GLOBAL TASK FORCE ON
CHOLERA CONTROL

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RISK FACTORS OF CHOLERA MORTALITY

A SCOPING REVIEW

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Summary

To better adapt current case management practices and address excess mortality in otherwise treatable cases will require better knowledge of the demographic characteristics of the patients and comorbidities which can make severe dehydration harder to tolerate physiologically. With this in mind, a scoping review was undertaken, to explore the literature and summarise the existing evidence on cholera mortality and reported risk factors. Following the scoping review framework proposed by Arksey and O'Malley (2005), Pubmed, EMBASE, Web of Science, LILACS, Scielo, Cochrane and Open Grey and African Journals Online, were searched on 24 November 2021. After screening and assessing the retrieved records, 78 studies were included in the final review. Eleven studies reported the place of death for cholera cases with percentage of community deaths ranging from 23-96%. A thematic analysis of comments on mortality was performed and the potential reasons explaining the observed mortality were classified in the following categories and sub-categories: Patient (Biological, Health conditions); Clinical (Symptoms and presentation, Complications); Healthcare (Health seeking behaviour, Access to care, Case management, Facilities); Public Health (Surveillance and preparedness, Outbreak response); Social (Individual, Household, Behavioural, Political and cultural); and Environmental. When exploring the patients' characteristics, the available data suggested that case fatality rates were higher among males and older people especially those aged 50 or above. Studies that examine age and sex differences with regards to cholera mortality are required to understand the observed variations and plan better interventions. In addition, the review revealed that evidence on comorbidities and cholera deaths is scarce. Collecting, reporting and analysing baseline characteristics such as age, sex and predisposing conditions can improve our understanding of cholera mortality risk factors and can guide future case management recommendations.

Introduction

Deaths due to cholera can be almost entirely avoided by early detection of cases, rapid access to adequate treatment and by preventing cholera transmission in the first place. The Global Task Force on Cholera Control (GTFCC) End Cholera 2030 roadmap has as one of its two main objectives the reduction of cholera-attributed mortality by 90% globally by 2030[1]. While the availability of oral rehydration solution (ORS) and medical workers able to give intravenous (IV) fluid replacement has reduced cholera case fatality rate (CFR), the standard CFR of <1% is often unmet. Reported data from 13 African countries indicate that in 2020 the regional CFR was 1.6%, with eight countries exceeding 1%[2].

Early access to appropriate care is key for successful outcomes, nevertheless, in countries at high risk of cholera outbreaks this is often hindered. Lack of access to care, delay in seeking care and poor case management increase the risk of cholera mortality, in facilities or in the community. Cholera cases and deaths occurring at the community level are less likely to be reported to surveillance systems, resulting in an underestimation of the burden of cholera. Identifying cholera cases and cholera related deaths at community level is key to designing and improving cholera treatment strategies.

Among patients treated in health facilities, specific groups are known to be at higher risk of dying. In addition to more severe level of dehydration, these are children with severe acute malnutrition and pregnant women, with risk mostly related to foetal mortality. However, experience shows that there are further groups at risk of dying from cholera. These include older patients (>50-60 years old) or those with one or more comorbidities (hypertension, diabetes, kidney disease) in all ages.

Adequate case management, provided for a patient on presentation to a health facility or for a case within the community is a crucial intervention to reduce mortality. To better adapt current case management practices to address excess mortality in otherwise treatable cases will require better knowledge of the demographics and comorbidities which can make severe dehydration (and even its usual therapy) harder to tolerate physiologically. With both physiological and community aspects in mind, a scoping review was undertaken to explore the literature and summarise the existing evidence on cholera mortality and reported risk factors.

Methods

This scoping review was conducted following the framework proposed by Arksey and O'Malley (2005)[3]. A scoping review was preferred over other types of review as it focuses on the breadth of available information and it permits the identification of research gaps. The implementation of the five stages of the Arksey and O'Malley framework (Table 1) for the needs of this work is described below.

Table 1. Scoping review methodological framework proposed by Arksey and O'Malley (2005)

Stage	Task
Stage 1	Identify the research question
Stage 2	Identify relevant studies
Stage 3	Study selection
Stage 4	Chart the data
Stage 5	Collate, summarize and report the results
Stage 6	Consultation exercise (optional)

Stage 1. Research questions

Two research questions were formulated:

1. What has been described about cholera mortality, both in community and health facilities?
2. What are the reported risk factors for cholera mortality?

Stage 2. Identify relevant studies

An extensive search of the databases Pubmed, EMBASE, Web of Science, LILACS, Scielo, Cochrane and Open Grey and of the journal African Journals Online, was conducted on 24 November 2021, without restrictions. The key words and MeSH terms used were "cholera", "mortality", "death", "fatal outcome", "fatal" and "case fatality rate". The full search strategy is provided in the Supplementary material (Supplementary table).

Stage 3. Study selection

The retrieved records were uploaded on the application Rayyan QCRI for Systematic Reviews. The software identified duplicates, but de-duplication required manual confirmation. A three-step selection was then applied.

(i)Title and/or abstracts screening

Records were excluded if they studies described: (i) were non-human; (ii) infections with *Vibrio species* other than *Vibrio cholerae*; (iii) infections with non- O1/non- O139 *Vibrio cholerae*; (iv) reported zero deaths; and (v) referred to periods prior to 1900.

(ii)Full-text record assessment

At this stage any remaining reviews, commentaries, letters to editor and case reports were removed. Full-texts were considered eligible for the final review if they provided a description of decedents or case fatality rates, which was not limited to geographic or temporal characterisations.

(iii) References scanning

The reference lists of the included studies and of important reviews were checked manually to identify relevant studies that were missed during the database search.

Stage 4. Data charting

A data extraction form was prepared and translated into an Excel file that served as the database for this scoping study. The included records were reviewed to extract data describing the studies, participants, decedents, CFR and any key information relevant to the research questions (Supplementary box). In addition, we recorded findings or comments about the mortality and/or the CFR observed in the study, as explained by the authors in the discussion. For the latter, all records were considered, not only those which aimed to investigate mortality. Any comments or observations from graphical presentations about the temporal pattern of CFR/deaths were noted.

Stage 5. Collating, summarising and reporting the data

The database created in stage 4 was used to guide the analysis. The main characteristics of the included studies were summarised in tables (frequencies and percentages) and others were described in-text. The microbiological characteristics were also summarised; if there was no information about the laboratory investigation, then the features of the species related to the detected outbreak were reported instead.

The findings and comments about mortality and/or CFR and potential risk factors were collated. A thematic analysis was performed based on the detected factors.

The frequency of records that reported CFR per age group and per sex was calculated. If a study did not report CFR per age group or per sex, the charted data were used to compute these values; the number of

deaths in a specific category was divided by the total number of cases in the same category (if adequate information was provided). For the case-control studies, the percentage distribution of age groups and sex among decedents and survivors was used instead of the CFR. The purpose of this step was to identify the most affected age group and sex.

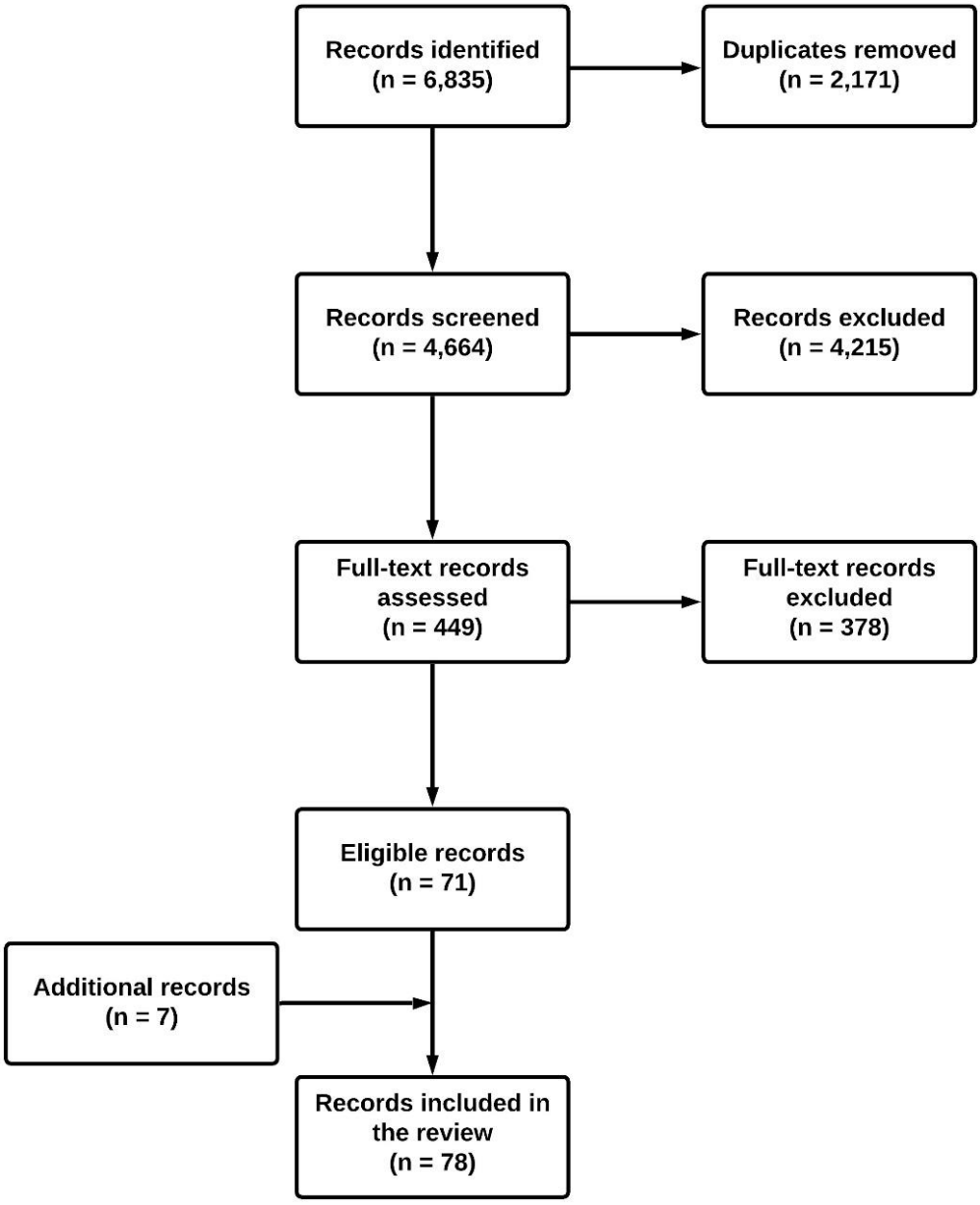
Finally, the analysis was narrowed down to the studies that assessed cholera mortality, examined characteristics of cholera-related deaths and investigated risk factors for this adverse outcome.

Results

Study identification and selection

The database search yielded 6,835 documents and the breakdown of the search hits is listed in the Supplementary material (Supplementary table). Of these, 71 records were eligible to be included in the review and another 7 were identified from reference scanning (Figure 1). Thus, the total number of articles described in this review summed up to 78 [4–81].

Figure 1. Flow diagram of the study selection process



Main characteristics of the included studies

The main characteristics of the included studies are presented in Table 2. The publication year ranged from 1958 [27] to 2021 [29]. There has been an increasing pattern in publications over the last 20 years (Figure 2) and almost half of the included studies (n=38, 48.7%) were published in the decade 2011-2020 (Table 2). All studies were in epidemic and/or endemic settings. Forty-nine (62.8%) studies referred to cholera cases and deaths in the African region (WHO region classification). There was an overlap in records reporting outbreaks in Ghana [30,54], Nigeria [32,33] and Zambia [53,68]. These studies focused on the same geographic area and period and for the case of Nigeria and Zambia the author group was similar. None of these studies was removed from the analysis, as the information presented was complimentary. For data that was duplicated in multiple studies, only one record was retained and included in the data descriptions. The number of cases varied from 50 in a small outbreak in Kaduna State, Nigeria[39] to 1,103,683 during a three-year period in Yemen[17]. Eleven studies reported less than 10 deaths[6,21,25,36,39,41,47,63,71,79,81], while the maximum number of deaths reported was 7,436 during the first two years of the Haiti 2010 epidemic[11].

Figure 2. Number of studies per publication period

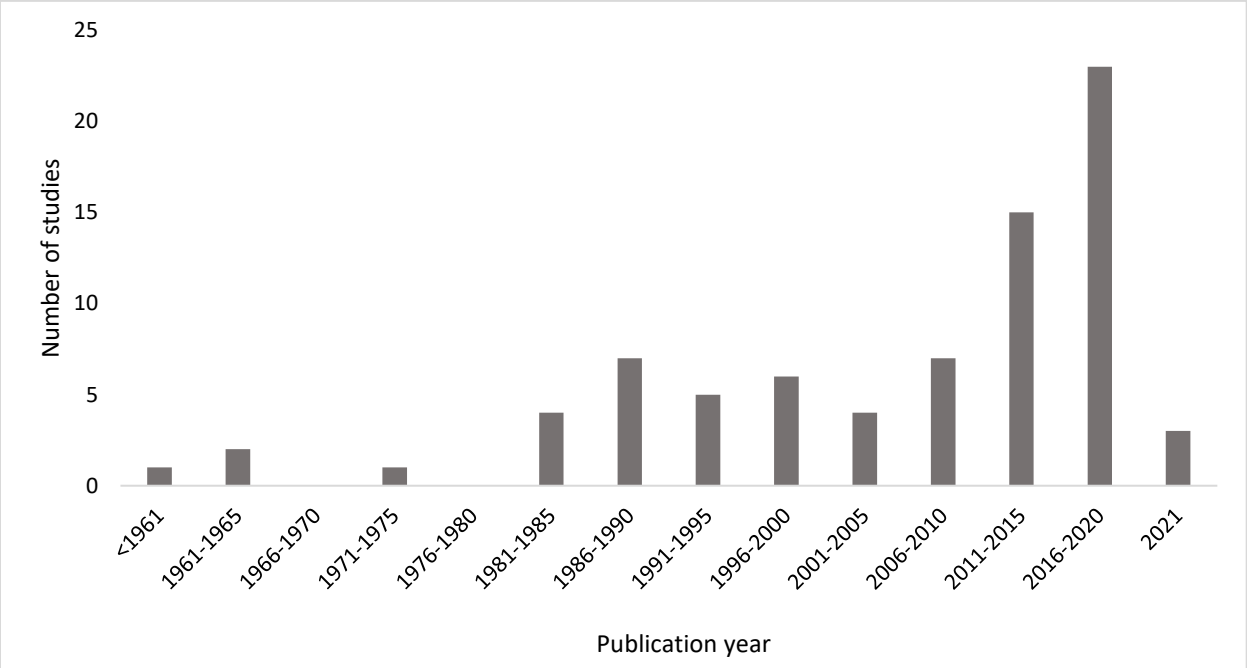


Table 2. Main characteristics of the included studies (n=78)

Characteristic	N	(%)
Type		
Conference abstract	2	(2.6)
Peer-reviewed paper	73	(93.5)
Report	2	(2.6)
Review	1	(1.3)
Date of publication		
≤ 1991	15	(19.2)
1991-2000	11	(14.1)
2001-2010	11	(14.1)
2011-2020	38	(48.7)
2021	3	(3.8)
WHO Region		
African (AFR)	49	(62.8)
Americas (AMR)	8	(10.3)
Eastern Mediterranean (EMR)	4	(5.1)
European (EUR)	1	(1.3)
South-East Asian (SEAR)	10	(12.8)
Western Pacific (WPR)	6	(7.7)
Context of transmission		
Epidemic	43	(55.1)
Endemic	4	(5.1)
Epidemic and endemic/ inter-epidemic periods	30	(38.4)
Unspecified	1	(1.3)
Setting		
Population-based	68	(87.2)
Facility-based	9	(11.5)
Unspecified	1	(1.3)
Study design		
Descriptive	40	(51.3)
Descriptive and analytical	38	(48.7)
Case fatality rate reported or calculated		
Yes	68	(87.2)
No	10	(12.8)
Mortality assessment or death investigation was one of the objectives of the study		
Yes	27	(34.6)
No	51	(65.4)
Regression analysis or significance tests were used for mortality		
Yes	27	(34.6)
No	51	(65.4)

Microbiological characteristics

Table 3 shows the main microbiological features of the studies included species. Three in four studies (n=59, 75.6%) mentioned culture techniques or the use of rapid diagnostic tests. Focusing on the studies that provided microbiological information, *Vibrio cholerae O1* was reported in all of them and *Vibrio cholerae O139* in three. El Tor (35.1%) and Ogawa (31.2%) were the most common biotypes and serotypes respectively.

Table 3. Microbiological characteristics of the included studies (n=78)

Characteristic	N	(%)
Culture or RDT		
Yes	59	(75.6)
No	5	(6.4)
Unspecified	14	(18.0)
Biotype		
El Tor	28	(35.9)
Unspecified	50	(64.1)
Serogroup		
O1	46	(58.9)
O1 and O139	2	(2.6)
O1 and non-O1	4	(5.1)
O1, O139 and non-O1	1	(1.3)
Unspecified	25	(32.1)
Serotype		
Ogawa	24	(30.8)
Inaba	9	(11.5)
Ogawa and Inaba	8	(10.2)
Ogawa, Inaba and Hikojima	1	(1.3)
Unspecified	36	(46.2)

Case fatality rate

Sixty-eight studies reported the overall CFR or provided total number of deaths and cases (Table 2). The CFR ranged from 0.09% during the first wave of the 2016-2017 cholera outbreak in Hodeidah City, Yemen[6] to 29% in a famine area in Mali during the 1984 epidemic[74]. The unweighted average of CFR was 4.8% (n=61, for the pairs of overlapping studies only one study was used). Thirty-eight studies (48.7%) used analytical methods, while 27 (34.6%) employed regression analysis or tests of significance specifically for mortality.

The occurrence of deaths or the changes in CFR in relation to the progression of the epidemic was reported in nine studies[15,19,33,37,47,56,74–76]. Indirectly, this information was obtained from tables and graphs from another 17 studies. We observed that in epidemics that lasted for more than 1 month, deaths occurred mostly in the early stages of the corresponding epidemics (12/26 studies) within the first week or first month [11,15,18,28,38,47,50,54,56,59,71,74]. In short outbreaks of less than a month, the CFR pattern was not very clear, as deaths occurred throughout the outbreak [39,44]. The findings from multi-wave studies were not conclusive; in two studies the CFR was highest during the first wave [17,72] while two other studies found highest CFR during the third and fourth waves [33,75].

Mortality risk factors

The characteristics of patients who died or hypotheses presented by authors explaining the mortality or CFR observed in the included studies are summarised in Table 4. Note that these factors were not restricted to quantitative information provided in the studies; many of them were extracted from comments and interpretations provided by the authors in the discussion. The thematic analysis resulted in creating six categories and sub-categories i.e. Patient (Biological, Health conditions), Clinical (Symptoms and presentation, Complications), Healthcare (Health seeking behaviour, Access to care, Case management, Facilities), Public Health (Surveillance and preparedness, Outbreak response), Social (Individual, Household, Behavioural, Political and cultural) and Environmental. These categories and sub-categories were not defined a priori but emerged after data collation.

Apart from age and sex which are described in more detail below, severe dehydration, not seeking care, delay in seeking care or late presentation, poor access to care (distance, remote areas) were a few of the most frequently reported factors.

Table 4. Thematic analysis of the comments and findings about cholera mortality

Patient	Risk Factor
Biological	Sex (male)
	Age (older)
Health conditions	Comorbidities
	Underlying infections (HIV, malaria) / pre-existing illness
	Chronic pulmonary heart
	Pregnancy hypertension
	Poor nutritional status (children <10)
	Drug addiction
Clinical	
Symptoms and presentation	Severe/ acute dehydration
	Severe diarrhoea
	Rice water stools
	Abdominal pain
	Leg cramps
	Vomiting
	Headache
	Uraemia
	Longer suppression (of urine)
	Longer duration of symptoms
	Poor health/ poor condition
	Intoxicated at illness onset
Complications and co-infections	Severe disease
	Acute heart failure
	Concomitant infection (pneumonia/ pneumonia and *j* spp. bacteraemia/ sepsis)
	Acidosis
	Febrile death associated with >24h in the IV tent
	Hypovolemic shock
Healthcare	
Health seeking behaviour	Did not seek care / treated at home
	Delay in seeking care / late presentation
	Went to temporary community treatment centre
	Visited unqualified village practitioners or quack doctors / used low-cost services
	Reluctance to visit government health facilities
	+ Vaccination
	+ Went to a cholera treatment centre
	+ Preference for health facilities instead of private or non-allopathic clinics
	+ Healthcare sought at secondary hospital or cholera treatment centre
	+ Received home-based rehydration prior to seeking care
	+ Sought care from physicians
Access to care	Limited access to proper care
	Areas only accessible by foot / hilly areas / long distance/ remote / inaccessible
	Neglect of affected elderly, as they rely on others for care
	+ Decentralization of cholera treatment unit
Case management	Low suspicion and late detection
	Delay in treatment at the facility
	Inadequate/poor management
	Inadequate initial hydration/ delay in hydration
	Did not receive hydration therapy or received IV alone
	Under-utilisation of ORS
	IV fluids not given to all patients
	Lack of monitoring fluid output
	Over-hydration
	Premature discharge from facilities
	Relatively long duration between admission and death/longer hospitalisation
	Did not receive antibiotics
	+ Immediate provision of ORS
	+ An additional night at the CTC
	+ Hospitalisation/ hospitalisation for at least 1 night
Facilities	Health care not available (early in the outbreak)
	Shortage of supplies
	Lack of emergency resuscitation facilities
	Lack of knowledge among health workers
	Lack of experience in establishing intravenous infusions

	Semi-trained community-based health workers
	Lack of supervision
	Health workers shortages / <0.5 nurses per treatment place / lack of skilled health workers
	Patient load / overcrowded governmental health facilities / long queue
	Poor coordination between primary and secondary care
Public Health	
Surveillance and preparedness	Heterogeneity in case definition
	Over-reporting of cases
	Non-reporting of mild illnesses
	Underestimation due to passive facility based surveillance
	Delays in identifying and reporting the outbreak
	+ Robust early warning system
	+ Alerting of health structures before the outbreak of the first cases in the province
Outbreak response	Lack of management at the beginning of the response
	Delays in implementing control measures
	Low number of professionals to initiate response
	Inadequate cholera or ORS messages to the public
	Community health workers probably lacked sufficient information, experience, and resources
	Inadequate availability of ORS
	+ Early establishment of CTCs
	+ Enhanced prevention and control activity
Social	
Individual	Education <primary
	Lack of transport or unaffordable transport
	Paddy field workers
	Lower socioeconomic status
	+ Married (for those that did not go to CTC)
Household	Thatched roof
	Positive chlorine residual in stored water
	Disruption of access to clean water
	Living in a peri-urban area (vs rural)
	Knowledge on home case management is lacking
	Caregivers lacked knowledge on ORS
	+ Living in a urban area (vs rural)
Behavioural	Did not consume ORS / inadequate dose
	Lack of knowledge on ORS
	Did not think ORS would help
	Home antibiotic treatment
Political and cultural	Conflict or war
	Movement restricted by insecurity
	Displacement
	Elections and post-election violence
	Religious festivals
Environmental	
	Rainy season
	Flooding
	Contamination of water
	Damaged footpaths due to heavy rain
	Month of onset of symptoms

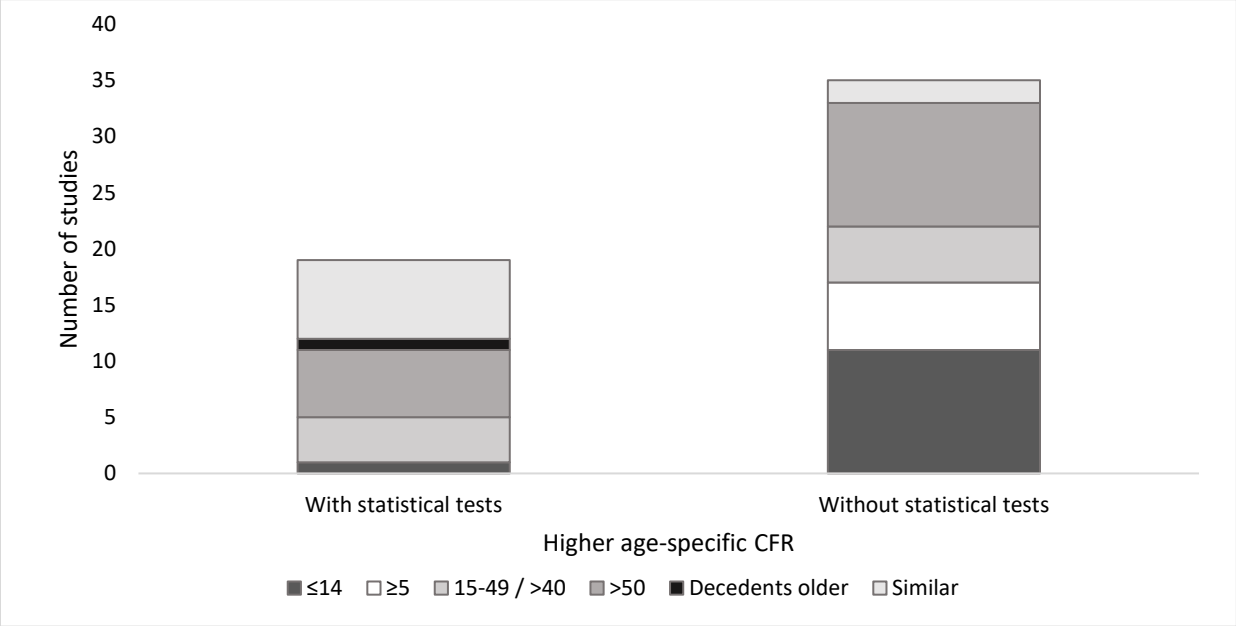
IV : intravenous, ORS : oral rehydration solution, + : protective factor

Age

The age-specific CFR (or the age distribution of decedents and survivors in case-control studies) was extracted from 54 studies. There was heterogeneity in the range of the age groups and a few studies presented the results in terms of continuous age. Collating and aggregating the findings was not straight-

forward and there was age overlap in the categories (Figure 2). Of the 54 studies, 12 found a statistical difference in CFR across the age groups including 4 studies that reported higher CFR in those aged above 40 (>40, ≥45) and six above 50 (>50, >55, >60, >65). Seven studies did not find significant differences. The other 35 studies provided CFR values or data to derive CFRs but did not compare the different age groups with tests of significance. Of the 35 studies, 11 observed higher CFR among those aged 50 or above (>50, ≥65) while 11 studies reported higher CFR among children less than 14 years (<1, <4, <5, <10, 5-14).

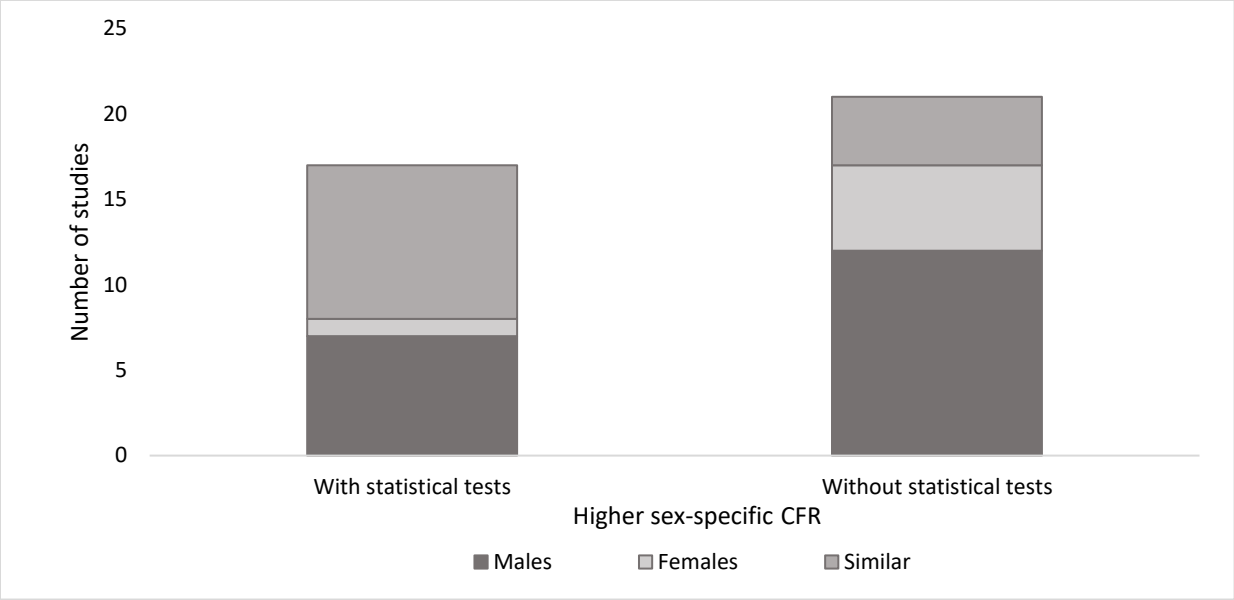
Figure 3. Age groups with highest case fatality rate (n=54)



Sex

Seventeen studies compared the sex-specific CFRs (or the distribution of sex among decedents and survivors in case-control studies) using statistical models or tests. Of these, nine found no statistical difference, seven reported a greater CFR in men and one reported more females in decedents compared to survivors. Another 21 studies provided sex-specific CFRs (or data to compute them) but they did not compare them with tests. In 12 studies, CFR was higher in males. Half of the included studies (39/78) did not report CFR for males and females.

Figure 4. Sex with highest case fatality rate (n=38)



Pregnancy

The study selection process identified five studies reporting cholera-related maternal deaths[9,18,82–84] of which three[9,82,83] have been previously included in a systematic review and meta-analysis on cholera and maternal mortality[85]. We could not retrieve one study[82] and the other two reported only one maternal death[83,84], thus only two studies were included in the final analysis of this scoping review.

One study specifically focused on females; female cholera patients of different ages who were initially treated in a comprehensive cholera unit were followed and comparisons were made between pregnant and non-pregnant women[9]. The study described an outbreak that occurred during 1979-1980 in Ile-Ife, Nigeria (long before the current case management protocols were in place). There were 46 fatal cases (CFR 19.4%), with the highest CFR observed among females ≤15 years (41.6%), followed by females aged 50 or above (25.0%). There were no decedents among women aged 15-29. Four deaths were observed among the pregnant women (n=4/61, CFR 6.6%) and 42 among the non-pregnant (n=42/176, CFR 23.6%). Of the four maternal deaths, three occurred in women aged 30-39 years. The author commented that the CFR pattern observed could be attributed to patients' better attitudes to health matters during the reproductive prime.

In a case-control study, the proportion of pregnant woman in decedents was higher than in survivors[18]. However, the reported OR was not significant.

Nutritional status

Three studies examined the association of the nutritional status of cholera patients and mortality. Two were conducted in a diarrhoeal disease hospital in Bangladesh[13,42] and one in Nigeria[14]. The earlier work of Islam and Shahid (1986)[42] found that the nutritional status of hospitalised children less than 10 years old was associated with increased mortality[42] and Ryan et al.[13] reported a significant association between the nutritional status of in-patients and cholera mortality at the univariate level. In the recently published study of Bragança and colleagues (2021)[14], the nutritional status in children aged 2-5 years in Nigeria was not associated with death from cholera but malnutrition was associated with a longer length of stay at the CTC.

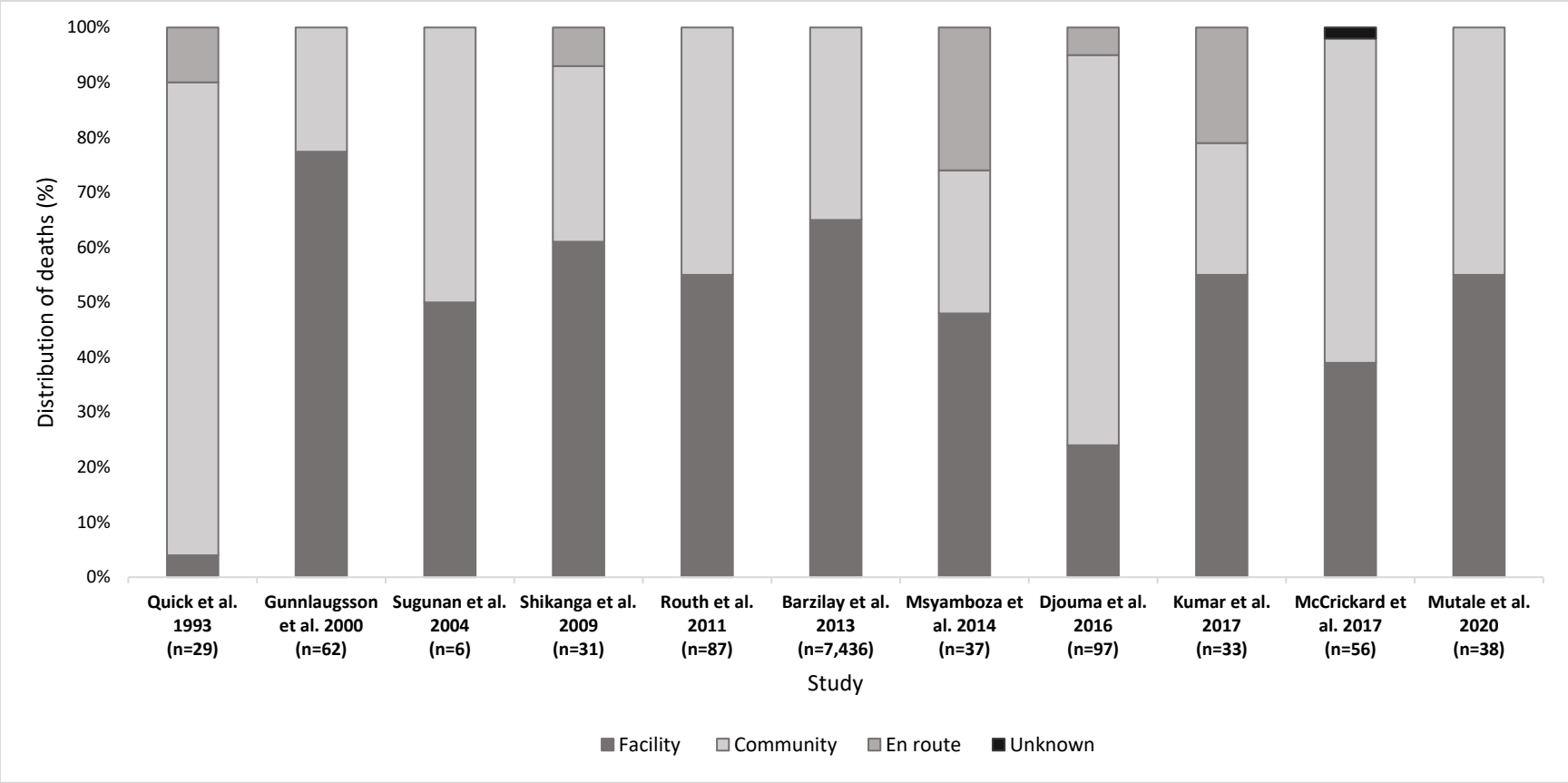
Comorbidities

References and analyses of comorbidities and cholera deaths were identified in five studies[18,22,52,56,64]. Lack of data and low power restricted the ability of the investigators to examine the association of cholera mortality with malaria and with chronic medical conditions such as cancer, tuberculosis or HIV[18,56,64].

Facility vs community deaths

The location of deaths was noted in eleven studies[8,11,37,50,52,53,56,59,60,62,63]. Deaths occurred in facilities (hospitals, cholera treatment centres) or in the community (at home, en route to the facility or soon after arriving at the facility, community temporary treatment centre). Figure 4 depicts the distribution of deaths; note that some studies specified the percentage of the en route deaths while others used only the community classification. There was variation in the distribution of deaths. The highest percentage of community deaths (96%) was observed in a study from Peru, during the 1991 epidemic[59]. In the remaining studies, the percentage of community deaths ranged from 23-76%. There was limited information about the characteristics of decedents stratified by place of death. Gunnlaugsson et al. (2000)[37] described only the decedents treated at a health centre and found that the risk of dying from cholera was higher in males and those aged 45 or above. Routh et al. (2011)[62] undertook a rapid mortality assessment during the Haiti 2010 epidemic and compared facility and community decedents. Their findings showed that more facility decedents had used ORS before seeking care (n=23/48, 48%) than community decedents (n=9/39, 23%). The median time from illness onset to death was longer for decedents in health facilities compared to community. Proxies of 81% (n=30/39) community decedents and 69% (n=33/48) health facility decedents reported receiving information about cholera after the outbreak started.

Figure 5. Location of death occurrence



n: number of deaths

Mortality assessment and studies that examined mortality risk factors

The final step of the analysis was the exploration of studies that specifically focused on cholera mortality. A third of the included studies (26/78) aimed to assess cholera mortality, identify reasons for lower or excess mortality or determine risk and protective factors.

Of the 26 studies, 21 were analytical and applied significance tests or regression analysis to determine factors associated with mortality. The main risk factors identified in these studies are presented in Table 5. Moreover, the tables lists other factors that were included in the analysis of each study but did not reach statistical significance. The number of the reported decedents or (decedents-cases for case-control studies) ranged from 7 to 817. There was diversity in the factors examined across the different studies and include the thematic categories of patient, clinical, healthcare, social and environmental. Furthermore, variables found to be determinants of cholera mortality in one study, were not significant for other studies.

Many of the studies, but not all, included age and sex in their analyses. An age greater than 40 years (>40, ≥45, >50, >55, >60) was a risk factor for cholera in eight studies[12,18,33,37,38,49,53,57], another reported that decedents were older[45] and one study found a greater risk among children younger than five years[8]. In two case-controls studies it was not possible to examine the effect of age, as the age group was the matching variable[51,56]. Being a male was associated with greater risk of cholera-related death in six studies[15,32,37,45,51,64] and only Siddique et al. (1998)[67] found a greater proportion of females among the decedents. The measures of association of cholera death with age and sex that were found to be significant when applying regression models are presented in Table 6.

Not seeking care or seeking care at village practitioners were found to be risk factors for cholera mortality while seeking care at a healthcare facility and receiving treatment including ORS, IV fluids and antibiotics were protective.

The other five studies[24,34,50,52,62] described decedents both in the community and/or in health facilities, without applying analytical methods (Table 7).

Table 5. Analytical studies that examined cholera mortality – main characteristics and findings (n=21)

Study	Country and period	Study design	Participants	Number of cholera cases	Number of fatal cases	Number of cases (deaths) vs controls (survivors)	Statistical methods	Risk factors	Factors found not to be significant
Islam et al. 1986[42]	Bangladesh 1980-1981	Secondary analysis	Patients admitted with diarrhoea	222	11	NA	Chi-square tests	Nutritional status in children < 10 years	Age
Siddique et al. 1988[67]	Bangladesh 1985	Outbreak investigation incl. case-control	Reported fatal cases and survivors affected by the disease	795	51	39 vs 31	Chi-square tests	Female Lower socioeconomic status Treated village practitioners (vs qualified doctors) Longer distance from health facility (among those of higher socioeconomic status)	Age
Quick et al. 1993[59]	Peru 1991	Case-control	Reported cholera-like fatal cases and survivors of episodes of diarrhoea	222	30	29 vs 61	Univariate regression	Treated only at home	Use of ORS Use of homemade sugar-salt solution
Jacoby et al. 1994[43]	Peru 1991	Case-control	Cholera fatal cases and survivors treated at the hospital	NA		42 vs 109	Univariate & multivariable regression	Severe dehydration Among those 65 or above, arriving after 8 hours of disease onset	Home use of ORS Age
Gunnlaugsson et al. 2000[37]	Guinea-Bissau 1994	Outbreak investigation incl. case-control	Persons who had a cholera-like illness (fatal cases and survivors)	1,169	62	16 vs 32	Univariate & multivariable regression	<u>Overall</u> Male Age ≥45 Catchment area + Age 2-14 <u>Case-control</u> In poor health/ intoxicated at illness onset	<u>Overall</u> Distance to health centre <u>Case-control</u> Not attending a health centre
Ryan et al. 2000[13]	Bangladesh 1996	Secondary analysis	Inpatients with microbiologically confirmed cholera	19,100 incl. 887 admissions	33	NA	Univariate & multivariable regression	Bacteraemia Radiographic evidence of pneumonia Acidosis	NA
Manga et al.2008[49]	Senegal 2004-2006	Secondary analysis	Reported cases and cases admitted to infectious diseases clinics	2,942	30	NA	NA	Delay in treatment Age >60 Severe dehydration at admission	NA

Shikanga et al. 2009[56]	Kenya 2008	Outbreak investigation incl. case-control	Reported cholera-like illness cases and cases from active case finding	396	45	31 vs 55	Univariate & multivariable regression	+ Home antibiotic treatment + Hospitalisation + Treatment in government operated health facilities + Receiving education about cholera by health workers	<u>Univariate</u> Sex, educational level, having other cholera cases in the home, household crowding, duration of transport, transport fare to the nearest admitting facility, socioeconomic status, clinical presentation. <u>Multivariable</u> Protected water source for drinking water, safe stool disposal, stored water in narrow-mouthed container, chlorine absent in home water, chronic medical condition (cancer, TB, HIV), not working at time of illness onset
Cartwright et al. 2013[18]	Cameroon 2009	Cross-sectional and case-control	Reported cases (fatal and survivors)	NA	NA	25 vs 72	Univariate regression	Age >50 Thatched roof Positive chlorine residual in stored water + Seek care outside home (any type of care, visited healthcare facility) + Received oral rehydration salts + Received intravenous fluids + Received antibiotics	Sex, religion, marital status, education, literacy, employment, household assets, water sources, water storage or water treatment practices, quantity of diarrhoea, symptoms, clinical comorbidities (pregnancy, alcohol use), treatments undertaken at home, transport time ≤20 min
Kolo et al. 2013[45]	Nigeria 2011	Secondary analysis	Admitted cholera cases	1,220	38	NA	T-tests and Chi-square tests	Age (decedents older) Longer duration of hospitalisation Longer duration of symptoms before hospitalisation Male	NA
Morof et al. 2013[51]	Zimbabwe 2008-2009	Descriptive & Case-control	Community cases (died outside institution and survivors)	NA	NA	55 vs 110	Univariate & multivariable regression	Male + Received home-based rehydration + Went to cholera treatment centre Among participants that did not go to CTC, married had lower odds of death (sensitivity analysis)	<u>Univariate</u> Married, religion, education, received information on cholera, access of ORS in village, could afford sugar <u>Multivariable</u> Average number of persons sleeping in the house at night, any income
Valcin et al. 2013[78]	Haiti 2010-2011	Secondary analysis	Patients admitted to CTC	4,070	15	NA	Univariate regression	Severe dehydration	NA
Page et al. 2015[57]	Haiti 2011	Cross-sectional	Rural communities	2,034	224	NA	Multivariable regression	Age ≥ 60 Greater severity of illness	District, sex

			(episodes of diarrheal illness and deaths)					Living in remote areas (mode of transport foot) Not seeking care	
Bekolo et al. 2016[12]	South Sudan 2014	Secondary analysis	Cholera cases seen at cholera treatment facilities	4,115	62	NA	Univariate & multivariable regression	Severe disease Age ≥ 50 + Hospitalisation	Vaccination (no power to detect any association)
Djouma et al. 2016[8]	Cameroon 2009-2011	Case-control	Community members who developed a cholera-like syndrome (active case finding)	NA	NA	97 vs 187	Univariate & multivariable regression	Age <5 (in univariate, data not shown for multivariable) Household case management Management in a community temporary cholera treatment centre ≥4 hours between onset of symptoms and the decision to seek care	<u>Univariate</u> Sex, year, taking medicine at home
Bwire et al. 2017[15]	Uganda 2011-2015	Secondary analysis and cross-sectional survey	Reported cases from outbreaks in fishing villages	1,827	43	NA	Univariate & multivariable regression	Male Month of onset (July or September)	NA
Semá Baltazar et al. 2017[64]	Mozambique 2011-2015	Secondary analysis	Reported suspected cases	1,863	23	NA	Multivariable regression	Male Rice water stools Abdominal pain Leg cramps + Duration of 1-4 days between onset and consultation	Age, hospitalization, attended a market in the last seven days, primary source of drinking water
Hemmer et al. 2019[38]	Cameroon 2004	Secondary analysis	Cholera cases in treatment centres	4,915	63	NA	Chi-square tests, univariate & multivariable regression	Age >40 0.5 (vs. <0.5) nurses per treatment place	Sex
Elimian et al. 2020[32]	Nigeria 2018	Secondary analysis	Reported cases	41,394	815	NA	Univariate & multivariable regression	Age 41-59, ≥60 Male Peri-urban setting Rainy season Flooding in 2018 >2 days to seek health Did not seek care (home) + Urban vs rural + Sought care at secondary hospital + Sought care at cholera treatment centre + Hospitalisation	<u>Univariate</u> Sample collected for rapid diagnostic test Positive rapid test outcome <u>Multivariable</u> Area under armed conflict

Mutale et al. 2020[53]	Zambia 2018	Case-control	Reported cases: fatal (CTC or community) and patients admitted to CTC who were discharged alive	NA	NA	38 vs 76	Univariate regression	Age >55 Education <primary + Immediately receiving oral rehydration solution	Sex, employment, household size, household assets, primary water source, household member with cholera, household shares latrine, cholera vaccination Care at home (ORS, time from illness to initiation of ORS, received antibiotics) Clinical symptoms, clinical care (received IV fluids, antibiotics, time from illness to arrival, duration of stay in CTC. Knowledge and behaviours of cholera and drinking water treatment.
Bragança et al. 2021[14]	Nigeria 2018	Secondary analysis	Patients admitted to CTC	500 children	7	NA	Fisher's tests	NA	Nutritional status Treated for dehydration Treatments given

Table 6. Analytical studies that examined cholera mortality using regression models– significant measures of association for mortality with age and sex (n=9)

Study	Number of cholera cases	Number of fatal cases	Number of cases (deaths) vs controls (survivors)	Variable	Type of measure of association	Measure	95% CI
Gunnlaugsson et al. 2000[37]	1,169	43	NA	Age 2-14 (vs 15-44)	RR	0.1	0.02-0.33
				Age ≥45 (vs 15-44)	RR	4.1	2.5-7.1
Cartwright et al. 2013[18]	NA	NA	25 vs 72	Age >50 (vs ≤50)	aOR	3.8	1.3-11.1
Page et al. 2015[57]	2,034	34	NA	Age >60 (vs 5-59)	aRR	2.25	NA
Bekolo et al. 2016[12]	4,115	62	NA	Age ≥50 (vs 5-49)	aOR	3.42	1.65-7.08
Elimian et al. 2020[32]	41,394	815	NA	Age 41-59 (vs 2-5)	aOR	1.81	1.40-2.35
				Age ≥ 60 (vs 2-5)	aOR	2.96	2.31-3.79
Mutale et al. 2020[53]	NA	NA	38 vs 76	Age >55 (vs ≤55)	Matched OR	6.3	1.2-63.0
Gunnlaugsson et al. 2000[37]	1,169	43	NA	Male (vs female)	RR	1.9	1.1-3.4
Morof et al. 2013[51]	NA	NA	55 vs 110	Male (vs female)	OR	2.56	1.27-5.00
Bwire et al. 2017[15]	1,827	43	NA	Male (vs female)	aOR	2.6	1.2-5.6
Semá Baltazar et al. 2017[64]	1,863	23	NA	Male (vs female)	aOR	3.10	1.06-9.05
Elimian et al. 2020[32]	41,394	815	NA	Male (vs female)	aOR	1.30	1.12-1.50

RR: relative risk; OR: odds ratio; aOR: adjusted odds ratio.

Table 7. Descriptive studies that examined cholera mortality – main characteristics and findings (n=5)

Study	Country and period	Study design	Participants	Number of cases	Number of fatal cases	Description of decedents
Faruque et al. 1986[34]	Bangladesh 1983	Cross-sectional	Reported cases	NA	92	37% died within 12 hours and 30% within 13-24 hours 51% received care from village practitioner and 20% from qualified doctor 47% received IV therapy + ORS + antibiotics and 32% ORS alone
Routh et al. 2011[62]	Haiti 2010	Cross-sectional	Hospital and community fatal cases	NA	87	Facility vs community decedents: More used ORS before seeking care Longer median time from illness onset to death Fewer reported receiving information about cholera after the outbreak started
Msyamboza et al. 2014[52]	Malawi 1998-2012	Secondary analysis and cross-sectional	Reported fatal cases	1806	38	47.4% died because of poor case management 26.3% were community deaths –did not seek care
Davies-Teye et al. 2015[24]	Ghana 2014	Secondary analysis	CTC fatal cases	20,199	121	Mean age 41 65.7% males 90.9% no health insurance 51% severe dehydration
McCrickard et al. 2017[50]	Tanzania 2015-2016	Case-series	Suspected cholera fatal cases through active case finding	NA	101	Median age 23 (2–80) 57% male 59% community death 80% died within 24h of symptom onset 10% consumed ORS

IV: intravenous, ORS: oral rehydration solution, CTC : cholera treatment centre

Key recommendations

While undertaking the scoping review, we tried to identify gaps in research and public health practices. Based on the information provided in the published studies, the following key recommendations are proposed (Box).

Box. Recommendations for analyses of outbreaks and further research

Describing outbreaks (based on routinely-collected data):

- Analysis of the number of cases and deaths by age groups.
- Analysis of the number of cases and deaths by sex.
- Analysis of the number of deaths by location (facility vs community)

Research gaps:

- Age and/or sex have been identified as risk factors of cholera mortality in some settings but there are limited explanations or hypotheses to explain the results. Further research is needed to explore and understand the patterns observed.
- There are no comparisons in terms of the main characteristics of the patients per death location i.e. in facility and community. Such analysis is essential to explore who is not reaching care and why (access to care vs health-seeking behaviour etc.).
- There are only a few reports on comorbidities and cholera mortality and analyses are often underpowered (due to the number of cases and deaths). Even though collecting more information about cholera patients during large outbreaks will add to the workload of healthcare providers, it is important to understand which underlying conditions could increase the risk of cholera death.

Discussion

A comprehensive search of the literature was conducted to explore what has been written about cholera mortality and its risk factors. The information extracted from the 78 studies included in this review was analysed and the potential risk factors of cholera mortality were grouped into six themes and sub-themes: Patient (Biological, Health conditions); Clinical (Symptoms and presentation, Complications, Other); Healthcare (Health seeking behaviour, Access to care, Case management, Facilities); Public Health (Surveillance and preparedness, Outbreak response); Social (Individual, Household, Behavioural, Political and cultural); and Environmental. Often, there was not clear division of the suggested reasons for the mortality observed in studies as cholera mortality is a multi-dimensional problem and the reasons are interlinked. Despite this, the evidence on the potential determinants of cholera mortality summarised in this review can provide guidance for future actions to reduce cholera-related deaths.

The analysis suggested that the most frequently reported variables were age and sex, pertaining to the theme of Patient (Biological). However, not all the included studies considered these dimensions in their description or analysis. Not only this, but in many studies the CFR or the distribution of age and sex groups among deaths was not directly provided. Instead, the extracted data were used to compute these variables which highlights a reporting gap. Age and sex are key demographic factors and these data are routinely collected, both for outbreaks and surveillance purposes. Describing CFR per age group and sex can be informative for public health interventions, especially during outbreaks and has been recommended elsewhere [86].

Disentangling the effect of age and identifying the most vulnerable group was challenging, as there was a wide variety in the reporting form of age. Different studies used different age group categories or reported age in the form of median. Despite this issue, the reported data suggested that the CFR was higher among the elderly, especially those 50 years or above. Six studies that employed analytical methods, found significant measures of association between age and cholera death (Odds and Risk Ratios), with values well-above one. Dalhat et al. (2014)[22] suggested that the high CFR observed among those aged 65 or above could be associated with comorbidities in this age group. Kolo et al. (2013)[45] added that cardiovascular disease could impair their ability to adjust to fluid loss and hypotension[87]. In addition, older patients may not have adequate immune response towards the infectious agent and thus experience more severe disease[45]. Another explanation was that the elderly are often neglected as they rely on others for care[28,72].

Only 39 studies reported sex-specific CFR or used sex as a variable in their analysis. Among those, nine studies did not observe significant differences between men and women while seven studies identified being a male as a risk factor of cholera death. Regarding the studies that did not use statistical tests to compare the CFR, more than half (12/21) observed higher CFR in males. Yet, not many attempts have been made to explain this observation. If males were more exposed to *Vibrio cholerae* due to daily activities, this would have also been reflected in the distribution of cases, not only in decedents. Of the 20 studies that observed higher CFR in males (or higher proportion of males among the decedents), 12 had higher proportion of female cholera cases or similar distribution across the two groups. In most settings, females are the caregivers and provide care to cholera cases. Furthermore, females are frequently involved in water-fetching activities. These activities suggest that the females are potentially more exposed (context-specific). One possible explanation comes from Bwire et al. (2017) who observed a 2.5 fold higher CFR in males and suggested that this could be a result of poor access to care: men fell ill while on the lakes fishing and in places distant from treatment facilities[15]. Apart from limited access to care, lack of awareness of cholera in males[60], different health-seeking patterns in males (e.g. not seeking care, delay in seeking care) or not being vaccinated could explain this variation in CFR. Failure or delay to seek care may also be linked to socio-economic reasons in settings where the man is the head and the provider of the family[60]. To examine this hypothesis, we need to know the sex distribution and the location of deaths (facility, community, en route). In addition, more research is required to compare the health-seeking behaviour, knowledge and attitude about cholera and cholera mortality in females and males.

Other than age and sex, health conditions are the third component under the patient-related risk factors. One of the key findings of this review was that the evidence around comorbidities and cholera mortality was particularly scarce. It is suggested that in some settings, higher CFR could be attributed to HIV and malaria[52], nonetheless, the lack of data on underlying conditions does not permit testing of this hypothesis[64]. Only one of the included studies examined the association of chronic medical conditions (cancer, Tuberculosis and HIV) and cholera mortality: none of these conditions was found to be a predictor of cholera mortality and the analysis was underpowered[56]. Collecting information on predisposing conditions could be time and resource-consuming. Nevertheless, this information is crucial in understanding who is at higher risk of death, especially when underlying conditions (both infectious and non-infectious) are prevalent in the population. Therefore, we recommend the systematic collection of data on underlying diseases, to plan more targeted interventions and adjust prioritisation in case management.

Eleven studies reported the place of death for cholera cases, with the percentage of community deaths ranging from 23-96%. Limited or no access to care, delay in seeking care or failure to do so, may result in death in the community or en route to the facility. At the same time, patients who eventually make it to the facility often present severe and irreversible dehydration. Access to care is often impeded by remoteness of the affected population[8,35,57,63], insecurity in the area[12,32] or displacement as a result of flooding[22] or conflicts. Unfortunately, these barriers to care are difficult to overcome as they depend on environmental and socio-political factors. Notwithstanding, there are certain prevention measures that can be implemented to help reduce the risk of severe dehydration and subsequent death. In the included studies, there was evidence that the use of homemade sugar-salt solutions or ORS was limited[18,62], especially in the beginning of the outbreak[62], when the suspicion of cholera was low. The distribution of ORS was also limited and when ORS was used at home, the dosage was not as frequent as required[59]. Moreover, proxies of the decedents could not determine the correct recipe ratio of sugar to salt[18,59]. Ensuring a sustained provision of ORS sachets and educating communities about cholera and rehydration are fundamental in improving home case management. Messages should be clear, tailor-made for the specific community and emphasize the proper use of ORS as well as the preparation of homemade sugar-salt solutions. Averting severe dehydration can increase the odds of survival both in the community and at the facility. At the same time, raising awareness about the disease and its complications can ameliorate health-seeking behaviour and reduce delays in seeking care.

Poor case management of cholera patients at health facilities or temporary community treatment centres could increase the risk of death from cholera. Inadequate initial hydration, under-utilisation of ORS or IV fluids, overhydration and lack of monitoring fluid output were some of the key issues raised in the included studies. Community deaths were observed among patients that had been discharged from health facilities[50,62], hinting premature discharge or poor management. After reviewing case reports of cholera decedents, Msyamboza et al. (2014)[52] suggested that one of the risk factors for the high CFR (>1%) observed in Malawi (1998-2012) was the early discharge from treatment sites, leading to worsening of the disease at home. In addition, the study underlined the shortage of supplies, the lack of knowledge among healthcare workers or semi-trained community workers, as well as the lack of supervision provided by trained medical and nursing personnel. Improving cholera case management and ensuring that the health facilities have enough supplies and trained personnel can reduce cholera deaths.

This study is limited by the scoping review methodology design. A scoping review aims to examine the breadth of available information and not the depth, which is often the aim of a systematic review[3]. The

scoping review does not answer a specific question, but rather a broad question, summarizing the existing research without performing quality appraisal of the studies. Moreover, the analysis can have a narrative or thematic nature and a quantitative synthesis cannot be undertaken due to the heterogeneity of the studies. Despite these limitations, a scoping review permits a comprehensive exploration and presentation of existing evidence which is not restricted by the design of the included studies nor by publication bias. A scoping review was ideal for the purpose of this work as it also addresses gaps in research.

Conclusion

This scoping review was conducted to explore what has been written about cholera mortality and its risk factors. The identified factors contributing to cholera mortality were multi-dimensional and inter-dependent. Based on the thematic analysis these factors were classified into six main categories and sub-categories i.e. Patient (Biological, Health conditions), Clinical (Symptoms and presentation, Complications), Healthcare (Health seeking behaviour, Access to care, Case management, Facilities), Public Health (Surveillance and preparedness, Outbreak response), Social (Individual, Household, Behavioural, Political and cultural) and Environmental. The findings showed that case fatality rate was higher among males and older people especially those aged 50 or above, nonetheless not all the studies reported this information. Studies that examine age and sex differences in cholera mortality are required to understand the observed variations and plan better interventions. This scoping review highlighted the research gap in the association of comorbidities and cholera mortality. Collecting, reporting and analysing characteristics such as age, sex and underlying conditions can improve our understanding of cholera mortality risk factors and can guide future case management recommendations.

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Supplementary material

Supplementary table. Data sources and search outcomes (24/11/2021)

Databases	**Number of documents**
Pubmed (("cholera"[MeSH Terms] OR cholera[Text Word])) AND ("mortality"[MeSH Terms] OR mortality[Text Word] OR "death"[MeSH Terms] OR death[Text Word] OR "Fatal Outcome"[MeSH Terms] OR fatal[Text Word] OR "case fatality rate"[Text Word])	1,717
EMBASE (excluding MEDLINE) ('cholera'/exp OR 'cholera') AND ('mortality'/exp OR 'mortality' OR 'death'/exp OR 'death' OR 'fatality'/exp OR 'fatal' OR 'case fatality rate'/exp OR 'case fatality rate') AND ([embase]/lim OR [embase classic]/lim)	2,547
Web of Science (ALL=(cholera)) AND (ALL=(Mortality) OR ALL=(death) OR ALL=(fatal) OR ALL=(case fatality rate))	2,004
LILACS/VHL (excluding MEDLINE) (mh:("Cholera") OR cholera) AND ((mh:("Mortality")) OR mortality OR (mh:("Death")) OR death OR fatal OR "case fatality rate") AND (db:("LILACS" OR "WHOLIS" OR "PAHOIRIS" OR "PAHO" OR "IBECS" OR "BINACIS" OR "HISA" OR "LIPECS" OR "CUMED" OR "LIS" OR "MedCarib" OR "MULTIMEDIA" OR "DECS" OR "DESASTRES" OR "SMS-SP" OR "ARGMSAL" OR "BDENF" OR "INDEXPSI" OR "MINSAPERU"))	408
Scielo cholera AND (mortality OR death OR fatal OR "case fatality rate")	37
African Journals Online cholera AND (mortality OR death OR fatal OR "case fatality rate")	34
Cochrane  #28 MeSH descriptor: [Cholera] explode all trees — MeSH — 254 #29 cholera — Limits — 699 #30 MeSH descriptor: [Vibrio cholerae] explode all trees — MeSH — 114 #31 Vibrio cholerae — Limits — 281 #32 (#28 OR #29) AND (#30 OR #31) — Limits — 245 #33 MeSH descriptor: [Mortality] explode all trees — MeSH — 13735 #34 mortality — Limits — 103899 #35 MeSH descriptor: [Death] explode all trees — MeSH — 2280 #36 death — Limits — 72980 #37 fatal — Limits — 8398 #38 case fatality rate — Limits — 584 #39 #33 OR #34 OR #35 OR #36 OR #37 OR #38 — Limits — 154148 #40 #32 AND #39 — Limits — 24 #41 #28 OR #29 — Limits — 699 #42 #41 AND #39 — Limits — 89	35 reviews 2 protocols 45 trials 4 clinical answers
OpenGrey cholera AND (mortality OR death OR fatal OR "case fatality rate")	5

Supplementary box. List of variables included in the data extraction form

Authors, First author, Year of publication, Publication period, Document type, Study title, Study country, WHO Region, Study objective, Study objective includes mortality, Transmission, Study/outbreak period, Outbreak/study duration in months (if applicable), Approach, Study design, Study type, Matching variable (if case-control), Place, Person, Setting, Data sources, Study conducted only in a camp, Sample size, Sampling method, Culture, Rapid diagnostic test, Any test, Serogroup, Biotype, Serotype, Number of cases, Attack rate(per 10,000), Age groups, Age group % distribution of cases, Sex % distribution of cases, Number of deaths, Case fatality rate (%), Case fatality rate per age group, Case fatality rate per sex, Case fatality per site, Regression analysis, Significance tests, Regression or tests, Risk factor 1, Risk factor 2, Risk factor 3, Risk factor 4, Factors not significant, Variability of CFR over time, Possible reasons explaining the CFR observed, Clinical characteristics of decedents, Limitations, Age group with highest CFR, Sex with highest CFR, Comments