

*Full Length Research Paper*

# **Pathogenicity, epidemiology and antibiotic resistance of *Vibrio cholera* strains in some West African Countries: A Systematic Review**

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**Cholera is an epidemic disease and a real public health problem throughout the world, particularly in West Africa. This study provides a comprehensive overview of the pathogenicity, epidemiology and *Vibrio cholerae* strains's antibiotics resistance in West Africa. A literature review was conducted online in English using the keywords "Cholera", "*Vibrio cholerae*" "West Africa", "Epidemiology", "Antibiotic resistance". These keywords were entered into using electronic databases such as PubMed, Google Scholar, Scopus and Elsevier and articles were used according to the reliability of their sources, study areas, and subjects. This review was based on the collected data from different databases. One hundred and twenty-three articles were identified. After the initial and final sorting of the collected data in order to eliminate duplicate copies, eighty-three were retained while seventy articles were selected, respectively, for this review. Though some studies had recommended for a system of monitoring cholera in West African countries, nevertheless, there is the need to create more awareness. Furthermore, hygienic practices and environmental wastes management in these countries need to be improved.**

**Key words:** Cholera, epidemiology, *Vibrio cholerae*, antibiotic resistance, West Africa.

## **INTRODUCTION**

Since 1817, seven Cholera pandemics whose causative agent is *Vibrio cholera* have been documented (Webb, 2019). Cholera has continued to be a threat to the health of many communities worldwide. Annually, about 3 to 5

million people are affected by cholera and 100,000 to 120,000 lives are lost (WHO, 2014; Ali et al., 2012). Since the first pandemic which occurred in West Africa (Webb, 2019), some outbreaks have been frequently

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reported in Benin, Ghana, Nigeria, Ivory Coast and Togo (WHO, 2016). However, only a few small-scale studies have examined the dynamics of recent cholera outbreaks in West Africa. Overall, cholera epidemics throughout the study region have shown different characteristics depending on the country. In West African countries like Benin and Togo, cases of cholera occur every year, but with a relatively low incidence (Moore et al., 2018; Landoh et al., 2013). However, many countries in the northwest, including the Gambia, Senegal, and Mauritania, have registered multi-year cholera epidemics with high incidence (Manga et al., 2018). Several epidemics have occurred following natural disasters (flooding, earthquake, etc.) and major population displacements. This is the case of Senegal in 2004-2006 (Manga et al., 2018). Nowadays, cholera remains endemic in Asia and Africa, due to the shortages in sanitary systems of these countries coupled with the social-cultural behavior of populations, as well as the lack of hygienic practices and environmental sanitary activities (Sule et al., 2017). Recent studies carried out in some West African countries, including Nigeria, Republic of Benin, Togo, Ghana, and Ivory Coast, for a period of 20 years (1987-1994) on the relationships between climate, inter annual variability and cholera revealed temporo-spatial synchrony between cholera incidence and rainfall in all the countries besides Ivory Coast (Boeckmann et al., 2019). Thus, cholera is a waterborne disease caused by ecological factors (Ruenchit et al., 2019). During the seventh pandemic, antibiotic resistance as well as the virulence of *V. cholerae* strains increased and another variant of the cholera biotype occurred (Safa et al., 2010).

The global spread of antibiotic-resistant strains of *V. cholerae* is now threatening the effective treatment and control of cholera, particularly in low- and middle-income countries. Current evidence shows that cholera represents a serious threat to the African continent (Sambe-Ba et al., 2017). Because of this situation in West African countries and the worrying public health phenomenon of antimicrobial resistance (WHO, 2016), it has become very necessary to create more awareness on the resistive nature to antibiotics of *V. cholerae* strains particularly in West African countries. The present article review was aimed at identify, through a review of related literatures, information on pathogenicity, epidemiology and antibiotics resistance of *V. cholerae* strains in West Africa.

## METHODOLOGY

### Methods of search and article selection

The review work was conducted using the following keywords "Cholera", "*V. cholerae*" "West Africa", "Epidemiology", "Antibiotic

resistance". These keywords, with the use of PubMed, Google Scholar, Scopus and Elsevier, assisted in collating reliable articles based on source, study area, and subject. The search strategy was based on three components: (1) Epidemiology of cholera in West Africa; (2) *V. cholerae* in humans; (3) Characterization of *V. cholerae* in food, environment and feces; (4) Antibiotic resistance of isolated *Vibrio cholerae* strains. The following descriptors and Boolean operators were used, while searching for articles, no language or timeline restrictions were applied. The initial selection was based on the title and summary of all articles found. Duplicate articles were eliminated, and all potentially relevant articles were uploaded for eligibility assessment.

### Data extraction, exclusion, and inclusion criteria

The exclusion of the articles was based on well-defined criteria, as follows: (1) studies on *Vibrio* strains, and (2) studies that were non-journal papers such as editorials, dissertations and thesis, book, editors' letters, Master or Doctoral theses, book chapters, and articles whose complete text was unavailable. Reference lists of the selected articles were also examined to find potentially relevant documents. The criteria used for inclusion were based on articles relevance on: epidemiology of cholera; cholera and transmission of *Vibrio cholerae* through food, as well as food products and the environment, and antibiotic resistance of strains of *Vibrio cholerae*. Such criteria were defined to fulfill the proposed objective: the epidemiology of cholera in West Africa, the transmission of *V. cholerae* through food, the environment and the antibiotic resistance of these strains. Qualitative data were extracted from all the selected articles. The data extraction was classified as follows: (1) characteristics of the publication: author, year, journal, and country; (2) characteristics of the *V. cholerae*: source; antibiotic resistance and main results of the study.

## RESULTS

This systematic review is the result of data collection carried out in different databases. One hundred and thirty-three articles were identified. After a first sort duplicate articles were eliminated, and all potentially relevant articles were uploaded for eligibility assessment. We, therefore, retained 83 articles. An in-depth reading of the articles led to the second selection of 70 articles for this study. Figure 1 shows the item selection diagram according to the PRISMA statement.

### Epidemiology of Cholera in West Africa

In Africa, the studies of Ramamurthy et al. (2019), clearly describe the epidemiology of cholera in Africa. Seven cholera pandemics have been experienced globally and it continues to cause outbreaks locally and regionally across the African continent (WHO, 2019; Moore et al., 2018). According to WHO (2019), there were about 1.3 to 4.0 million reported cases and about 21,000 to 143,000 recorded deaths as a result of cholera globally in 2018. Between 1970 and 2011, Democratic Republic of Congo,

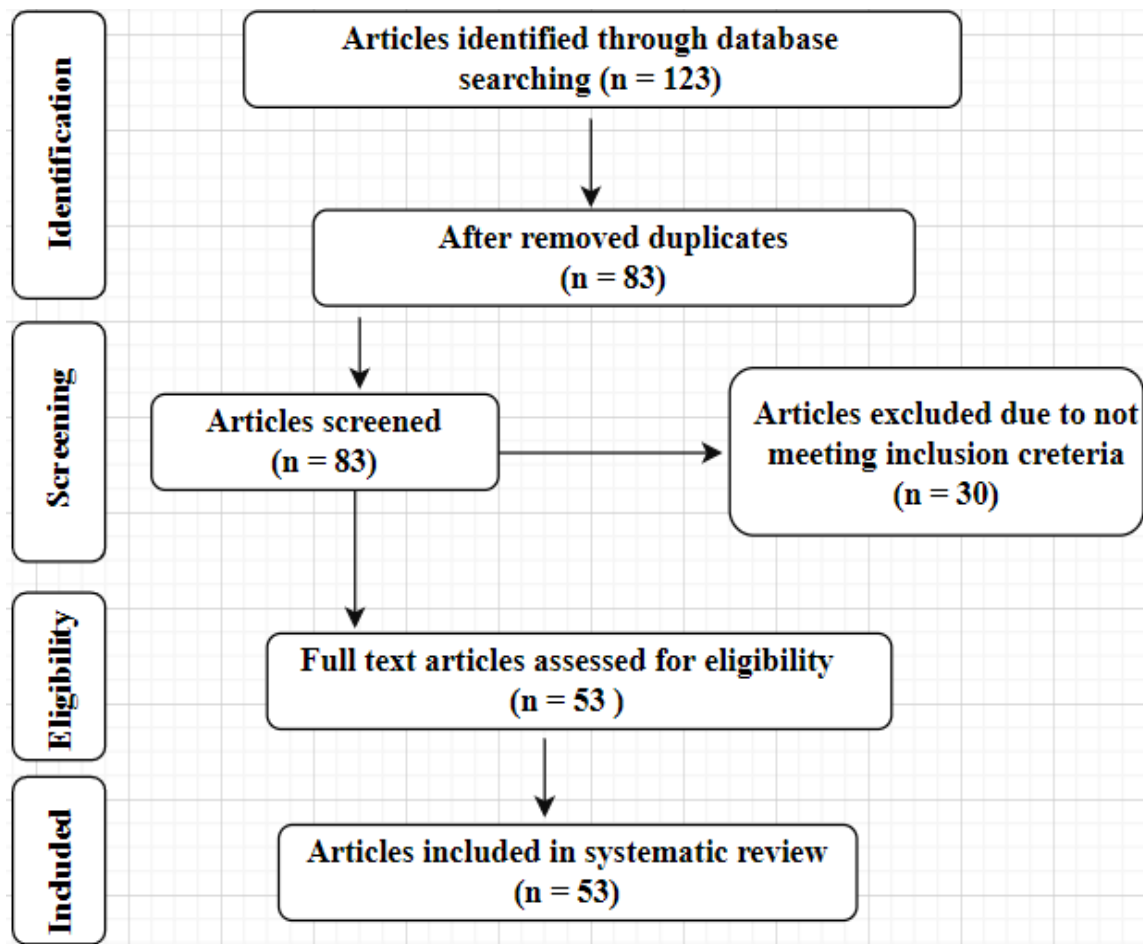


Figure 1. PRISMA model study design process. n: number of articles.

Mozambique, Nigeria and Tanzania recorded pooled estimate of about 260,000 to 390,000 cases of cholera diseases and 11,000 to 25,000 deaths (Mengel et al., 2014). The genomic approach has made it possible to identify cases of cholera transmission from South Asia to Africa (T1, T3-T13) and from Africa to America (T2) or Asia (T13). Of these, T1-T5, T6-T8, T9-12 are wave 1, wave 2, and wave 3 respectively (Weill et al., 2017). T1 occurred in the 1970s in southeastern Asia and follow-up in the Middle East and Russia. In Europe, only imported cases of cholera have been reported in the recent past. European T1 isolates from the early 1970s originated in West and North Africa. T2 (1989-1991) was responsible for the spread of cholera from West Africa. The South Asian origin T7 (1982-1984) was detected in isolates from several epidemics in North and West Africa. The T8 subline from the Middle East was associated with epidemics in South Africa in 2001-2002. Outbreaks in Zimbabwe in 2008-2009 were associated with T8 and

T11. Most of the African countries were effected with T9–T12 from 1990–2014 and these sub-lineages originated in South Asia. In West Africa, number of reported cases increased to 16,088 compared to 3,074 in 2010 (Goita, 2014). Other isolates from western and southern Europe in the early 1970s were found to originate from West or North Africa. After being introduced into West Africa in 1970, cholera was detected several times in that region, with extensions into the Gulf of Guinea region and the Lake Chad basin :T7 (dates of introduction: 1982 to 1984), T9 (1988 to 1991), and T12 (2007) (Weill et al., 2017).

Ghana has experienced numerous epidemics since the first outbreak reported in 1970 (WHO, 2019; Noora et al., 2017). Over the past two decades, the country has reported an average of 3,066 (range: 50-10,628) cholera cases with a fatality rate of 1.7%, although WHO (2013) estimated that over 40,000 cases occurred every year during the outbreaks (Noora et al., 2017). The epidemic

in 2012, which recorded 9,548 cases in 9 regions and killed 100 (WHO, 2013, Ghana Health Service, 2013). With more than 28,975 cases and 243 deaths, the cholera outbreak from 2014 to 2015 in Ghana was the worst outbreak on record in the country. Later in 2016, a small wave of the disease was recorded in the central region of Ghana, accounting for 596 cases (UNICEF-Ghana, 2016).

Cholera disease is said to be endemic, epidemic and it is frequently occurring in Nigeria (Cholera annual Report, 2011). According to surveillance data obtained from the Epidemiology Division of the Federal Ministry of Health, between January 2004 and December 2008, cholera outbreaks were reported in 12 states in Nigeria with 74,881 cases and 1,387 deaths (Gidado et al., 2018). The 2010 cholera epidemic was the largest outbreak in Nigeria since 1991, when 59,478 cases and 7,654 deaths were reported (WHO, 2010; Dalhat et al., 2014). From September to December 2013 in Nigeria, a total of 6,600 cholera cases, including 229 deaths, were reported in 94 local authorities (LGAs) in 20 states (including Kaduna State). Kaduna State has been in the forefront during the latest cholera outbreaks in Nigeria. On August 1, 2015, an epidemic of suspected cholera cases was reported in Zaria LGA. With over 40 cases and over 10 registered deaths (WHO-Cholera, 2016; WHO, 2016b).

After the seventh cholera pandemic in 1970 caused by *V.cholerae* O1 biotype El Tor, Guinea-Bissau, located along the West African coast in northern Guinea, reported outbreaks for the first time in 1987 (Dalsgaard et al., 2000; WHO, 1987), which was followed by an epidemic in 1994 which spread in early 1995 (Dalsgaard et al., 2000). The epidemics of 1987 and 1994–1995 were determined through phenotypic and genotypic analyzes to be caused by different O1 strains, with the 1994-1995 epidemic strain probably having been introduced by fishermen or travelers from Guinea (Dalsgaard et al., 2000). The most recent outbreak in Guinea-Bissau began in October 1996, spread throughout 1997, and included a total of 26,967 reported cases, with an increased case fatality rate (Dalsgaard et al., 2000).

Togo has experienced endemic cholera for at least the past 40 years, mainly in the coastal region (Constantin et al., 2007; Bockemühl and Meinicke, 1976; Bockemühl and Schröter, 1975; Amedome et al., 1971). Outbreaks have sometimes been large, with case fatality rates reaching 10% (Bockemühl and Schröter, 1975). More recently, cholera continues to be rampant in Togo, including in 2011, when Togo experienced hundreds of cases and over 30 deaths (Landoh et al., 2013). In addition to the risk of cholera linked to diseases located in Togo itself, it is possible that Togo is exposed to the risk of cholera imported from neighboring countries, as the disease is endemic in a large part of West Africa

(Landoh et al., 2013; Gbary et al., 2011; Thompson et al., 2011; UNICEF, 2011). The current evaluation of surveillance data from the National Ministry of Health was undertaken as part of Togo's participation in the African Cholera Surveillance Network (Africhol; available at: <http://www.africhol.org>; consulted on 4 June 2020) to describe the epidemiology of cholera, including the suspected incidence, to better inform public health decision-making.

In Benin, the lakeside commune of Sô-Ava, which is directly connected to Nigeria via Lake Nokoue and Yewa River, reported cholera outbreaks every year since 2010 and was often the first and hardest-hit commune. In 2013, Sô-Ava reported 40% of cholera cases in 2013 and 30.4% of cases in 2014 (Manga et al., 2018). Cotonou, the economic capital of Benin, was affected by cholera epidemics in 2010, 2011 and 2013, in neighborhoods characterized by fishing activity and significant population movements (WHO, 2019).

In many countries of northwestern West Africa, such as The Gambia, Senegal and Mauritania, have experienced marked lulls for several years (Somayyeh et al., 2018; Aidara et al., 1998; Roquet et al., 1998). Many major epidemics have erupted in the wake of violent civil conflicts that have generated a humanitarian and public health crisis or massive population movements like that of Senegal in 2004-2006 (WHO, 2019; Somayyeh et al., 2018, Ekra et al., 2009) (Table 1). The vast majority of cases have also been reported in large cities following increased rainfall (Somayyeh et al., 2018, Ekra et al., 2009; Rebaudet et al., 2014; Wendo, 2003). Although many studies have been limited to a single epidemic / neighborhood or to a short period, common risk factors have been found across the region: overcrowded living conditions, poor sanitation, and limited access to clean water (Palma et al., 2011; Gbary et al., 2011).

### Transmission of *V. cholerae* in Africa

According to Weill et al. (2017) recurrent transmissions have been observed for cholera epidemics in Africa. Different sub-pandemic ages of the seventh *V. cholerae* El Tor (7PET) cholera pandemic from Asia were repeatedly introduced into two main regions: West Africa and East/Southern Africa. Epidemic waves then propagated regionally, in some instances spreading to Central Africa, over periods of a few years to 28 years. Only two notable instances of subline-age exchange between these two circulation hotspots were identified: The spread of a subline-age between Angola and Mozambique during the Portuguese colonial war in 1970s (Echenberg, 2011) and the spread of a subline-age from the African Great Lakes Region to the western part of the Democratic Republic of Congo (Rebaudet et al., 2013)

**Table 1.** The number of suspected cases of cholera reported in each country included in the study per year.

Country	Suspected cholera cases reported							Total
	2009	2010	2011	2012	2013	2014	2015	
<b>Coastal West African countries included in the epidemiological study</b>								
Ivory Coast	5	32	1261	424	56	235	199	2212
Guinea	42	0	3	7350	319	1	0	7715
Benin	74	983	775	668	528	832	0	3860
Togo	218	72	33	61	194	262	35	875
Liberia	1070	1546	1146	219	92	44	0	4117
Sierra Leone	0	0	0	23124	377	0	0	23501
Ghana	1294	438	10387	9563	20	28944	692	51338
Guinea-Bissau	5	0	0	3068	969	11	0	4053
Senegal	4	3	5	1	0	0	0	13
Mauritania	0	0	46	0	0	0	0	46
The Gambia	0	0	0	0	0	0	0	0
<b>Countries neighboring the study region</b>								
Burkina Faso	0	0	20	143	0	0	0	163
Nigeria	13691	44456	23377	597	6600	35996	5290	130007
Niger	0	1154	2324	5284	585	2059	51	11457
Mali	0	0	2220	219	23	0	0	2462

Source: WHO (2016a).

and the Central African Republic via the Congo River and its tributaries in 2011 to 2012.

### V. cholerae resistance mechanisms

The resistance among *V. cholerae* strains is attributed to target modifications or acquisition of resistance genes from mobile genetic elements. The major source of antibiotic resistance in cholera pathogens among the various mobile genetic elements are the Integrative conjugative elements (Banerjee et al., 2014). Bio mechanical mechanisms that the micro-organisms use to express resistance against antimicrobial agents include; drug alteration or inactivation by production of enzymes such as  $\beta$ - lactamases that act by hydrolyzing the  $\beta$  lactam ring, aminoglycoside-modifying enzymes and chloramphenicol acetyltransferases; modification of drug binding sites, changes in cell permeability thus leading to a reduction in intracellular drug accumulation, for instance presence of efflux pumps which expel the drugs and also loss of porin, a protein present on the outer membrane of gram negative bacteria; biofilm formation (Munita and Arias, 2016).

### Antibiotic resistance of *V. cholerae* in West Africa

According to Marin et al. (2013) Cholera outbreaks in

Nigeria are associated with multidrug resistant atypical El Tor and Non-O1/NonO139 *V. cholera* (Marin et al., 2013). We can understand that antibiotic multidrug resistance is becoming increasingly common among the atypical *V. cholerae* strains, mostly associated with acquisition of genes and/or modification in the antibiotic target genes. They remark that the current O1 Nigeria strains were resistant to streptomycin, trimethoprim and sulfonamides (Table 2). In *V. cholerae*, these resistances are frequently associated with class 1 and 2 integrons and SXT element, which is a *V. cholerae*-derived integrating and conjugative element (ICE). Thus, we investigated the presence of these elements in the Nigeria strains. All the current O1 strains harbor an ICE element, determined by the presence of the SXT integrase gene. No evidence was found for the presence of class 1 and 2 integrons (Opajobi et al., 2004; Okeke et al., 2001). All these genes were identified, explaining the resistance profile of the current O1 strains. Majority of the 2009/2010 Nigeria O1 strains showed reduced susceptibility to ciprofloxacin as well as resistance to nalidixic acid (Table 2).

Dalsgaard et al. (2000) from Guinea Bissau demonstrated resistance to ampicillin, aminoglycosides, cotrimoxazole and tetracycline. Only colistin remained effective from their study. They also demonstrated that resistant isolates possessed a multiresistance transmissible plasmid that encoded trimethoprim (dhfrXII) and aminoglycoside resistance.

**Table 2.** Antibiotic resistance of *V. cholerae* O1 strains responsible for cholera in West Africa.

Countries	Years of outbreak	Number of <i>V. cholerae</i> strains	Antibiotic resistance of strains of <i>Vibrio cholerae</i>	Authors and year of publication
Ghana	2012-2015	168 strains of <i>Vibrio cholerae</i> isolated from feces of hospitalized patients: 154 serogroup O1 and 14 non O1/O139 serogroup. 151 serotype Ogawa and 3 Inaba	Sulfamethoxazole-Trimethoprim, Nalidixic acid, Azithromycin, Gentamicin and Flucloxacillin.	Danso et al. (2020)
Ghana	2015-2016	51 strains of <i>Vibrio cholerae</i> O1. 40 strains were isolated from cholera patients between 2014-2015 and 11 strains were isolated from environmental.	92.5% of clinical isolates and 18.2% of environmental isolates were resistant to Erythromycin. 72.5% of clinical isolates and 27.3% of environmental isolates were resistant to Nalidixic acid.	Abana et al. (2019)
Nigeria	2009-2010	15 strains of <i>Vibrio cholerae</i> O1 and 5 non O1/O139.	Streptomycin, Trimethoprim-Sulfamethoxazole, Sulfonamides, Nalidixic acid, Chloramphenicol	Opajobi et al. (2004)
Nigeria	2007-2013	115 strains of <i>Vibrio cholerae</i> O1. 103 strains among serogroup Ogawa and 12 Inaba; 92 strains isolated from clinical samples and 23 strains from environmental samples.	8 to 100% of these strains were resistant to Nalidixic acid, 4 to 100% of strains to Streptomycin and 4 to 100 % of strains to Trimethoprim-Sulfamethoxazole	Adevale et al. (2016)
Guinea-Bissau	1987; 1994-1995	19 strains of <i>Vibrio cholerae</i> O1. 5 strains were isolated in 1987 and 14 strains isolated in 1994-1995.	Only strains isolated in 1987 were resistant to Polymycin B. The strains isolated in 1994-1995 were resistant to Polymycin and Trimethoprim-Sulfamethoxazole	Dalsgaard et al. (1996)
Togo	2008 to 2011	58 strains of <i>Vibrio cholerae</i> O1: 12 strains in 2008, 11 strains in 2009, 24 strains in 2010 and 11 strains in 2011.	All strains isolated in 2008 were resistant to Erythromycin, Chloramphenicol and Trimethoprim-Sulfamethoxazole. Regarding strains isolated in 2009, they were resistant to Tetracycline, Erythromycin, Chloramphenicol and Trimethoprim-Sulfamethoxazole. About strains isolates in 2010, they were resistant to Ampicillin and Trimethoprim-Sulfamethoxazole. For 2011 isolates, they were resistant to Ampicillin, Tetracycline, Chloramphenicol, Nalidixic Acid and Trimethoprim-Sulfamethoxazole.	Landoh et al. (2013)

Okeke et al. (2001) investigated an outbreak of acute gastroenteritis from Niger state, north-central Nigeria, where eight *V. cholerae* organisms were isolated. They all had the O1-serogroup and El Tor biotype. All of them were sensitive to tetracycline but resistant to trimethoprim, sulphonomide, spectinomycin and chloramphenicol, detected 34 strains of *V. cholerae* in Jos University Teaching Hospital (Nigeria) over a one-year period (WHO, 1987). They were all of the O1 serogroup, El Tor biotype and Inaba serotype. They were all resistant to chloramphenicol, ampicillin, cloxacillin and penicillin G, but sensitive to tetracycline, ofloxacin

and erythromycin. A study done by Quilici et al. (2010) using the *V. cholerae* isolates from the September/October 2009 outbreak of acute watery diarrhea in north-eastern Nigeria implicated the serogroup O1 of the El Tor biotype and Ogawa serotype as the causative serotypes (Quilici et al., 2010). The toxigenic genes of *ctxA* and *ctxB* were elaborated, in addition to detected mutations in the genes responsible for quinolone resistance. All of them were resistant to trimethoprim-sulphamethoxazole, ciprofloxacin, sulphonomide and nalidixic acid. All the isolates were resistant to tetracycline, but moderately susceptible to chloramphenicol and ampicillin

(Quilici et al., 2010).

In Senegal, the study of Sambe-Ba et al. (2017) identified atypical El Tor *Vibrio cholerae* O1 Ogawa that were resistant to streptomycin and cotrimoxazole. An increasing trend of resistance to cotrimoxazole was observed from many studies (Sambe-Ba et al., 2017). This is worrisome, because, until now, cotrimoxazole was considered the drug of choice against *V. cholera* (Table 2).

## DISCUSSION

In addition to the seven cholera pandemics

recorded around the world and Africa in particular, local and regional outbreaks continue to be recorded on the African continent (WHO, 2019; Moore et al., 2018). The genomic approach has made it possible to identify the typical strains responsible for pandemics in Africa. Among these typical strains, strain T7 was reported between 1982 and 1984; strain T9 (1988 to 1991); strain T12 in 2007 and strains T8 and T11 (2008 to 2009) reported in Zimbabwe (Weill et al., 2017; Goita, 2014). This indicates that there were the same strains which had ravaged the entire continent, and responsible for the different epidemics. This is justified by the fact that the epidemic episodes take place in practically the same periods in each of the countries. In West Africa many countries face frequent epidemics of cholera. Ghana experienced the worst cholera outbreak from 2014 to 2015 with more than 28,975 cases and 243 deaths (UNICEF-Ghana, 2016). In 2010, Nigeria experienced its largest cholera epidemic with 59,478 cases and 7,654 deaths (WHO, 2010; Dalhat et al., 2014). Guinea, Togo, Benin, Gambia, Senegal and Mauritania have also experienced cholera epidemics since 1970 to date (Dalsgaard et al., 2000; Landoh et al., 2013; Manga et al., 2018; Somayyeh et al., 2018). The countries of West Africa face the same realities due to extremely large population, lack of sanitation infrastructure, lack of potable water, the majority of the population illiterate. Risk factors for cholera epidemics such as overcrowded settlements, lack of hygienic practices and sanitation infrastructures, and limited access to potable water are common in the West African zone (Luquero et al., 2011; Gbary et al., 2011). This is justified by the fact that cholera epidemics occur in West Africa countries of almost every year.

Resistance of *V. cholera* strains to antibiotics is due to the acquisition of resistance genes from integrative conjugative elements (Banerjee et al., 2014). In West Africa, the strain of *V. cholerae* responsible for cholera epidemics is the atypical EI to strain of serogroup O1. This strain which circulates in the region is multidrug resistant and its resistance profile is practically the same in West African countries (Marin et al., 2013). In Ghana, Danso et al. (2020) and Abana et al. (2019) showed that from 2012 to 2016, nearly 75% of *V. cholerae* O1 strains isolated from the feces of hospitalized patients were resistant to Sulfamethoxazole-Trimethoprim, 92.5% were resistant to Erythromycin and 72.5% with nalidixic acid. In Nigeria, from 2007 to 2013, virtually all strains of *V. cholerae* O1 isolated from clinical and environmental specimens were resistant to Sulfamethoxazole-Trimethoprim, nalidixic acid and streptomycin (Adewale et al., 2016). In Togo, Landoh et al. (2013) presented similar results with the resistance of all strains of *V. cholerae* O1 isolated from 2008 to 2011 from clinical samples to Sulfamethoxazole-Trimethoprim, Erythromycin

and nalidixic acid.

## Conclusion

Cholera continues to be a real public health problem that is difficult to manage for West African countries sanitary system. This is due to the correlation between its epidemiological impact and the precarious hygiene of the population. For a more efficient fight, a mixed strategy based on sanitation to reduce the risks of contamination and on the development of more effective therapies to circumvent antibiotic resistance is required.

## CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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