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Research Article

Factors Influencing Fatal Outcome during an Outbreak of Cholera, Gadarif, Sudan

Hassan E El Bushra[1*], Mohamed A Alkhidir[3], Ahmed AA Haroun[3], Osman Basher MA Osman[2], Marwa MH Ali[2], Maha AA Qassim[2], Mutaz OS Bukhari[2], Ahmed AM Osman[1], Elmamoon I Mohamed-Elkhair[2], Mawada E. E. Eljenaid[2]

[1]Consultant Medical Epidemiologist, Sudan

[2]State Ministry of Health, Gadarif, Sudan

[3]World Health Organization Country Office (WHO), Sudan

[*]**Corresponding author:** Hassan E. El Bushra, Consultant Medical Epidemiologist, Othman Digna Street, Corner Nile Avenue, Eastern Gate, Khartoum, P.O Box 2234 Khartoum, Sudan

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Abstract

We studied risk factors associated with fatal outcome of cholera patients during the outbreak in Gadarif State, Sudan in 2023 using the surveillance data and patients' medical records, Forty-six out of 1,904 patients with cholera died (case-fatality rate [CFR] 2.4 (95 CI: 1.8-3.2). The CFR among females patients (2.84, 95 CI: 1.86-4.13), (p>0.05) from CFR among males (CFR=2.34, 95 CI: 1.43-3.59). The CFR among patients aged 70 years or more was 3.81 (95 CI: 1.05-9.47). The mean (SD, IQR) of the duration between the onset of diarrhea and reaching the CTC was 0.58 (1.27, 0.0–1.0) and 0.5435 (0.81, 0.0–1.0) days for survivors and fatal cases (p>0.05). Unconditional multi-variate analysis revealed that patient is living in a rural area were more likely to die from cholera than others (OR= 3.28, 95% CI: 1.61-6.68). We concluded that accessibility to medical services during cholera outbreaks are critical to reduce CFRs.

Keywords: Cholera; Case-fatality ratio; Sudan; Outbreak; Outcome; Determinant

Introduction

Cholera, a highly contagious diarrheal disease, is an indicator of inequity and lack of social development [1,2]. The disease remains a global disease threat and a major public health problem, primarily in countries with poor sanitary conditions, regions affected by natural disasters, and where access to safe drinking water is limited [3]. It is estimated that every year, there are roughly 1.3 to 4.0 million cases and 21,000 to 143,000 deaths worldwide due to cholera [4]. The Case-Fatality Rates (CFR) due to cholera are high in the African and the Eastern Mediterranean Region; especially, in countries with limited resources [5]. Several social and environmental risk factors, conflicts, disruption to health services, loss of income, and internal displacement of populations contributed significantly to higher attack and Case Fatality Rates (CFR) [6,7].

Cholera continues to be a public health problem in Sudan. Previous outbreaks of cholera, also referred to as Acute Watery Diarrhea (AWD), in Sudan have been reported to have occurred in 1966, 1970, 1970, 1972, 1980, 1981, 1999, 2006, 2008, 2010, 2014 and 2016 that, including Gadarif, varied in magnitude, geographical distribution within the state and severity [8]. Despite

being a preventable and treatable disease, cholera outbreaks continue to emerge in different states of Sudan and result in high CFRs that ranged between 2.3% and 7.3%, which were relatively high as compared to other countries [7]. Yet, there is paucity of knowledge on risk factors associated with these cholera outbreaks.

The Federal Ministry of Health (FMOH) declared emergence of a cholera outbreak in Gadarif State. The first suspected case was reported on September August 25, 2023. More than 260 suspected cases of cholera were reported, including 22 laboratory-confirmed cases. Bacteriological diagnosis of cholera was confirmed by the National public Health Laboratory (NPHL) in Port Sudan. More suspected cholera cases were also reported from Khartoum and South Kordofan States. The emergence of a current outbreak of cholera in Gadarif State amidst unstable and hostile political conditions that compromised the governance of the national preventive and curative health services rendered implementation of appropriate interventions difficult and more challenging. The objective of this study is to identify factors associated with fatal outcome of cholera patients during an outbreak of cholera that occurred in Gadarif State.

Material and Methods

Background

Gadarif State is one of the 18 states of Sudan. The State shares an international border with Ethiopia to the east; and with other four states in Sudan. There are twelve localities in Gadarif State and the population in Gadarif State (N=2,854,132) is diverse, composed of various Sudanese ethnic groups tribes that contribute to a multicultural tapestry. In addition, there are communities from neighboring countries, including, Ethiopians, Eritreans, Yemenis and others West African countries. There are 143 sentinel sites for surveillance in Gadarif State; of which 22 (15.4%) are in Gadarif City. Cases of cholera were reported from 11 localities in Gadarif State. As part of the response activities, the State Ministry of Health (SMOH), Gadarif established two Cholera Treatment Centers (CTCs), the main one was in the center of Gadarif City with a capacity of 30 beds and a total number of 6 medical doctors. The second CTC had more than 50 beds and was operated by an International Non-Governmental Organization (NGO).

A case of cholera was defined as any person aged 2 years or older presenting with acute watery diarrhoea (AWD) and severe dehydration or dying from AWD with or without vomiting and severe dehydration or dying from AWD during the outbreak period [9]. The Outbreak Investigation Team (OIT) reviewed the surveillance data during the period between August and December 2023. Detailed data were obtained by reviewing the medical records of 199 cases who survived and 46 patients with a fatal outcome using a standard data collection form. Abstraction from medical records was done by the doctors working in the CTCs. We conducted telephone interviews with the discharged or relatives of deceased cases to collect data on co-morbidity and other potential risk factors.

Data were entered in Excel subsets and Epi Info version 7.2 (Centers for Disease Control and Prevention, Atlanta, GA, USA). Epi Info was used for calculation of mean, standard deviation (SD) and the Inter-quartile Range (IQR), statistical associations, Case-Fatality Ratios percent (CFR%), odds ratios (OR) and the corresponding 95% confidence intervals using bivariate and multivariate analyses to identify risk factors for fatal outcomes of cholera. Only potential risk factors that turned out to be significant using 2 X2 tables were re-run using multi-variate analysis (unconditional logistic regression) to control for potential confounding. Stratified by (adjusted OR) by gender, age and locality.

Results

During the study period, a total number of 1,997 cases of AWD were identified by the surveillance system in Gadarif State. One hundred (5.0%) patients were 2-year old or younger; they were excluded from further analysis as they did not conform to the case-definition used by the investigators. Of the remaining 1897 patients, 983 (50.5%) were females and 985 (48.3%) were males; the gender of 24 (1.3%) patients was not reported (Table 1); difference was not statically significant (difference between two proportions, p-value= 0.087).

Locality	Gender				Total	
	Female		Male			
	N	%	N	%	N	%
East Gallabat	70	50.7	68	49.3	138	7.4
Qorysha	61	55.0	50	45.1	111	5.9
Baladyat Gedarif	583	50.5	572	49.5	1155	61.5
Wasat Gedarif	98	55.1	80	44.9	178	9.5
West Gallabat	112	56.9	85	43.2	197	10.5
Al-Rahad	4	80.0	1	20.0	5	0.3
Almafaza	1	33.3	2	66.7	3	0.2
Alfao	3	50.0	3	50.0	6	0.3
Alfashaga	25	41.7	35	58.3	60	3.2
Basounda,	2	66.7	1	33.3	3	0.2
Al-Butana	4	19.1	17	81.0	21	1.1
Total	963	51.3	914	48.7	1877	100.0

Table 1: Number of cases of cholera by locality during an outbreak of cholera in Gadarif State, eastern Sudan, by locality, 2023.

Eight hundred eighty-eight patients (48.0%) presented to a health facility on the same day of onset of symptoms, 606 (32.8%)

on the second day and 355 (19.2%) after the second day. The mean (SD, IQR) of the duration between the onset of diarrhea and reaching the CTC was 0.5817 (1.27, 0.0 – 1.0) and 0.5435 (0.81, 0.0 – 1.0) days for survivors and fatal cases, the difference was not statistically significant (t-test difference between two means, p>0.05). The mean (SD, IQR) of the duration between the onset of diarrhea and reaching the CTC was 0.58 (1.27, 0.0 – 1.0) and 0.54 (0.81, 0.0 – 1.0) days for survivors and fatal cases, the difference was not statistically significant (t-test difference between two means, p>0.05) (Tables 2 and 3).

	N	Mean	SD	Median
Locality				
East Gallabat	138	0.3	0.7	0
Qorysha	111	0.1	0.4	0
Baladyat Gadarif	1076	1	1.3	1
Wasat Gadarif	169	0.9	1.2	1
West Gallabat	180	0.9	1.1	1
Al-Rahad	5	1	1.7	0
Almafaza	3	2.7	1.5	3
Alfao	6	1.3	1	1
Alfashaga	60	0.6	1.1	0
Basounda,	3	0.3	0.6	0
Al-Butana	21	1.5	1.5	1

Table 2: Duration between onset of symptoms of cholera and presenting at a health facility during an outbreak of cholera in Gadarif State, Sudan, 2023.

	N	Mean	SD	Median	Mode	IQR	*p*-value
Overall	1941	29.9	21.2	26.0	2.0	13.0- 42.0	
Female	983	30.5	20.6	28.0	2.0	15.3 - 42.0	P>0.05
Male	958	29.2	21.9	25.0	2.0	10.0 - 2.0	
Outcome of the disease							
Deaths	45	32.6	18.2	30.0	3.0	11.0-50.0	P>0.05
Alive	399	32.5	21.2	29.0	27.0	20.0 -45.0	
Locality							
East Gallabt**	138	18.7	20.1	8.0	3.0	5.0 - 32.0	P>0.05
Qorysha	111	20.9	18.6	14.0	2.0	6.0 - 33.0	
Baladyat Gedarif	1155	30.9	20.8	27.0	2.0	20.0 - 42.5	P<0.0001
Wasat Gedarif	178	34.8	19.5	32.0	2.0	23.0 -46.3	P<0.0001

Table 3: Summary of the mean age distribution of cases, deaths and in the most affected localities.

Out of 916 females, 26 died (CFR = 2.84, 95 CI: 1.86 - 4.13), whereas there 20 death among 856 males with cholera (CFR = 2.34, 95 CI: 1.43 -3.59); the difference is not statistically significant (p>0.05, test difference between two proportions, Z = 0.66, p= .507). The CFR increased significantly in the age group 30-40 years (CFR= 2.58, 95 CI: 1.04 - 5.25) and remained high in patients aged 40 years or older (CFR= 3.57, 95 CI: 1.32 - 7.61); a non-significant difference between two proportions, Z = 0.38, p = .704. The highest CFR was in patients aged 70 years or more (CFR= 3.81, 95 CI: 1.05 -9.47); a non-significant difference between two proportions, Z = 0.93, p = .351 (Table 4). Forty-six out of 1,904 patients with cholera died (case-fatality rate [CFR] 2.4 (95 CI: 1.8 - 3.2), The CFR was relatively high in Gallabat Ash-Sharqia (CFR= 7.5%; 95% CI: 4.1 – 13.0) and Wasat Gadarif (CFR= 5.6%; 95% CI: 3.0 – 9.9). However, the difference in CFR between East Gallabat and Wasat Gadarif as compared with Qorysha (referent group) was not significant (difference between two proportions, p >0.05). The high CFR in West Gallabat was high, 16.7. Twenty-one cases died before reaching the CTC; this made the CFR% in the CTC 1.5 (0.95 -2.16) (Table 5).

Age group	Females				Males				Total			
	Cases	Deaths	CFR	95% CI	Cases	Deaths	CFR	95% CI	Cases	Deaths	CFR	95% CI
0-4	129	1	0.8	1.4 – 4.3	103	1	1.0	0.2 – 5.3	232	2	0.9	0.2 – 3.1
5--9	101	3	3.0	1.0 – 8.4	87	2	2.3	0.6 – 8.0	188	5	2.7	1.1 – 6.1
10--14	57	2	3.5	1,0 – 12,0	44	3	6.8	2.3 – 18.0	101	5	5.0	2.1 – 11.0
15--19	63	1	1.6	0.3 – 8.5	93	0	0.0	0.0 – 4.0	156	1	0.6	0.1 – 3.5
20--24	101	1	1.0	0.2 – 5.4	96	2	2.1	0.6 – 7.3	197	3	1.5	0.5 – 4.4
25--29	88	1	1.1	0.2 – 6.2	91	2	2.2	0.6 – 7.7	179	3	1.7	0.6 – 4.8
30--34	62	1	1.6	0.3 – 8.6	82	1	1.2	0.2 – 6.6	144	2	1.4	0.4 – 4.9
35--39	67	0	0.0	0.0 – 5.4	77	2	2.6	0.7 – 9.0	144	2	1.4	0.4 – 4.9
40-44	39	2	5.1	1.4 – 17.0	71	3	4.2	1.4 – 12.0	110	5	4.5	2.0 -10.0
45-49	28	0	0.0	0.0 – 12.0	41	2	4.9	1.3 – 16.0	69	2	2.9	0.8 – 10.0
50-54	38	3	7.9	2.7 – 21.0	45	1	2.2	0.4 – 12.0	83	4	4.8	1.9 – 12.0
55-59	24	2	8.3	2.3 – 2.6	27	1	3.7	0.6 – 18.0	51	3	5.9	2.0 – 16.0
60-64	70	0	0.0	0.0 – 5.2	60	1	1.7	0.3 – 8.9	130	1	0.8	0.1 – 4.2
65+	62	3	4.8	1.7 – 13.0	58	5	8.6	3.7 – 19.0	120	8	6.7	3.4 – 13.0
	929	**20**	**2.2**	**1.4 – 3.3**	**975**	**26**	**2.7**	**0.2 – 3.9**	**1904**	**46**	**2.4**	**1.8 – 3.2**

N: Number of population in respective gender; CFR: Case-fatality rate percent; Cases: Number of cases of cholera in respective gender; 95 CI: 95 Confidence interval for respective CFR

Table 4: Age-Sex specific Case-fatality rates (CFR) percent during an outbreak of cholera in Gadarif State, eastern Sudan, by locality, 2023.

Locality	Female				Male				Total			
	Cases	Deaths	CFR%	95% CI	Cases	Deaths	CFR%	95% CI	Cases	Deaths	CFR%	95% CI
Al Butanah	0	0	0		0	0			0	0		
Al Fao	3	1	33.3	6.1 – 79.0	3	0	0.0	0.0 – 56.0	6	1	16.7	3.0 – 56.0
Al Fashaga	35	2	5.7	1.6 – 19.0	24	0	0.0	0.0 – 14.0	59	2	3.4	0.9 – 12.0
Al Galabat Al Gharbyah - Kassab	83	0	0.0	0.0 – 4.4	114	3	2.6	0.9 – 7.5	197	3	1.5	0.5 – 4.4
Al Mafaza	2	0	0.0	0.0 – 66.0	1	0	0.0	0.0 – 79.0	3	0	0.0	0.0 -56.0
Al Qureisha***	50	0	0.0	0.0 – 7.1	59	3	5.1	1.7 – 14.0	109	3	2.8	0.9 – 7.8
Ar Rahad-GD	1	0	0.0	0.0 – 79.0	4	0	0.0	0.0 – 49.0	5	0	0.0	0.0 – 43.0
Basundah	1	0	0.0	0.0 – 79.0	2	0	0.0	0.0 – 66.0	3	0	0.0	0.0 – 56.0
Gala'a Al Nahal	17	1	5.9	1.0 – 27.0	5	0	0.0	0.0 – 43.0	22	1	4.5	0.8 – 22.0
Galabat Ash-Shargiah	65	4	6.2	2.4 – 15.0	69	6	8.7	4.0 – 18.0	134	10	7.5	4.1 – 13.0
Madeinat Al Gedaref	590	6	1.0	0.5 – 2.2	596	10	1.7	0.9 – 3.1	1,186	16	1.3	0.8 – 2.2
Wasat Al Gedaref	82	6	7.3	3.4 – 15.0	98	4	4.1	1.6 – 10.0	180	10	5.6	3.0 – 9.9
Total	929	20	2.2	1.4 – 3.3	975	26	2.7	1.8 – 3.9	1,904	46	2.4	1.8 – 3.2

N: Number of population in respective gender; CFR: Case-fatality rate percent; Cases: Number of cases of cholera in respective gender; 95 CI: 95 Confidence interval for respective CFR; ***Referent group

Table 5: Case-fatality rates (CFR) percent by locality during an outbreak of cholera in Gadarif State, eastern Sudan, by locality, 2023.

Of all potential determinants of fatal outcomes of cholera, the results of the multi-variate analysis revealed that patient is living in a rural area (villages) were more likely to die from cholera than others (OR= 3.28, 95% CI: 1.61 - 6.68) (Table 6).

Term	Cases (N=46)		Controls (N=200)		Bi-variate analysis		Multi-variate Analysis	
	N	%	N	%	Odds Ratio	95% C.I.	Odds Ratio	95% C.I.
Living in a shelter for internally displaced population	0	0	11	5.5	Undefined	Undefined	0.00	0.00 - >1.0E12
Patient is living in a rural area (village)	24	52.2	22	25.1	3.19	1.65 – 6.7	3.28	1.61 - 6.68
Taking some other medicines regularly	11	36	26	174	2.10	0.96 – 4.65	2.65	0.71 - 9.81
Suffering from hypertension	8	17.4	38	10.0	1.89	0.78 – 4.62	1.38	0.31 - 6.10
Suffering from Diabetes mellitus	4	8.7	13	6.5	1.37	0.43 – 4.1)	0.53	0.12 - 2.47

Table 6: Determinants of fatal outcome of cholera, Gadarif 2023: Results of the case control study.

Discussion

The results of this study showed that the overall CFR% during the cholera outbreak in Gadarif State was higher than the desirable WHO target of 1.0%. The CFR% was relatively higher among old patients but there was no statistical difference in the CFR% between males and females across all age groups. Similar findings have been reported from Kenya and Nigeria [10,11]. In 2016-17, the cumulative caseload of cholera reached 36,460 with 818 deaths from all over Sudan 18 states with a CFR of 2.2% [12]. The high CFR in West Gallabat of Gadarif State (16.7%) is probably due to the small number of cases (one out six patients died).

The study also found that out of all potential determinants of fatal outcomes of cholera, that patients from rural areas were more likely to die from Cholera than patients in urban settings. This finding pointed out the critical role of medical seeking behavior and accessibility to medical services. High CFRs in Kenya were related to disparities in access to health and healthcare facilities, including availability of rehydration supplies [13].

Almost half of the identified fatal cases died before reaching the CTC. Moreover, the number of patient dying from cholera might have been even bigger as there were no means for Gadarif disease surveillance to ascertain the actual number of cholera patients who died within the communities [14]. Exclusion of the 21 cholera cases who died before reaching the CTC, makes the CFR among patients who received medical care at the CTC drop to 1.5% (0.95% - 2.16%). The 95% CI for a CFR of 1.0% among the same number of cholera patients admitted to the CTC is (1.0%, 95 CI: 0.05% -1.6%); hence, the CFR among cases reaching the CTC of 1.5% is an acceptable CFR according to WHO standards.

Delayed reporting to health facilities has been reported as a risk factor for fatal outcome of cholera in Nigeria [15]. The death of the patients before reaching the CTC could be explained delay in seeking medical care or severity of the disease. About half of the fatal cases did not seek medical care. Thus the calculated mean duration between the onset of diarrhea and reaching the CTC is biased would, therefore, partially explain why there was no significant difference between the mean duration of fatal cases and survivors. It is conceivable that proximity of the affected areas to the CTC made seeking medical care faster and lifesaving. Other factors that could influence survival of cholera patients may include one or more other factors; e.g., the performance of services at medical facilities, affordability of patients to cover the transport and/or medical costs among others [16]. Active community-based case-finding during a civil unrest in Kenya showed that 200% more fatal cases were found more than reported, raising the estimated case-fatality rate from 5.5% to 11.4% [17]. In rural areas in Gadarif, many health facilities are staffed primarily with HCWs who had little or no formal education on case management of cholera cases. Attracting qualified and well-trained health professionals to work in these remote areas is challenging in Sudan, and would require improved living conditions and adequate compensation of such Healthcare Workers (HCWs). In resource-limited settings, many deaths may occur before patients can reach a health facility for treatment.

Timely accessibility to medical care should not be understood as the only factor determining the fatal outcome of cholera. The eruption of war in Khartoum, delayed endorsement of the newly revised and updated WHO guidelines for clinical management of cases of cholera. As a result, medical doctors used different regimens to manage cases of cholera, especially at the beginning of the outbreak. A high CFR% in Nigeria has been attributed to circulation of a highly virulent multidrug resistant atypical O1 El Tor biotype and non-O1/non-O139 *Vibrio cholerae* strains that were disseminated across the country by human travel [5] The high CFRs for cholera in Kenya and some other African countries high

CFRs were attributed to lack of adequate resources, health care infrastructures, healthcare access disparities, including availability of rehydration and supplies of treatment methods [18,19]. In other settings, slow rate of rehydration, inadequate use of oral rehydration therapy, use of inappropriate intravenous fluids, and inadequate experience of health workers in management of severe cholera were thought to be some of the factors associated with the failure to prevent so many deaths during the cholera outbreaks. Improvement of these factors could increase the odds of survival of cholera patients even in a disaster setting [20].

Suffering and dying from cholera is an indicator of inequity and inequality; cholera affects countries with increased vulnerability due to poverty, conflicts and limited availability of healthcare resources. Armed conflicts negatively affected public health infrastructure, and contributed to high CFRs mortality in some countries [21]. Three successive epidemic waves of cholera occurred in South Sudan during troubled times between 2014 and 2017, leading to tens of thousands of cases and hundreds of deaths, many among internally displaced individuals [22]. Oral Rehydration Salts (ORS) should be readily available in every single health post in rural areas together with clear guidelines that ensure use of clean water for its preparation. Ensuring availability of enough stockpiles of intravenous fluids and ORS at all times; especially Ringer's lactate is key for management of cholera cases.

The Global Task Force on Cholera Control (GTFCC) and partners roadmap to 2030' marks a new initiative for a unified approach to cholera prevention and control, targeting reducing cholera deaths by 90% and eliminating local cholera transmission in as many as to 20 countries by 2030 [6]. Although SMOH established two CTCs in Gadarif City to ensure timely and effective treatment for severe cholera patients with a low CFR, the differences in understanding the reasoning for establishing CTCs resulted in inadequate collaboration between the CTC and the main hospital in Gadarif City. The hospital refused to accept referrals of patients for other co-morbidities after treatment of cholera illness at the beginning of the outbreak. This led to congestion of critically ill patients in the CTCs. There is need to develop clear guidelines and SOPs that regulate discharge of cholera patients. The general hospitals should be prepared to receive cholera patients with other medical conditions; e.g., pregnancy, renal failure, orthopedic problems and the co-morbidities as soon as the CTC stabilizes them. There is need for developing Standard Operating Procedures (SOPs) for referral of patients between health facilities.

There is need to advocate about the importance of an effective implementation of a competent and functional surveillance of epidemic-prone diseases to improve their understanding of the decision-makers to achieve the desired objectives of goals of integrated disease surveillance; essentially, early detection and for making informed decisions and interventions to reduce morbidity and fatality from diseases such as cholera [23]. Timely detection, reporting, and response by the coordinated efforts of the EOC established that harmonized the outbreak response during a cholera outbreak has resulted in low CFR. As part of establishing CTCs, epidemiologist should prepare detailed data collection forms for reviewing deaths that occur at the CTC to identify determinants of the fatal outcome of cholera.

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Authorship

Dr El Bushra made the design of the study, analysis and interpretation of data, and drafting the article. All authors made substantial contributions to the conception and acquisition of data, revising it critically for important intellectual content. All authors approved the version to be submitted.

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