exacerbated by the human

TABLE 1 Numbers of reported cholera cases, deaths, and CFR in Africa and the Middle East in 2022 and 2023.

Region	Country	Total cases (suspected and confirmed cases)	Confirmed cases	Deaths	CFR (%)	Reporting timeframe	Reference
Africa	Burundi	81	66	1	1.2	January 1, 2023 to January 15, 2023	28
	Cameroon	15,117	1805	302	2	October 25, 2021 to January 5, 2023	
	Democratic Republic of the Congo	14,290	1356	262	1.8	January 3, 2022 to December 30, 2022	
	Ethiopia	911	27	27	3	September 17, 2022 to January 15, 2023	
	Kenya	3939	142	70	1.8	October 16, 2022 to January 8, 2023	
	Malawi	28,132	28,132	916	3.3	March 3, 2022 to January 20, 2023	
	Mozambique	3930	16	21	0.5	June 25, 2022 to December 18, 2022	
	Nigeria	20,768	-	498	2.4	January 1, 2022 to November 27, 2022	
	South Sudan	424	56	1	0.2	March 21, 2022 to November 20, 2022	
	Zimbabwe	2	2	0	0	November 24, 2022	
	United Republic of Tanzania	24	3	1	4.2	October 31, 2022 to December 11, 2022	
	Niger	72	14	1	1.4	September 1, 2022 to November 14, 2022	29
	Somalia	15,653	-	88	0.6	January 3, 2022 to January 1, 2023	30
	South Africa	10	10	1	10	March 30, 2023	31
The Middle East	Syria	77,561	1893	100	0.13	August 25, 2022 to January 7, 2023	32
	Lebanon	6158	-	23	0.37	October 6, 2022 to January 17, 2023	33
	Yemen	556	-	0	0	August 2022	34
	Iraq	3063	3063	19	0.6	July 6, 2022 to November 29, 2022	35

Abbreviation: CFR, case fatality ratio.

TABLE 2 *V. cholerae* classification and the major cholera pandemics, outbreaks, and case reports.

Serogroup	Biotype		Country	Year	Reference
O1	Classical		From 1st to 6th pandemics	1817–1923	66, 67
	E1 Tor		7th pandemic	1961–1975	68
			Indonesia	1961	69
			Lima and Peru	1991	70
			Haiti	2010	58
			Mozambique	1997–1999 and 2012–2014	71
			Cameroon	2010	60
			Yemen	2016–2017	72, 73
			Syria and Lebanon	2022	45
	Atypical E1 Tor	"MB El Tor"	Matlab in Bangladesh	1991 and 1994	74
		Altered El Tor	Bangladesh	2001	74
		Mozambique El Tor	Mozambique	2004	47, 48
		Hybrid El Tor	various African and Asian countries	1991 and 2004	75, 76
O139	-		The 8th pandemic	1992–2015	65
			Pakistan	1995–2010	61
			Thailand	1983–2013	62
			Bangladesh	2013–2014	64
			China	1993–2013	63
Non-O1/non-O139	-		Czechoslovakia	1960s	53
			Sudan	1968	52
			Lebanon	2015	55

conflicts that occur throughout Africa as well as the Middle East.[2,8,77,78] Transmission becomes simpler in crowded environments like refugee camps, prisons, and war zones.[10,79] Additionally, climate-related factors such as rainfall, flooding, droughts, and strong winds also propagate cholera (Figure 2).[2,77]

Several sociological factors have impacted cholera epidemics in Africa and the Middle East. In developing countries, high-density populations lead to sanitation issues such as unsuitable living conditions; clean water, sewage treatment, and clean, warm food may be limited or not available at all. These living conditions often do not allow for basic sanitation strategies with which the prevention of cholera can be achieved.[80,81] Water wells and rivers are common sources of water for displaced communities. Sewage treatment allows for the maintenance of a clean, non-contaminated water supply for the population and is lacking in many impoverished areas.[78] Sanitation applies to not only water sources but nutrition as well. Cold meals, lack of nutrition, and roadside food vendors all increase the likelihood of contracting cholera.[77] Helicobacter infection, which is common in young children and adolescents in developing countries in Africa and the Middle East, is another risk factor for cholera.[82–84] *Helicobacter pylori* plays a significant role in the pathophysiology of diarrheal illnesses like cholera by causing hypochlorhydria, gastric ulcers, and gastric cancer.[82,84] Clemens et al. found that infection with *H. pylori* was related to a considerable increase in the probability of life-threatening cholera. However, this was only observed in people who lacked natural immunity against *V. cholerae*.[85]

As of 2023, there were about 5.4 million refugees from Syria in neighboring countries.[8,86] The prolonged civil war within Yemen has led to the immigration and emigration of individuals who may have been carriers of cholera.[2] Due to the country's institutional gridlock and economic crisis, cholera affected Lebanon in 2022.[78] In Ethiopia, the conflict in the Tigray region has led to nearly 53,000 refugees entering Sudan to be housed in refugee camps.[8,87] Political conflicts have not only displaced people but have also prevented vaccines from reaching the targeted host population.[80] Cholera vaccinations are limited in impoverished countries due to factors such as political strife, vaccine costs, and the world's focus on other pathogens.[80]

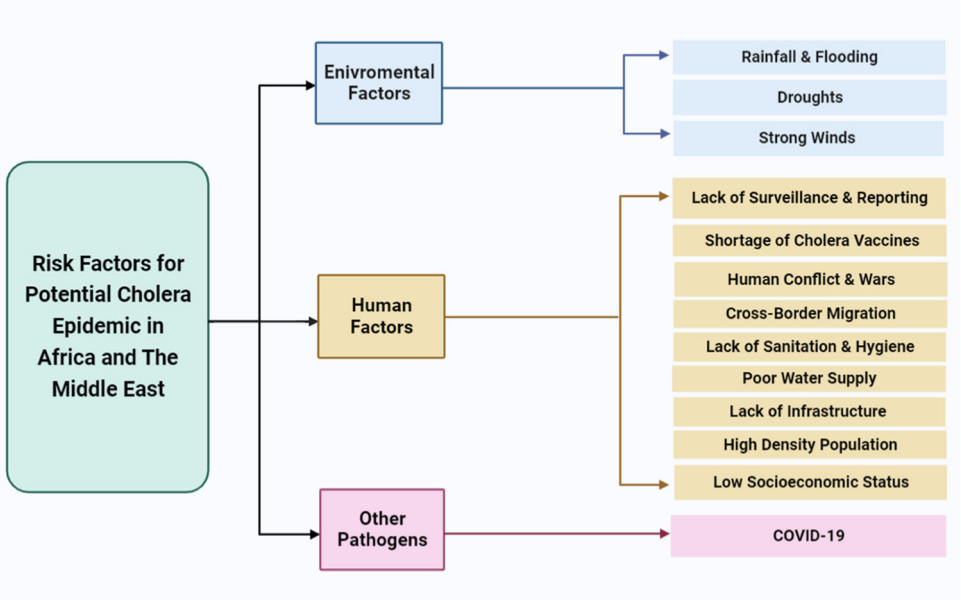

FIGURE 2 Risk factors of a potential cholera epidemic in Africa and the Middle East.

Cases of cholera outbreaks brought on by climate change, such as those associated with droughts, heavy rainfall, and the propagation of *V. cholerae* reservoirs and vector organisms have occurred in Africa.[46,77] Climate change is likely to worsen cholera outbreaks in Africa and the Middle East. Increases in air temperature were linked to increases in cholera cases in Africa.[88–93] Extreme weather events are predicted to increase with climate change[94] and both abnormally wet and drought events have been associated with increased cholera cases in Africa[95–98] and elsewhere.[90,91,99] Droughts can lead people to use poor-quality water for drinking, whereas flooding can cause sewage systems to overflow into drinking water.[92,100] The obtainment of clean water can be expensive; water wells are often sought after, which may have cholera propagating within them.[46,77] Droughts are often accompanied by times of economic hardship for individuals who partake in agriculture. Obtaining vaccines, sanitation supplies, water, and food may be difficult, and cheaper alternatives may be sought, which may contain *V. cholerae*.[77] Increased frequency of El Niño events can lead to more climatic extremes that increase cholera cases.[96,101–103] Changing ocean conditions favor the growth of *V. cholerae* bacteria through increased temperature[92] and higher zooplankton populations that are fed by higher phytoplankton populations that benefit from nutrient-rich runoff from agriculture and human waste.[88,99,100] Because *V. cholerae* is a temperature-sensitive pathogen, its populations grow within reservoirs at the ideal temperature. This in turn increases the likelihood of the pathogen increasing within the population.[77] Droughts can allow brackish water up into streams allowing cholera carrying plankton inland.[90,91,99]

The COVID-19 pandemic exacerbated cholera outbreaks in different countries in Africa and the Middle East.[16–22] As of February 2023, approximately 750 million confirmed cases and 6.7 million confirmed deaths have been attributed to COVID-19 globally.[104] The pandemic caused a shift in the focus of governments, organizations, and the media away from cholera.[81,105] The worst consequences of the COVID-19 pandemic were suffered by many developing countries in Africa and the Middle East.[106] The pandemic may negatively impact crucial cholera control measures like surveillance, a crucial defense against outbreaks and related mortality.[16] However, an increase in hand washing and sanitization in response to the COVID-19 pandemic is expected to reduce food and waterborne infections. Researchers believe that the restricted availability of clean water and poor waste disposal in many rural and peri-urban slums in Sub-Saharan Africa make efficient hand hygiene implementation difficult.[16]

5 | THE CHARACTERISTIC CLINICAL MANIFESTATIONS AND COMPLICATIONS OF CHOLERA

V. cholerae infection causes a range of symptoms, from asymptomatic intestinal colonization to severe diarrhea. Other typical symptoms include abdominal pain, borborygmi, and vomiting, especially in the early stages of the illness. The severe illness caused by cholera is attributed to the significant loss of electrolytes caused by diarrhea. The clinical signs of *V. cholerae* O1 versus O139 are similar.[107] A normal incubation period for cholera is 1–2 days; however, the duration of cholera incubation varies depending on the host's susceptibility and the amount of the inoculum and can range from a few hours up to 3–5 days.[108–110] While mild *V. cholerae* infection may be clinically indistinguishable from other causes of diarrhea, severe cholera is distinguished by rapid fluid and electrolyte loss. Cholera stools may contain fecal debris and bile in the early stages of the illness.[6] Nevertheless, the passing of copious "rice-water" stool, a watery stool with mucous particles, is a defining feature of severe cholera (cholera gravis) and usually has a fishy odor. The diarrhea is

normally painless and does not cause tenesmus. In the most severe instances, stool production in adults may approach 1 L per hour. The maximum rate of stool excretion in children with severe cholera is frequently between 10 and 20 cc/kg/h, and this rate of fluid loss is unusual in other types of diarrheal sickness.[111] Additionally, cholera patients' feces include a greater quantity of sodium, as well as considerable levels of potassium and bicarbonate, when compared to other causes of pediatric diarrheal disease.[112,113] Diarrhea is most severe in individuals treated with appropriate rehydration during the first 2 days and subsides after 4–6 days, with total volume loss of up to 100% of body weight occurring throughout the disease.[114] Vomiting, which is sometimes accompanied by watery emesis, is common and can occur before or after the onset of diarrhea. Patients may experience abdominal cramps, but not the intense abdominal pain associated with dysentery.[114]

The most common sequelae of acute cholera diarrhea are hypovolemia and electrolyte abnormalities due to rapid fluid and electrolyte loss. Severe hypovolemia can develop within hours of the onset of symptoms. The median time between the onset of symptoms and death in those who died before being admitted to a cholera treatment facility during the early stages of the Haitian cholera outbreak was 12 h.[115] Severe hypovolemia might cause sunken eyes, dry mouth, chilly, clammy skin, reduced skin turgor, or wrinkled hands and feet. The majority of patients exhibit apathy. Kussmaul breathing could develop from lactic acidosis brought on by inadequate perfusion in addition to acidosis from loss of stools' bicarbonate (Figure 3). Pneumonia is a common comorbidity in children with cholera, possibly as a result of aspiration during vomiting, and has been linked to death.[116] Because fever is uncommon, the presence of a high temperature should raise the possibility of a concomitant infection or consequence. In the absence of diarrhea, "Cholera sicca" is a unique type of illness in which fluid collects in the intestinal lumen; circulatory collapse and even death may follow.[117]

Most cholera cases with neurologic complications involve infants and neonates and manifest as meningitis,[118] but adults with a higher risk of intracranial infection have experienced neurological effects from cholera. A 58-year-old fisherman with left-sided paresis and a Babinski sign had an intracerebral abscess and bacteremia caused by *V. cholerae* that did not produce cholera toxin. He had a craniotomy 5 years before presentation for a subdural hematoma, which could have allowed the organism intracranial access.[119] There were no risk factors for a 10-day-old boy with *V. cholerae* meningitis, but recent water studies in his rural Indian village found non-O1 non-O139 *V. cholerae* in 41% of drinking water samples and 100% of water, sediment, and plankton samples from three nearby lakes.[118,120]

Cholera is particularly dangerous to pregnant women and their fetuses. Despite early research suggesting a high risk of fetal death

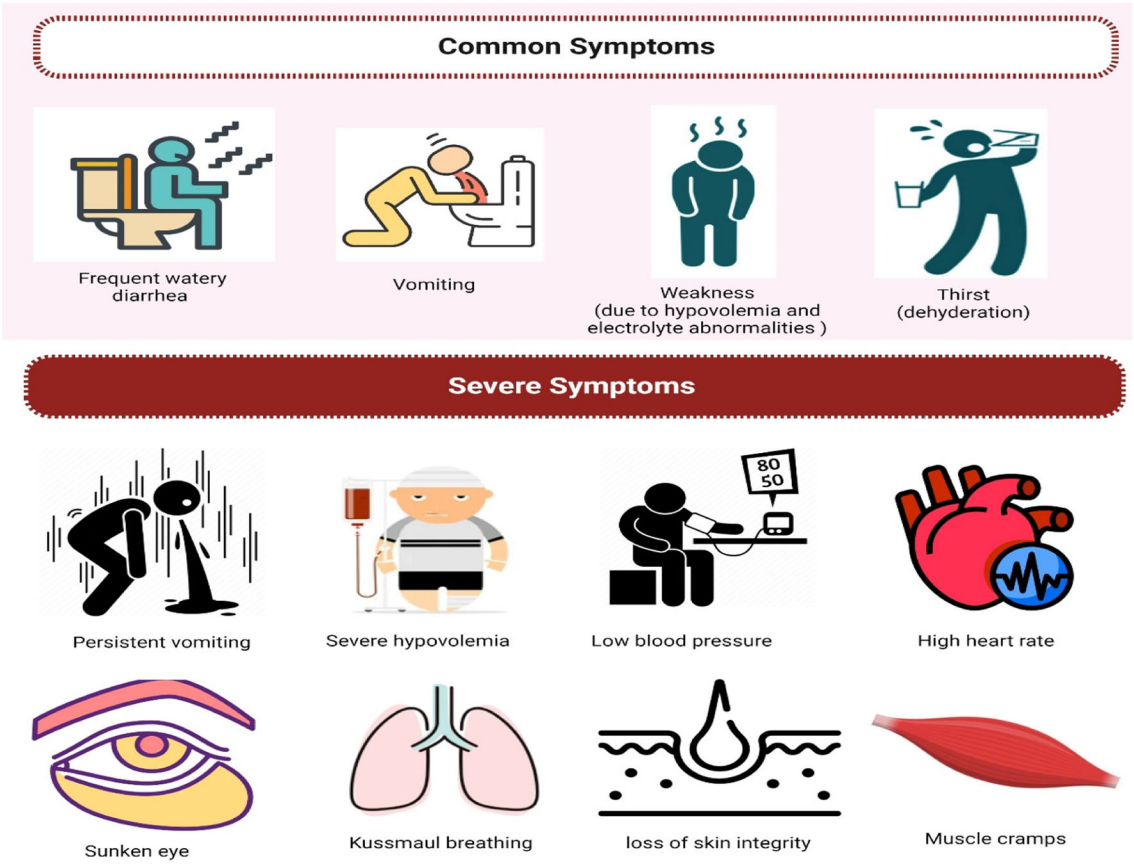

FIGURE 3 Common and severe symptoms of *Vibrio cholerae*.

linked to cholera during pregnancy (up to 50% during the third trimester), more recent research has revealed a decreased but still high risk (~8%).[114,121–123] According to one study from Guinea, most pregnant women affected by a 2012 cholera outbreak were in their third trimester. The classic clinical manifestations were associated with obstetric difficulties and maternal-fetal hazards. In addition to experiencing choleriform diarrhea in 100% of the women, dehydration was mild in 16%, moderate in 45%, and severe in 39% of the women. There were two threatened abortions, one preterm birth, four intrauterine deaths, and one maternal death.[124]

6 | DIFFERENT METHODS OF CHOLERA DIAGNOSIS

In developing countries and poor settings where advanced laboratory diagnostic techniques are limited, cholera is diagnosed by clinical symptoms and manifestations. After the incubation period of *V. cholerae* (median = 1.4 days), outcomes range from symptomless intestinal colonization to mild or severe diarrhea.[125] Identification of endemic species of *V. cholerae* O1 and O139 by isolation and culture of a stool specimen in alkaline peptone water (APW) then subcultured in thiosulfate-citrate-bile salts sucrose (TCBS) agar or taurocholate tellurite-gelatin (TTG) agar is the gold standard in the diagnoses with Cary Blair media as the ideal media for transport.[126–128] Stool analysis is valuable for *V. cholerae* diagnosis as it enables further molecular phenotypic analysis of the specimen for antibiotic resistance and molecular characterization.[128] External factors such as improper sampling and shipment can affect the efficacy of stool analysis as a primary diagnostic tool.[128] Molecular detection and PCR have been developed for *V. cholerae* species identification and characterization. PCR requires a sample to be grown in pure culture without requiring viable strains. PCR can also detect the pathogen in food, water, and rectal swabs, it does not require a stool sample as most of the tests.[129]

Methods of diagnosis have been developed to replace complicated laboratory investigations in developing countries or endemic settings with poor healthcare quality.[130] Rapid diagnostic tests (RDTs) are used directly on rectal swabs, fresh stool only, or after enrichment of the specimen by alkaline peptone water for (4–6 h).[126,131,132] RDTs detect the pathogen qualitatively within a maximum of 30 min, which appears as a colored band that can be read with the naked eye.[130] Almost all RDTs work by detection of antigens specific for lipopolysaccharide (LPS) of serotypes O1 and O139 of *V. cholerae* using monoclonal antibodies.[133] These tests are developed to detect epidemics early to start cholera treatment for patients in their early stages to prevent the disease's progress. RDTs do not require experienced technicians to perform, are low-cost, and do not require cold storage.[126,134] These advantages of RDTs lead us to believe that they are more appropriate for use in refugee camps and impoverished regions of Africa and the Middle East. Table 3 shows the characteristics of the most common RDTs, including their sensitivity and specificity.[135,143]

TABLE 3 Characteristics of most common RDTs for cholera diagnosis (adapted from Falconer et al.[135]).

Test	Sample in the test	Test duration	*Vibrio cholerae* species	Test assay	Target	Country of population	Cost	Sensitivity (%)	Specificity (%)	Reference
Cholkit	Stool	15 min	O1	Immunochromatographic lateral flow assay	LPS antigen	Bangladesh	~$3	97.7	96.5	136, 137
Crystal VC-O1	Stool	15–30 min	O1	Immunochromatographic lateral flow assay	LPS antigen	Kenya	~$2/kit	97.5	100	138
Crystal VC	Stool	10–20 min	O1 and O139	Immunochromatographic lateral flow assay	LPS antigen	Bangladesh	$1.9/test	97.5	98.4	136
SD Bioline	Stool	10–20 min	O1 and O139	Immunochromatographic assay	*V. cholerae* O1 and O139 antigens	Zambia	~€2/test	90.9	95.2	139
Cholera DFA	Stool	Less than 30 min	O1	Fluorescent monoclonal antibody staining kit	"A" factor of *V. cholerae* O1 LPS	-	-	100	100	140
IP dipstick	Stool	3–58 min (In field practice)	O1 O139	Immunochromatographic dipstick assay	LPS antigen	Bangladesh	-	94.2 100	84.0 92.5	141
Artron RDT	Stool	15 min	O1 and O139	Immunochromatographic assay	LPS antigen	Haiti	-	98.6	69.1	142

Abbreviations: LPS, lipopolysaccharide; RDT, rapid diagnostic test.

TABLE 4 Characteristics of current available OCVs.

Vaccine name	Vaxchora®	Dukoral®	Shanchol™ and Euvichol®/ Euvichol-Plus
Manufacturer	Emergent Travel Health[144]	Valneva Canada Inc[145]	Sanofi Healthcare India Private Limited (Shanchol™)[146] EuBiologics Co., Ltd. (Euvichol®/ Euvichol-Plus)[147]
Composition	Contains 4×10^8 to 2×10^9 CFU of live attenuated *V. cholerae* CVD 103-HgR[148]	Contains inactivated WC *V. cholerae* O1 Inaba, Ogawa, classic and El Tor strains (31.25×10^9 vibrios of each), and rCTB 1 mg from classic biotype[149]	Contains WC *V. cholerae* O1 and O139 without CTB[150]
Age	2–64 years[150]	2 years and older[151]	1 year and older[151]
Regimen and dose	Single dose, 10 days before potential exposure to cholera[144]	Adults and children >6 years old: 2 doses Children aged 2–6 years: 3 doses[149]	Individuals older than 1 year old: 2 doses, 14 days apart[152]
Pharmaceutical form	Suspension[151]	Suspension and granules for suspension[151]	Suspension[151]
Vaccination effectiveness duration	3–6 months minimal[153]	2 years[153]	3 years minimal (for 2 doses) Short-term protection (for 1 dose)[153]
Booster dose	No recommendation[154]	Adults and children >6 years old: every 2 years Children aged 2–6 years: every 6 months[149]	No recommendation[155]
Cost	$270/dose[156]	~$4.7–9.4/dose[155]	Shanchol: $1.85/dose[155] Euvichol: $1.7/dose[155] Euvichol-Plus: $1.30/dose[157]
Need for buffer	Yes[27]		No[27]
Type of vaccine	Oral live attenuated[151]	Oral killed[151]	
Licensure	FDA 2016 (June)[156]	WHO qualified[152]	
Storage temperature	(−25°C to −15°C)[150]	(2–8°C)[149,158]	

Abbreviations: CFU, colony-forming units; OCV, oral cholera vaccine.

7 | CURRENT AVAILABLE OCVS

There are four main vaccines for the prevention of cholera in the market. Vaxchora®, Dukoral®, Shanchol™, and Euvichol®/Euvichol-Plus have been prequalified by the WHO (Table 4).

7.1 | Vaxchora

CVD 103-HgR marketed as Vaxchora is a recombinant live OCV vaccine. This strain comes originally from O1 classical Inaba strain 569B.[151] This specific strain has been genetically modified by removing the gene encoding the cholera toxin A subunit to prevent the production of cholera toxin, which made the vaccine strain different from the wild type. This was achieved by the company Berne Biotech. Vaxchora is currently approved by the USD FDA for being used by individuals from 2 to 64 years old.[150]

A single dose of oral vaccination CVD 103-HgR offers quick protection, starting 10 days after administration.[151] CVD 103-HgR vaccine can produce the immunogenic nontoxic cholera toxin B-subunit protein (CTB) in the gastrointestinal tract (GIT) and cause a rise in vibriocidal antibodies which help in the protection against *V. cholerae*.[151] A human trial study conducted on 197 healthy adults ranging between 18 and 45 years old found that the vaccine prevents the symptoms of cholera in people who are in contact with this bacterium. Out of the total individuals enrolled, 95 received the vaccine, and 102 received a placebo. Out of the 95, 68 were introduced to the pathogen at different time points (35 subjects after 10 days of the vaccine dosage and 33 subjects after 3 months of vaccination). Only two subjects experienced moderate or severe diarrhea (5.7%) after 10 days of the dosage challenge, and four subjects (12.1%) experienced moderate or severe diarrhea after 3 months of vaccination. 59.1% of the individuals in the placebo group experienced moderate or severe diarrhea suggesting a strong protective effect of the vaccine against this symptom. The overall results suggest a 90.3% protection effect of the vaccine 10 days after the dosage, and 79.5% effectiveness 3 months postvaccination.[150,151,159,160] In individuals with blood group O, the vaccine

efficacy was 78.4% in the 10-day challenge group, while it was 82.5% in the 3-month challenge group.[159] This was a relevant finding because individuals with blood group O are more susceptible to developing severe symptoms from cholera.[161]

Another major study with a total of 3146 participants evaluated the levels of rapid serum vibriocidal antibody (SVA) and cholera toxin in individuals receiving the vaccine up to 181 days after vaccination. The results supported previous evidence with a cumulatively significant 96% SVA seroconversion rate in the postvaccination group compared to 4% in the placebo group.[151,162] Vaxchora protects against the serogroup O1, but not against O139, the strain found mainly in the Southeast area of Asia. Even though the evidence suggests that the vaccine is effective against the disease, it has an average cost of $270 per single dose.[156] It also requires a cold chain to maintain the vaccine (between −25°C and −15°C). This limits the use of this vaccine to specific travelers from the United States to other countries.[150]

7.2 | Dukoral

Dukoral was licensed internationally in 1991.[152] Dukoral is a killed whole-cell (WC) monovalent (O1) vaccine that contains the recombinant cholera toxin B subunit (rCTB). This vaccine contains equal parts of four different strains of *V. cholerae*.[150] It was licensed in Sweden, especially for travelers, and later used in other countries in Europe. To prevent the acid-labile CTB component from being degraded by gastric acid, the vaccination must be administered with a sodium bicarbonate buffer.[152,163] The population receiving the vaccine consists of children and people over 6 years old, receiving two doses in less than 6 weeks. Children between 2 and 6 years old receive three doses.[149]

The specific composition of this vaccine consists of the heat-inactivated *V. cholerae* O1 Inaba classic strain and the Ogawa classic strain. These two are combined with the formalin-inactivated *V. cholerae* El Tor strain and Ogawa classic strain, along with CTB.[164] The vaccine induces antibodies for CTB and bacterial components simultaneously.[149] The exact mechanism behind the immunologic system behind this compound is still unknown; however, a recent study suggested that the quality of the immunological response elicited after oral administration of the Dukoral vaccine may be regulated by toll-like receptor (TLR) pathways. Sirskyj et al. propose that MyD88/TLR signaling, rather than Trif signaling, is responsible for CD4+ T-cell proliferation in response to *V. cholerae*.[164]

The first challenge study for this vaccine was conducted at the University of Maryland. They enrolled healthy participants between the ages of 19 and 35 years old. The goal of the study was to compare the effectiveness of formulations of WC vaccines containing CTB (referred to as WC-CTB) to those without CTB (referred to as WC). Three doses, spaced by 2 weeks of either WC-CTB (containing 5 mg of CTB) or WC were administered to the participants. El Tor Inaba *V. cholerae* was given to the vaccinated participants and unvaccinated controls 4 weeks after the third dose of WC and 5 weeks after the third dose of WC-CTB. The WC and WC-CTB vaccines were shown to be 56% and 64% effective, respectively. Vaccinated individuals in both groups who contracted cholera experienced fewer severe symptoms than unvaccinated individuals and were completely protected from severe diarrhea.[150,165] In Bangladesh, 89,596 individuals, including women over the age of 15 and children aged 2–15, participated in a study of the original WC-CTB formulation. Three doses of the WC-CTB, the Killed WC vaccine, or a placebo were given to individuals at random. The protective effectiveness was maintained in adults and children older than 5 years of age for 2 years; however, protection was only maintained for 6 months in children 2–5 years of age, indicating that this age group needed to receive doses more frequently. Effectiveness against El Tor *V. cholerae* was shown to be significantly lower than against classical *V. cholerae*. Additionally, this study revealed that a two-dose regimen was just as efficient as a three-dose program given at intervals of 6 weeks.[152,166–168]

In Peru, a study involving 1563 military personnel was done to evaluate the efficacy of WC-CTB. With an average follow-up of 5 months, the short-term preventive effectiveness in the Peruvian military study was 86% (95% confidence interval [CI] = 37–97, $p < 0.01$). In a high transmission environment, this study showed that an accelerated and shorter regimen (two doses given within 14 days) can induce protection within 2 weeks of immunization in a population that is primarily blood group O and is thought to be highly immunologically naïve.[169] In Zanzibar, a longitudinal cohort study revealed that after a 15-month follow-up period, the protective efficacy of two doses of WC-CTB was 79% (95% CI = 47–92). WC-CTB also offered significant indirect (herd) protection in the observed circumstance in addition to direct protection. As the neighborhood's vaccination rate rose, the risk of cholera among unvaccinated locals decreased, demonstrating the existence of herd protection.[170] According to the findings, expanding the use of cholera vaccinations will significantly reduce the burden of cholera in endemic areas by offering both direct and indirect protection to those who receive them as well as indirect protection to those who do not receive them.

The WHO approved the use of Dukoral after the results of many field studies demonstrated its high efficacy and effectiveness against cholera. It has not been demonstrated that Dukoral protects against cholera caused by Vibrio species other than *V. cholerae* serogroup O139. Additionally, because of its expensive cost, short duration of protection, and logistical difficulties with vaccine delivery, it has not been regularly embraced for use in public health.[152] The cost of a single dose of Dukoral is $6 to the public sector[150]; however, a cost-effectiveness study in Mozambique in 2017 revealed that the cost of a two-dose vaccine in an urban area was $2.09, without adding the manufacturing cost of the vaccine, which is relatively high.[171,172] The vaccine did not require a rigorous cold chain like others; it only needed to be refrigerated between (2–8°C).[149]

7.3 | Shanchol and Euvichol/Euvichol-Plus

Shanchol and Euvichol/Euvichol-Plus are essentially the same vaccines but made by different providers. They are both currently available for vaccination and have been used in campaigns with more

than 20 million doses administered.[173] Shanchol is a killed WC vaccine consisting of killed WC O1 and O139 serogroups but without CTB. Shanchol is an oral vaccination that must be administered two times, at least 2 weeks apart. Immunity against cholera is anticipated to develop in 7–10 days following the second dose.[150] This vaccine is intended for anyone aged more than 1 year with no current data for infants below a year of age.[158] It has been demonstrated that giving the vaccine orally, which develops local immunity, is efficacious. A similar IgA antibody response (including memory) is elicited by the vaccination locally in the GIT to that induced by the cholera disease itself. The colonization of *V. cholerae* O1 and O139 is hampered by the intestinal antibacterial antibodies that stop the bacteria from adhering to the intestinal wall.[158] Both Shanchol and Euvichol/Euvichol-Plus are stored at (2–8°C) and not frozen.[158]

A study was conducted in Kolkata, India to assess the effectiveness of Shanchol when administered in two doses separated by 2-week intervals. Twenty cholera incidents occurred throughout the 2 years of follow-up in the vaccine group, compared to 68 incidents in the placebo group, demonstrating a protective efficacy of 67% (one-tailed 99% CI, lower bound 35%, $p < 0.0001$). Furthermore, the vaccine protective effectiveness was 65% during the third year of follow-up (one-sided 95% CI, lower bound 44%, $p < 0.001$). At 5 years, the vaccine's cumulative protective effectiveness was 65% (95% CI = 52–74, $p < 0.0001$). Age-related differences have been noted: 1–4 years: 42% (95% CI = 5–64); 5–15 years: 68% (95% CI = 42-82); and 15 years and older: 74% (95% CI = 58-84).[174–176]

The catastrophic cholera outbreak in Haiti, which resulted in over 8000 deaths, and other significant cholera outbreaks in 2010 all helped to increase awareness of the OCV among the worldwide community and afflicted nations.[177] The cooperation between the International Vaccines Institute (IVI) and EuBiologics Co., Ltd. was established in 2010 to conduct an OCV technology transfer and establish a second producer to accommodate the rising worldwide demand. Euvichol was licensed and subsequently WHO prequalified upon the results of a non-inferiority trial in 2016 since the production method and composition were identical to those of Shanchol. To further enhance Euvichol, EuBiologics switched the vaccine's packaging from traditional glass vials to plastic tubes (Euvichol-Plus), making it easier to administer in crises or during emergencies.[177]

A randomized, non-inferiority trial evaluating the safety and immunogenicity of two doses of either Shanchol or Euvichol/Euvichol-Plus was carried out in the Philippines on a total of 1263 healthy Filipino individuals (777 adults and 486 children). The results demonstrated that Vibriocidal antibody responses against *V. cholerae* O1 Inaba elicited by Euvichol/Euvichol-Plus were non-inferior to those generated by Shanchol in children (87% vs. 89%) and adults (82% vs. 76%). Comparable results were seen for *V. cholerae* O1 Ogawa in children (91% vs. 88%) and adults (80% vs. 74%). In addition, no significant adverse effects were recorded in either vaccination group.[178]

Since the creation of Euvichol, 100 million doses have been administered in over 20 countries.[150] With the collaboration of the Pan American Health Organization (PAHO), 1.17 million doses of Euvichol arrived in Haiti on December 12, 2022. Over half a million doses were expected to arrive in the next several weeks to stop the spread of cholera.[179] On November 7, 2022, Lebanon received 600,000 doses from the International Coordination Group (ICG), which manages the supplies of vaccines worldwide. The aim is to achieve a 70% vaccination by administering 200,000 doses in less than 2 weeks.[180] The city of Damascus in Syria received two million doses of OCV on November 30, 2022.[181] Both Shanchol and Euvichol/Euvichol-Plus are the selected vaccines for mass immunization since they are affordable and easy to distribute. The goal is to eliminate the transmission of cholera in 20 countries before 2030 arrives.[182]

8 | CHOLERA VACCINE SHORTAGE CRISIS AND NEW PROMISING OCVS

The ICG managed the distribution of emergency vaccines and drugs to nations during significant outbreaks and received the global cholera vaccine stockpile from Shantha Biotechnics and EuBiologics. The WHO, UNICEF, and the International Federation of Red Cross all have representatives on the ICG. In 2022, outbreaks have been recorded from 30 countries, compared to an average of less than 20 during the past 5 years.[183,184] Cholera vaccines are in critically short supply, according to the WHO.[183,184] There is no short-term way to enhance production because vaccine manufacturers were already operating at full capacity. As of October 2022, a total of 24 million of the 36 million doses anticipated to be produced in 2022 have already been shipped for vaccination campaigns, and an additional 8 million doses have been approved by the ICG for a second round of emergency vaccination in four countries, highlighting the severe lack of the vaccine.[185]

The ICG had been forced to temporarily halt the standard two-dose vaccination regimen in cholera outbreak response campaigns in favor of a single-dose strategy that may allow the doses to be used in more countries, during a period of unprecedented increase in cholera outbreaks globally. Despite the paucity of data on the precise period of protection and the fact that protection seems to be substantially lower in children, the one-dose approach has been successful in controlling outbreaks. Despite the temporary interruption of the two-dose strategy causing a decrease and shortening of immunity, the advantage of administering one dosage still trumps administering none.[186] A recent modeling study demonstrated that rapid vaccination campaigns with a single dose of OCV are likely to prevent more cases and fatalities than a two-dose pro-rata campaign in an epidemic environment with a limited vaccine supply.[187]

The COVID-19 pandemic caused collateral damage by affecting the production of Vaxchora. Due to a significant decline in international travel as a result of the COVID-19 pandemic, the vaccine manufacturer informed the FDA in May 2021 that they had decided to temporarily stop the production and distribution of Vaxchora in the United States.[188] In addition, Shantha Biotechnics announced that the production of Shanchol, which comprises 15% of the global stockpile, would stop in 2022, and the distribution by the end of 2023.[189,190]

A licensing and technology transfer agreement has been signed by the South African biopharmaceutical company Biovac and the IVI

for the development and production of OCVs. This will help enable Biovac to create the antigen/raw materials needed for manufacturing vaccines. The goal of this collaboration is to expand the production rates to alleviate the severe worldwide vaccine shortage required to prevent cholera. This knowledge transfer will also create and show off capability for good manufacturing process scale-up, local manufacturing of clinical trial products, and end-to-end vaccine production in Africa as the production of the first trial batches is scheduled to begin in 2024.[191]

9 | MANAGEMENT, ANTIMICROBIAL DRUG RESISTANCE, AND PROMISING CHOLERA TREATMENTS

Most cholera cases will be treated with oral rehydration therapy, which will be used to correct fluid and electrolyte imbalances[192] (Figure 4). The primary treatment for cholera is rehydration therapy. Antibiotic therapy is also recommended for patients with severe illness and high-risk patients, such as those who are immunocompromised, pregnant, or have comorbid conditions (Table 5).[193–195]

9.1 | Rehydration treatment

One of the complications of cholera is dehydration. Adequate rehydration is critical for the patient's recovery. Depending on the patient, different modes of rehydration therapy can be administered.[195] Oral rehydration salt (ORS) should be given immediately to patients with no or some dehydration. High-sugar drinks should be avoided in case of unavailability of ORS because they aggravate diarrhea.[194] Intravenous rehydration is indicated in patients who have severe dehydration and conditions that interfere with the oral administration of rehydration solution such as loss of consciousness, and persistent vomiting.[194] The fluid amount can be adjusted according to the hydration status of the patient. In the treatment of severe dehydration with IV rehydration, ringer lactate is the fluid of choice.[195]

In the case of patients with severe acute malnutrition, a rapid bolus infusion of 20 mL/kg Ringer lactate (RL) is given over 30 min, if the severity signs of dehydration are not resolved, the procedure can be repeated up to two times. Once severity signs have resolved, the patient should receive a continuous infusion of 70 mL/kg RL over 6 h, in addition to adding 100 mL of 50% glucose to each liter of ringer lactate. When the patient is stable and can drink in the absence of excessive vomiting, the patient can be started on standard hypo-osmolar ORS.[193] Pregnant women do not bear any greater risk of being infected with cholera than the general population. Dehydration, on the other hand, can cause fetal complications. As such, treatment is given to correct the patient's dehydration and maintain the systolic blood pressure (SBP) >90 mmHg to ensure adequate perfusion of the fetus.[193,194]

9.2 | Zinc supplement

Zinc supplementation reduces the severity and duration of diarrhea in children aged 6 months to 5 years with watery diarrhea.[193] 20 mg

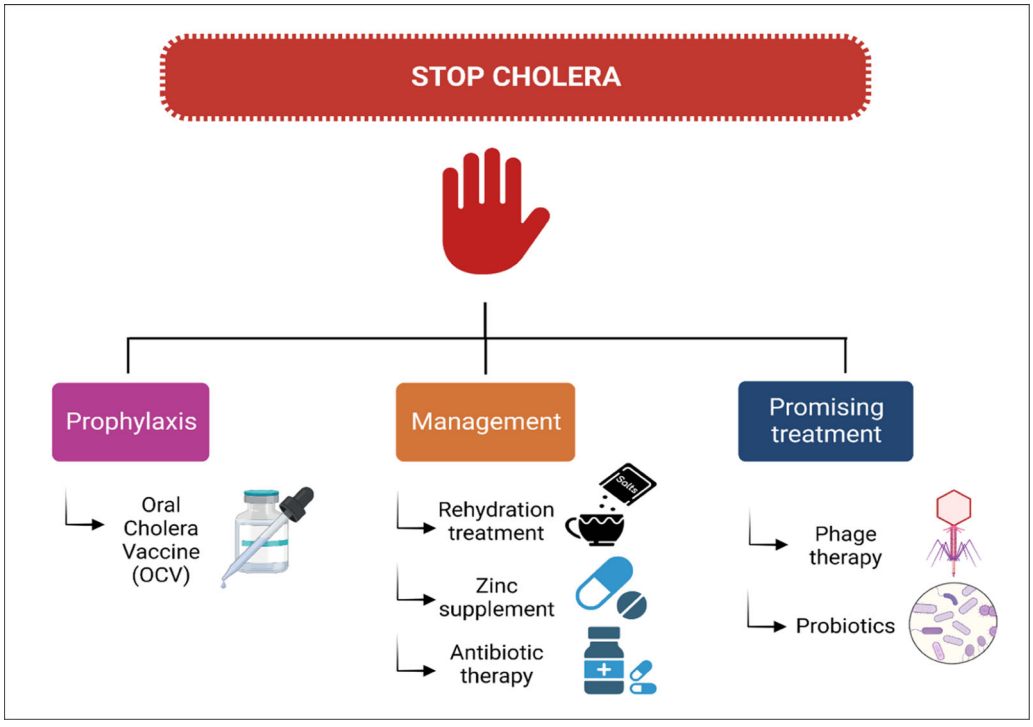

FIGURE 4 Management protocol for controlling and stopping cholera.

TABLE 5 Different lines in management and treatment of cholera patients.

Patient group	Rehydration therapy	Antibiotic therapy	Zinc
Adults	1. Patients with severe dehydration: 30 mL/kg of intravenous RL over 30 min, repeat once if danger signs are still present, then followed by 70 mL/kg of RL over 3 h. 2. Patients with some dehydration: 75 ml/kg of ORS over 4 h, repeat if dehydration signs are still present. 3. Patients with no dehydration: at least 200–250 mL of ORS after each loose stool until diarrhea stops.	1. First choice: Doxycycline 300 mg single oral dose. 2. Alternatives: Azithromycin 1 g P.O. single dose or Ciprofloxacin 1 g P.O. single dose.	20 mg of zinc sulphate per day for 10 days
Children	1. Children with severe dehydration (<5 years): 20 mL/kg of intravenous RL over 15 min, repeat up to two times if danger signs are still present, then followed by 70 mL/kg of RL over 3 h. 2. Children with some dehydration (<5 years): 75 mL/kg of ORS over 4 h, repeat if dehydration signs are still present. 3. Children with no dehydration: o If the age is under 2 years, 50–100 mL of ORS after each loose stool until the diarrhea stops. o If the age is 2–9 years, 100–200 mL of ORS after each loose stool until the diarrhea stops.	If the child is ≥12 years old: 1. First choice: Doxycycline 2-4 mg/kg P.O. single dose. 2. Alternatives: Azithromycin 20 mg/kg P.O. single dose or Ciprofloxacin 20 mg/kg P.O. single dose.	
Pregnant Women	1. Patients with severe dehydration or systolic blood pressure (SBP) ≤ 90 mmHg: bolus of 30 mL/kg RL over 30 min, repeat if the pulse is still weak or if SBP remains ≤90, then followed by 70 mL/kg of RL over 3–4 h. In case of the presence of little or no vomiting, at least 250 mL of ORS after each stool. 2. Patients with some dehydration and SBP > 90 mmHg: 75 mL/kg of ORS over 4 h and at least 250 mL of ORS after each stool. 3. Patients with no sign of dehydration and SBP > 90 mmHg: at least 250 mL of ORS after each stool and observation for 4–6 h.	1. First choice: Doxycycline 300 mg P.O. single dose. 2. Alternatives: Azithromycin 1 g P.O. single dose or Ciprofloxacin 1 g P.O. single dose.	
Ref.	193–195		

Abbreviations: ORS, oral rehydration salt; RL, Ringer lactate.

of zinc sulphate P.O. per day for 10 days should be started immediately. Concurrent administration of zinc with antibiotics such as Ciprofloxacin can impair antibiotic absorption. As a result, the antibiotic should be given 2 h prior or 4–6 h after the zinc supplement.[194,195]

9.3 | Antibiotic therapy

Although oral and intravenous rehydration are the first-line treatments for cholera, antibiotic therapy is recommended in a variety of situations, including severely ill patients, patients with comorbid conditions, pregnant women, and patients with persistently high stool output despite adequate rehydration therapy.[194,195] The antibiotic of choice for all ages, including pregnant women, is Doxycycline.[195] In the case of documented doxycycline resistance, Azithromycin and Ciprofloxacin can be considered. Antibiotic therapy should begin as soon as the patient is stable and capable of taking oral medication.[195]

9.4 | *V. cholerae*'s resistance to antimicrobial drugs

Antibiotic resistance is a growing concern in the treatment of infectious diseases. Cholera is no different, as several studies show the emergence of resistant variants of the pathogen for certain antibiotics. Resistance develops due to the misuse of antimicrobials, poor clinical care, poor water quality, and lack of proper regulations.[196] Misuse includes suboptimal dose and frequency of medication, overuse, and non-adherence. The resistance profile of the pathogen appears to vary depending on the geographical location and year of the cholera outbreak.[197] The pathogen develops resistance through mechanisms such as drug uptake limitation, drug inactivation, drug target modification, and efflux of drugs.[1]

Cholera antibiotic resistance in Mozambique from 2012 to 2015 showed an increase for Tetracycline, Nitrofurantoin, and Azithromycin. There was up to 100% resistance to Ampicillin and Nalidixic acid, but a decrease in resistance for doxycycline and no resistance for ciprofloxacin. They noticed that isolates that were 100% resistant to chloramphenicol in 2012 had a dramatic decline of approximately

TABLE 6 Summary of some studies' findings on the antimicrobial drug resistance to cholera.

Author(s), year	Study type	Country	Study subject	Outcome	Antimicrobial drugs with the highest resistance	Antimicrobial drugs with the least resistance	Reference
Yuan, X. H., et al., 2022	Meta-analysis	Global	648 Environmental *V. cholerae* O1/O139 isolates	Resistance rate of environmental *V. cholerae* to antibiotics	Nalidixic acid, Cotrimoxazole, Tetracycline, Furazolidone	Fluoroquinolones, gentamicin, ceftriaxone, doxycycline, kanamycin	199
Miwanda, B., et al., 2015	Laboratory study	Democratic Republic of the Congo	1093 isolates from major outbreaks in the DRC during 1997–2012	Long-term evolution of antimicrobial drug susceptibility of *V. cholerae* isolates	Nalidixic acid, Tetracycline, Ampicillin, Chloramphenicol, Erythromycin	Fluoroquinolones Cyclines	200
Dengo-Baloi, L. C., et al., 2017	Laboratory study	Mozambique	159 Rectal swabs from cholera cases during cholera outbreaks from 2012 to 2015	Antibiotics resistance pattern of *V. cholerae*	Ampicillin, Nalidixic acid, Tetracycline, Cotrimoxazole	Ciprofloxacin Azithromycin	198
Eibach, D., et al., 2016	Laboratory study	Ghana	92 *V. cholerae* isolates collected in 2011, 2012, and 2014	Molecular Epidemiology and Antibiotic Susceptibility of *V. cholerae*	Sulfamethoxazole/trimethoprim Nalidixic acid Ciprofloxacin Ampicillin	Chloramphenicol Gentamycin Tetracycline	201
Sambe-Ba, B., et al., 2017	Laboratory study	Senegal	50 *V. cholerae* serogroup O1 strains isolates	Genetic determinants of virulence and antibiotic-resistance in *V. cholerae* O1 isolated	Sulfamethoxazole/trimethoprim Streptomycin	Tetracycline	202

50% in 2013 with a subsequent increase.[198] In a recent meta-analysis, 20 studies that investigated 648 environmental *V. cholerae* O1/O139 isolates from Asia, Africa, America, and Europe were included. Fluoroquinolones, gentamicin, ceftriaxone, doxycycline, kanamycin, and cefotaxime were shown to have low resistance rates. Nevertheless, antimicrobial resistance is increasing, and the major focus is on the emergence of antimicrobial resistance in *V. cholerae* strains, particularly in low-income nations or endemic areas.[199] Although the antimicrobial resistance profile of fluoroquinolones such as Ciprofloxacin is favorable, the risk of resistance development remains as the association between Nalidixic acid resistance and the reduced susceptibility profile of fluoroquinolones has been reported.[200] Table 6 shows the characteristics of some studies' findings on the antimicrobial drug resistance to cholera.[198–202]

9.5 | Promising methods for treating cholera

Phage therapy can play a critical role in cholera treatment. Bhandare et al. demonstrated that oral treatment of a single Podoviridae phage may prevent clinical cholera symptoms in infant rabbits with no development of resistance to the phage. The results showed that animals treated with phage therapy had shown no clinical signs of infection when compared to the 69% of untreated controls.[203] From sewage water in Baghdad, Yassein et al. isolated virulent phages lytic for the isolate of *V. cholerae* O1. They then analyzed the spectrum of their activity and created phages in a phage cocktail to broaden the host range for the individual phages included in the cocktail. All of the phages identified in their research had a limited host range of 34%–65% against isolates of *V. cholerae* O1; however, a cocktail of eight phages had 100% activity against those isolates. Phage cocktail formulations may provide an alternative treatment for cholera since they are highly efficient against *V. cholerae*. Phage cocktails may be very useful in the field of water processing, cholera prevention, and treatment procedures.[204]

During a major outbreak of cholera in India, researchers isolated Vibrio phage VMJ710 from a sewage sample. This phage can lyse 46% of multidrug-resistant *V. cholerae* O1 strains. Within the first 4–6 h of treatment, the phage VMJ710 dramatically decreased the bacterial density in a mouse model. Additionally, they demonstrated that when given 6–12 h before the bacterial challenge, the phage VMJ710 can prevent the progression of *V. cholerae* infection and ailment. This phage could be a good choice for oral delivery and could help treat cholera infections brought on by pathogenic multidrug-resistant *V. cholerae* strains.[205] Another promising cure for cholera is probiotics. The goal of probiotic treatment for cholera infection is to bring back balance to the gut bacteria and stop *V. cholerae* strains from taking over the digestive system.[206] The conventional use of Rosaceae plant infusions for diarrhea seems applicable to cholera. The plant extracts impede the binding of the cholera toxin to receptors or prevent the internalization of the toxin, both of which reduce the development of pathogenic bacteria. While the plant extracts do not kill bacteria, they may slow it down, which may help other antibiotic treatments. The plant extracts may eventually be shown to be helpful additions to current ORS in the fight against cholera.[207]

10 | CONCLUSION

V. cholerae is a complex bacterium that can persist in both human host populations and aquatic environments. In humans, the bacteria can cause severe diarrhea and death. The Middle East and Africa have suffered the brunt of the recent outbreaks of cholera and the purpose of this study was to review the causes and potential solutions for cholera in this region. The study's narrow temporal and geographical focus on cholera outbreaks in Africa and the Middle East may not provide a comprehensive understanding of cholera dynamics globally and limits the generalizability of findings. The impact of COVID-19 likely exacerbated local outbreaks of cholera in Africa and the Middle East as well as led to an undercounting of the number of cases. Going forward there are headwinds and promises toward combating cholera in Africa and the Middle East. Poverty, inadequate sanitation, inadequate water supply, overpopulation, and conflict continue to create environments susceptible to cholera. Conflicts in nations such as Syria, Ethiopia, and Sudan have led to crowded living conditions with reduced access to clean drinking water and cholera treatment. Climate change threatens to exacerbate cholera conditions by increasing the occurrence of flooding and drought in the region.

RDTs that do not rely on expensive laboratory materials will help detect outbreaks sooner, leading to more rapid population-level interventions. Vaccination efforts have been hindered by reduced production and increased demand for vaccines. Eubiologics' Euvichol/Euvichol-Plus will be increasingly relied upon as a relatively inexpensive and effective vaccine for Middle Eastern and African nations. As Africa and the Middle East emerge from the COVID-19 pandemic, renewed efforts will need to be made to address the increasing threat of cholera. Prevention and treatment strategies will likely require a multi-pronged combination of prevention and treatment strategies.

AUTHOR CONTRIBUTIONS

Abdulrahman K. Ahmed: Conceptualization; writing—original draft; validation; data curation. **Victor Coll Sijercic**: Investigation; writing—original draft; visualization; writing—review and editing; resources. **Mahad S. Akhtar**: Writing—original draft; methodology; visualization; software. **Ahmed Elbayomy**: Conceptualization; investigation; resources; data curation; formal analysis. **Mohamed A. Marouf**: Investigation; writing—original draft; data curation; methodology. **Mahlet S. Zeleke**: Conceptualization; writing—original draft; project administration; data curation; validation. **Reem Sayad**: Investigation; writing—original draft; formal analysis. **Abdelrahman Abdelshafi**: Writing—original draft; resources. **Nicholas J. Laird**: Writing—original draft; investigation; formal analysis; data curation. **Mohamed A. El-Mokhtar**: Supervision; project administration; writing—original draft. **Gregory R. Ruthig**: Conceptualization; writing—original draft;

writing—review and editing; visualization; supervision; project administration. **Helal F. Hetta**: Writing—original draft; project administration; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

TRANSPARENCY STATEMENT

The lead author Mahlet S. Zeleke affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

All generated data are included in this manuscript.

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