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Effectiveness of Oral Cholera Vaccines in Controlling Outbreaks: A Matched Case-Control Study in Luapula Province, Zambia

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Research Article

Keywords: Oral Cholera Vaccine, Vaccine efficacy, Matched case-control study, Cholera outbreak, Zambia, Herd immunity

Posted Date: May 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9487809/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Oral cholera vaccines (OCVs) are widely recommended and utilized for the prevention and control of cholera in developing countries(1). In 2021, Zambia conducted a mass oral cholera vaccination campaign targeting the districts of Nchelenge, Chiengi, and Mwasabombwe in Luapula Province, a region recognized as cholera-endemic(2). However, less than two years following this intervention, these same districts experienced a significant cholera outbreak in 2023. This study, therefore, had two primary objectives: first, to assess the effectiveness of the OCVs administered during the 2021 campaign; and second, to investigate the factors contributing to the subsequent outbreak, particularly given that vaccination coverage levels remained below the established herd immunity threshold of 80% or higher required for population-level cholera prevention(3). Accordingly, this study aimed to evaluate OCV effectiveness and to elucidate why a cholera outbreak occurred despite a vaccination campaign that failed to achieve the herd immunity threshold of ≥ 80%.

Methods

A quantitative matched case-control study was utilized, involving 254 participants sampled randomly from the population. 127 participants were classified as having the disease (Cases). The study covered three Districts in Luapula province of Zambia, with a population of 482, 508 and six health facilities. Retrospective data from the health facilities' medical records were utilized(4). Leveraging this extensive data allowed for a detailed exploration of the effectiveness of the OCV in the prevention of cholera. The study analyzed participants' cholera incidence concerning their vaccination status, and the OCV doses they received (single or two-dose oral OCV). Then, we used the exposure odds ratio and odds ratio to assess the effectiveness and efficacy of OCV(5).

Results

The study comprised 254 participants, 127 were cases, and 127 controls, making a 1:1 ratio. The odds of being infected with cholera were 51.1 times more likely in those vaccinated with a single OCV dose compared to those who were not vaccinated with OCV, with Vaccine efficacy (VE) of 83.5% (EOR 51.1; 95% CI: 11.245, 304.49; VE = 83.5%; P value < 0.001). The odds of being unvaccinated against cholera were 5.0 times higher among cases than among controls (OR = 5.0; 95% CI: 1.07–46.93; p = 0.18). The corresponding vaccine effectiveness was 80.0% (VE = 1–1/OR = 0.80). Although this result did not reach statistical significance, the analysis showed a significant association between OCV vaccination and protection against cholera, with variations observed across districts.

Conclusion

OCV significantly protects against cholera. However, regional disparities and seasonal factors necessitate integrated interventions. This study provides crucial insights for enhancing cholera control strategies in Zambia.

BACKGROUND

Cholera is an acute watery diarrheal disease caused by toxigenic strains of the bacterium Vibrio cholerae serogroups O1 and O139(1). The disease is estimated to cause over 2.9 million cases and more than 95,000 deaths annually in cholera-endemic countries alone, with frequent epidemics occurring in other settings characterized by poor water and sanitation infrastructure (1). Global annual estimates range from 1.4 to 4.8 million cases and 28,000 to 142,000 deaths (6). Cholera is characterized by the acute onset of watery diarrhea, leading to rapid dehydration and death if not promptly treated with fluid replacement and, for severe cases, antibiotics(7).

Cholera is transmitted through the fecal-oral route most frequently by way of contaminated water and food, hence primarily occurs in settings of poor water and sanitation infrastructure in sub-Saharan Africa, Asia, and, more recently, in Haiti(8). Additional complex humanitarian emergencies in recent times, with resulting infrastructure disruptions and population displacements, have added a significant cholera burden globally(9).

The prevention and control of cholera epidemics are typically based on a multidisciplinary integrated approach that may include community sensitization, intensified epidemiological surveillance, improved access to clean water, hygiene, and sanitation, treatment of confirmed and suspected cases, and oral cholera vaccinations (OCV)(10). In 2020, the World Health Organization (WHO) recommended the consideration of OCV alongside other traditional control measures, including health promotion, provision of safe water, and improved sanitation for the prevention and control of cholera in endemic areas(6).

The use of vaccines in an outbreak is considered "preemptive", while vaccination after an outbreak begins is referred to as "reactive"(6). Due to the lack of herd immunity and recurrence of cholera outbreaks, questions have arisen regarding the effectiveness of the cholera vaccine and as to why people are still getting cholera despite being vaccinated(11). In controlled trial settings, OCVs have demonstrated efficacy of 85–90% over six months and 50–60% over two years(12, 13, 23). A population-level herd immunity threshold of 80% vaccination coverage has been proposed to substantially reduce cholera transmission(1). This study aimed to assess the effectiveness of cholera vaccines in Luapula Province, Zambia, using a retrospective matched case-control design(14).

METHODOLOGY

Study design and Approach

We conducted a retrospective analysis of programmatic data from medical records in 3 districts of Luapula Province of Zambia (2023–2024).

This study used an observational, quantitative research methodology using a retrospective matched case-control design(4). This design was selected to generate appropriate and relevant data efficiently, with reduced financial costs and within a relatively short time frame.

Retrospective data were extracted from medical records of randomly selected health facilities in both rural and urban areas across three randomly selected districts. Random selection of facilities was performed to ensure representative sampling, minimize selection bias, and enable valid statistical inference(15).

Data extracted from medical records included the following variables:

- Vaccine doses received (single-dose oral cholera vaccine or two-dose oral cholera vaccine)
- Vaccination status (vaccinated or unvaccinated), recorded for both cases and controls
- Cholera status, categorized as infected (cases) or not infected (controls)
- Sociodemographic characteristics of participants

The primary limitations of this study were the absence of essential source documents and incomplete data records in some source documents. Where possible, missing information was retrospectively reviewed and completed in the data collection questionnaire.

Study Setting

The study was conducted in Luapula Province, Zambia, targeting three randomly selected districts: Nchelenge, Mwasabombwe, and Chiengi. The target population included individuals aged one year and older residing in the catchment areas of both rural and urban health facilities within these districts(2).

Eligibility and Recruitment

A total of 254 files were eligible and analyzed. Participants were randomly selected from the catchment areas selected (rural and urban health facilities) across the three districts. Data were extracted from the medical records of patients seeking care at these facilities. The sample comprised two groups: cases (individuals diagnosed with cholera) and controls (individuals admitted for conditions other than cholera). Cases were matched one-to-one with controls from the same specific health facility catchment area(5). Furthermore, to evaluate oral cholera vaccine efficacy, controls were individually matched to cases by location of residence. Whenever possible, controls were selected from among patients admitted for non-cholera causes during the same study period as the corresponding case(16).

Study variables

The **dependent variable** was cholera infection status, dichotomized as case (laboratory-confirmed or clinically diagnosed cholera) or control (admitted for non-cholera conditions during the same period)(13).

The **independent variables** included oral cholera vaccine (OCV) vaccination status (vaccinated vs. unvaccinated); OCV dose regimen (single dose vs. two doses); source of drinking water (borehole, tap water, well, or lake water); and sociodemographic factors including age, sex, education level, and district of residence(1, 5)

Data Collection

A review of medical records was conducted from August 2024 to April 2025, with the aid of trained research assistants for data collection(4). The medical records were used to extract information on participants who attended the health facilities and were sampled from the health facility medical records from the two rural health facility catchment areas in two rural districts and the two urban health facility catchment areas in the urban district. Data from the cholera line list and cholera registers were collected, including the number of vaccine doses received for both cases and controls (whether a single-dose or two-dose vaccination was received), vaccination status (vaccinated or not), and sociodemographic profile factors, which were also captured from medical records. The participant's cholera status was also collected and categorized as either infected (cases) or not infected (controls)(7, 17).

Data Analysis

Data was analyzed using STATA 14, Data were exported from REDCap application to Microsoft Excel 2013 for cleaning and coding. Data analysis was performed using StatCrunch. We employed descriptive statistics to summarize categorical variables through frequencies and percentages, while continuous variables were summarized using the median and interquartile range. The Shapiro-Wilk test was utilised to establish data normality. The association between two categorical variables were assessed using the chi-square test, and differences between two medians were evaluated with the Wilcoxon rank-sum test. The identification of factors associated with neonatal GIT conditions was conducted via univariable and multivariable logistic regression analyses.

RESULTS

A response rate of 100 Percent resulted from those participants who had cholera (Cases) and those without cholera (controls) who were admitted at various health facilities during the cholera outbreak in 2023. Overall, those who were admitted to various health facilities in the catchment areas represented a sample size of n = 254, with an overall population of N = 482,508, for the three districts. The study was conducted in six (6) health facilities, two health facilities from each district, the distribution of cases and controls sampled across these health facilities is presented in Table 1.

Table 1
Population distribution, Nchelenge, Mwansabombwe and Chiengi.

Districts	Health facility	Cases		Controls	
		Target	Sampled	Target	Sampled
Nchelenge	Kashikishi HAHC	38	38	38	38
	Nchelenge urban clinic	24	24	24	24
Mwasabombwe	Mukamba	5	24	5	24
	Mbereshi RHC	10	24	10	24
Chiengi	Kalambwe	18	18	18	18
	Puta RHC	32	32	32	32
	TOTAL	127	127	127	127

Characteristics of the study population

Table 2 shows the descriptive analysis of continuous variables, such as age, and categorical variables, such as sex. Descriptive statistics of categorical variables such as age, sex, and education provided insights into the variability and distribution of sex and education of participants in different districts. The percentage values for each region, along with their corresponding frequencies, indicated the average level of sex, education, and the degree of variability around these averages. Nchelenge district had 53 female samples representing 42.7% and males 71 representing 57.3% of the population, while Mwansabombwe had 28 females representing70% and 12 male representing30% of the total population. Nevertheless, Chiengi had 39 females representing 43% and 51 males representing 57% of the total population.

From the total, 121 respondents (47.6%) attended primary school education, 70 respondents (27.6%) had attended the secondary education level, and 24 respondents (9.4%) had attended their tertiary education; nevertheless, out of the total 254 respondents, 29 (15.4%) had neither attended the primary, secondary, nor tertiary education. (See Table 2).

With regards to age, Nchelenge district had a mean age of 26.5 and a standard deviation of 14.9, with a range of 3 to 65 years, indicating a relatively wide variability in the age of cases and controls. Mwasabombwe showed a higher mean age of 41.1 and a standard deviation of 18.7, with a range of 8 to 75 years. Chiengi showed a relatively lower age mean of 23.8 with a standard deviation of 18.7, and a range of 2 to 74 years. The mean age across all districts was reported as 27.6 with a standard deviation of 17.8, and the average age range of 2 to 75 years, indicating a significant variability in the combined dataset for the cases and controls.

Table 2
Descriptive statistics

District	Statistics	Age	Sex	Education			
Nchelenge			Female	Male	Primary	Secondary	Tertiary	None
	Frequency		53	74	51	38	14	21
	Percentage		42.7%	57.3%	41%	31%	11%	17%
	Mean	26.5						
	Std.	14.9						
	Minimum	3						
	Maximum	65						
Mwasabombwe	Frequency		28	12	18	6	4	12
	Percentage		70%	30%	45	15%	10%	30%
	Mean	41.4						
	Std.	18.7						
	Minimum	8						
	Maximum	75						
Chiengi	Frequency		39	51	40	24	6	20
	Percentage		43%	57%	44.4%)	27%	7%	22%
	Mean	23.8						
	Std.	18.7						
	Minimum	2						
	Maximum	74						

Combine water sources analysis among cases and controls.

The analysis showed that 140 respondents (55.2%) representing cases and controls use boreholes as a source of water for consumption. In comparison, 68 respondents (26.7) use tap water, and then 46 respondents (18.1%) use wells as a source of water for consumption (Table 3).

Table 3
Water source combined districts

Source of water (Combined Districts)	Types	Frequency	Percentage %
	Boreholes	140	55.2%
	Tap water	68	26.7%
	Wells	46	18.1%

Distribution of Oral Cholera Vaccine (OCV) Doses in three districts.

Table 4 showed the coverage of Oral Cholera Vaccine (OCV) among those sampled in Nchelenge, Mwasabombwe, and Chiengi districts. Nchelenge had OCV coverage of 12.9% cases vaccinated and 87.1% cases not vaccinated. For OCV dose coverage Nchelenge had 8 doses administered across, of which 87.1% were for dose one and 12.5% were for dose two. In comparison, Mwasabombwe district had an OCV coverage of 20% cases vaccinated and 80% cases not vaccinated. Concerning OCV dose coverage, the district had 4 doses administered, 75% for dose one and 13.3% dose two. Chiengi, on the other hand, had OCV coverage of 13.3% cases vaccinated and 86.7% cases not vaccinated. For the dose coverage, a total of 7 doses were administered 14.3% were for dose one and 85.7% for dose two. While for the controls, Nchelenge had OCV coverage of 95.2% controls vaccinated and 4.8% not vaccinated, 59 OCV doses were administered among controls in Nchelenge 6.78% were for dose one and 93.2% dose two. Mwasabombwe had 70% controls vaccinated and 30% controls not vaccinated, with regards to doses a total of 14 were administered, 14.3% for dose one, 85.7% for dose two. Nevertheless, Chiengi had 88.9% vaccinated and 11.1% not vaccinated, with OCV dose coverage of 40, representing a 10% for dose one, and 90% for dose two.

Table 4
Distribution of Oral Cholera Vaccine (OCV) Doses in three districts.

Districts	Status (Vaccination)	Cases		Controls	
		frequency	%	frequency	%
Nchelenge	Vaccinated	8	12.9%	59	95.2%
	Not vaccinated	54	87.1%	3	4.8%
	Dose 1	7	87.5%	4	6.78%
	Doe 2	1	12.5%	55	93.2%
Mwasabombwe	Vaccinated	4	20.0%	14	70.0%
	Not vaccinated	16	80.0%	6	30.0%
	Dose 1	3	75.0%	2	14.3%
	Dose 2	1	25.0%	12	85.7%
Chiengi	Vaccinated	6	13.3%	40	88.9%
	Not vaccinated	39	86.7%	5	11.1%
	Dose 1	6	85.7%	4	10%
	Dose 2	1	14.3%	36	90%

Combined analysis for the three districts on OCV coverage.

Table 5 shows the analysis of OCV coverage for the three districts. A total of 14.2% cases were vaccinated with OCV, and 85.2% were not vaccinated. With regards to the OCV doses, a total of 18 doses were administered to cases, 83.3% were for dose one (single dose), and 16.7% were for dose two (double dose). While for controls, 68.5% were vaccinated, indicating a high immunization coverage, and 31.5% were not vaccinated. A total of 113 OCV doses were administered, 8.85% dose one, and 91.2% were for dose two.

Table 5
Combined OCV distribution between cases and controls for Nchelenge, Mwasabombwe and Chiengi District in 2021.

Three districts (Cases) n = 127 (Controls) n = 127		Frequency	Percentage	Frequency	Percentage
	Vaccinated	18	14.2%	87	68.5%
	Not vaccinated	109	85.2%	40	31.5%
	Dose 1	15	83.3%	10	8.85%
	Dose 2	3	16.7%	103	91.2

Combined assessment of drinking water and the incidence of cholera

The data for the combined assessment of drinking water and incidence of cholera showed that 9.4% of cholera cases had a history of consuming water from boreholes, 70.1% of the cases had a history of lake water consumption, and 20.5% had consumed shallow well water. In comparison with the controls, 27.6% consumed shallow well water, while 72.4% had a history of borehole water consumption, and 0% had a history of lake water consumption (Fig. 1).

Oral cholera vaccination distribution for cases and controls.

The data showed that 54 participants out of 62 total cholera cases were not vaccinated, that's 90% cases sampled, while Mwansabombwe showed 16 out of 20 sampled cases not vaccinated, representing 88% unvaccinated rate among cases, Chiengi had a total of 39 cases out of a total 45 who were not vaccinated, representing 70% unvaccinated coverage among cases. In comparison with the controls, Nchelenge had 95% controls vaccinated and 5% unvaccinated, while Mwasabombwe had 70% controls vaccinated and 30% unvaccinated. Chiengi, on the other hand, had a total of 87% vaccinated and 13% unvaccinated. Evident from Fig. 2 that controls who were vaccinated far outnumber those who were not vaccinated. The opposite is true among cases; cases that were not vaccinated far outnumber those who were vaccinated. A suggestion, perhaps, that vaccination had some effect in controlling the epidemic of Cholera.

Sample distribution of oral cholera vaccination among cases and controls.

The dose vaccination analysis showed a total of 8 OCV doses were administered for Nchelenge, 87.5% dose one, and 12.5% dose two. While Mwansabombwe had 4 total doses administered, 75% dose one and 25% dose two. Chiengi had a total of 7 doses, 85.7% for dose one and 14.3% for dose two. In comparison to controls, Nchelenge had 59 doses administered, 93% received a two-dose OCV, while 7% received a single OCV dose. Mwansabombwe had a total of 14 control doses administered, 86% received a two-dose OCV, and 14% received a single OCV dose. Chiengi, on the other hard had 40 doses administered among controls, 90%. The summary provided in Fig. 3 is that among the controls, those who received dose two far outnumber those who received dose one. The opposite is the case with cases; there were fewer cases among those who received the second dose compared with those who received a single dose. Suggesting perhaps that a two-dose regimen was preferable to a single-dose regimen.

In Table 6, the cholera incidence among vaccinated and unvaccinated participants was compared using exposure odds ratio analysis across Nchelenge, Mwansabombwe, and Chiengi Districts of Luapula Province. In Nchelenge District, the odds of having cholera were 132.75 times higher among unvaccinated individuals compared to those who were vaccinated, with a 95% confidence interval ranging from 30.17 to 725.9, which does not include the null value of one, indicating statistical significance at a p-value of 0.0000 (OR 132.75; 95% CI 30.17, 725.9; P = 0.000). Similarly, in Mwansabombwe District, unvaccinated individuals were 21 times more likely to have cholera than their vaccinated counterparts, with a 95% confidence interval between 3.099 and 220.3, also excluding the null value and demonstrating statistical significance

with a p-value of 0.001 (OR 21; 95% CI 3.099, 220.3; P = 0.001). In Chiengi District, the odds of cholera were 52 times higher among unvaccinated individuals compared to those vaccinated, with a 95% confidence interval of 12.88 to 226.9, again excluding the null value and showing statistical significance at a p-value of 0.0000 (OR 52; 95% CI 12.88, 226.9; P = 0.000).

Table 6
EOR test of cholera incidence with regard to vaccination status

Exposure odds ratio Test						
District		**Cases**	**Controls**	**OR**	**p-value**	**95% Confidence interval**
Nchelenge	Unvaccinated	54	3			
n = 124	vaccinated	8	59			
				132.75	< 0.0001	(30.17, 725.9)
Mwansabombwe	Unvaccinated	14	6			
n = 40	vaccinated	4	14			
				21	0.0001	(3.099, 220.3)
Chiengi	Unvaccinated	39	5			
n = 90	Vaccinated	6	40			
				52	< 0.0001	(12.88, 226.9)
Note **Exposure odds ratio is significant at the < 0.05 level						

Combined odds ratio analysis on cholera incidence about vaccination status between cases and controls.

The analysis summarized in Table 7 revealed that unvaccinated individuals had 48.87 times higher odds of contracting cholera compared to their vaccinated counterparts (OR 48.87; 95% CI: 21.92, 111.1; p = < 0.0001). The 95% confidence interval did not include the null value of one, indicating statistical significance.

The calculated oral cholera vaccine efficacy was 83.5%. Consequently, the null hypothesis, which posited no significant difference in cholera incidence between vaccinated and unvaccinated individuals, was rejected at the 95% confidence level, as the p-value of 0.0000 was less than the 0.05 significance threshold. These findings demonstrate a statistically significant association between vaccination status and protection against cholera, confirming that vaccinated individuals were substantially less likely to develop the disease compared to those who remained unvaccinated.

Table 7
Combined exposure odds ratio for cholera incidence by vaccination status across three districts

Combined exposure odds ratio test							
Three District		**Cases**	**Controls**	**OR**	**VE**	**p-value**	**95% Confidence interval**
N = 254	Unvaccinated	109	14				
	Vaccinated	18	113				
				48.87	83.5	< 0.0001	(21.92, 111.1)

Table 7: Combined EOR of cholera incidence

Note **Exposure odds ratio is significant at the < 0.05 level;

Combined OCV Efficacy (VE) about vaccination status calculation.

$$Efficacy = \frac{Pr(Case/unvaccinated) - Pr(Case/Vaccinated)}{Pr(Case/unvaccinated)} = \frac{\frac{109}{127} - \frac{18}{127}}{\frac{109}{127}}$$

$\frac{91}{127}$ = $\frac{0.716535}{0.85827}$ = 083485966 x 100% = 83.485966

Therefore VE = 83.5%

The oral cholera vaccine effectiveness was found to be 83.5%, which indicated a strong vaccine protection against cholera episodes in Nchelenge, Mwasabombwe, and Chiengi.

Comparing the OCV dosage between cases and controls in Nchelenge, Mwasabombwe, and Chiengi in 2021.

The exposure odds ratio was computed to assess the effectiveness of a single-dose oral cholera vaccine compared to a two-dose oral cholera vaccine in the prevention of cholera.

Hypothesis

H $_0$: $EOR = 1$ versus **H$_1$**: $EOR > 1$

Where EOR = exposure odds ratio as defined below;

$$EOR = \frac{Pr\left(Dose\,1/Case\right)/Pr\left(Dose\,2/Case\right)}{Pr\left(Dose\,1\,/Control\right)/Pr\left(Dose\,2/Control\right)}$$

The analysis in Table 8 showed the effectiveness of a single dose compared to a two-dose oral cholera vaccine was conducted using the exposure odds ratio, where dose one was considered as unvaccinated

and dose two as vaccinated. The results for Nchelenge District showed an odds ratio of 96.25, indicating that the odds of developing cholera were 96.25 times higher among individuals who received a single dose compared to those who received two doses. However, the 95% confidence interval ranged from 0.3958 to 196.99, which includes the null value of one, and the p-value was 0.1797, indicating that the result was not statistically significant. Consequently, the null hypothesis was not rejected, leading to the conclusion that neither regime was superior in offering protection in Nchelenge District.

It was further noted that the validity of this finding may have been compromised by sparse data, as some cells contained counts of less than five. In Mwasabombwe District, the odds ratio was 45, suggesting that individuals receiving a single dose had 45 times higher odds of cholera compared to those receiving two doses. Nevertheless, the 95% confidence interval ranged from 0.1041 to 111.79, crossing the null value of one, and the p-value was 1.0000, indicating a lack of statistical significance. Again, the null hypothesis was not rejected, and no superior regimen was identified. Sparse data with cell counts below five were similarly observed, potentially affecting the validity of the test.

For Chiengi District, the odds ratio was 4, implying that those vaccinated with a single dose had four times higher odds of cholera than those vaccinated with two doses. The 95% confidence interval ranged from 0.3958 to 196.99, containing the null value of one, and the p-value was 0.1797, which was not statistically significant. The null hypothesis was therefore rejected in favor of concluding that neither regimen demonstrated superior protection. As with the other districts, sparse data with cell counts below five were present, which may have influenced the validity of the statistical test.

Table 8
Exposure odds ratio test of OCV doses effectiveness among cases and controls.

Odds ratio test of OCV doses						
District **N = 254**		**Cases**	**Controls**	**OR**	**p-value**	**95% Confidence interval**
Nchelenge	Dose 1	7	4			
n = 67	Dose 2	1	55			
				96.25	0.3750	(0.3958, 196.99)
Mwansabombwe	Dose 1	1	2			
n = 16	Dose 2	1	12			
				6	1.0000	(0.1041, 111.79)
Chiengi	Dose 1	5	4			
n = 128	Dose 2	1	36			
				45	0.3750	(0.3983, 196.99)

Table 8: EOR test of OCV doses effectiveness

Note **Odds ratio is significant at the < 0.05 level

Combined odds ratio test among cases and controls

The combined odds ratio analysis shown in Table 9 revealed a statistically significant association between the number of OCV doses received and the risk of cholera infection. At the 95% confidence interval ranging from 1.0655 to 46.930, the odds of developing cholera were 5 times higher among individuals who received a single dose of the oral cholera vaccine compared to those who received the full two-dose regimen (OR 5; 95% CI 1.0655, 46.930; P = 0.0386). This finding was statistically significant at the 0.05 level, leading to rejection of the null hypothesis in favor of the alternative hypothesis.

Consequently, the evidence demonstrates that the two-dose regimen offers superior protection against cholera compared to a single dose. It is noteworthy that while district-level analyses did not yield statistically significant results due to sparse data with small cell counts, the combined analysis with larger cell counts provided sufficient statistical power to detect the significant difference between the two dosing regimens. This underscores the importance of adequate sample sizes and cell counts for valid statistical inference in such analyses

Table 9
Combined OR test of the effectiveness of OCV doses

N = 254	**Combined odds ratio**							
	(Case n = 15) Controls (n = 113)							
	Cases	**%**	**Controls**	**%**	**OR**	**95% CI**	**VE**	**P value**
Dose 1	13	86.7%	10	8.8%				
Dose 2	3	13.3%	103	91.2%				
					5	(1.0655, 46.930)	97.2%	0.0386
Note **Odds radio is significant at the < 0.05 level; vaccine efficacy								

Combined vaccine Efficacy for OCV dosage among cases and controls calculation.

$$Efficacy = \frac{Pr(Case/unvaccinated) - Pr(Case/Vaccinated)}{Pr(Case/unvaccinated)} = \frac{\frac{13}{127} - \frac{3}{127}}{\frac{13}{127}}$$

$\frac{10}{127}$ = $\frac{0.78740}{0.81024}$ = 0.971810821x 100% = 97.1810821

Therefore VE = 97.2% (2dcp)

The oral cholera vaccine efficacy with regard to vaccine doses among cases and controls was found to be 97.2%, which indicated a strong vaccine protection against cholera episodes in Nchelenge, Mwansabombwe, and Chiengi.

DISCUSSION

This matched case-control study assessed the efficacy of the oral cholera vaccine (OCV) in three endemic districts of Luapula Province, Zambia, following a 2021 mass vaccination campaign and a subsequent outbreak in 2023(2, 4). The findings demonstrate that OCV provides significant protection against cholera, with an overall vaccine efficacy (VE) of 83.5% among vaccinated individuals compared to their unvaccinated counterparts. This aligns with the World Health Organization's position that OCVs are effective tools for cholera control(6). Notably, the study revealed a stark disparity in vaccination coverage between cases and controls; over 85% of cases were unvaccinated, whereas nearly 70% of controls had received the vaccine. This pattern strongly suggests that the vaccine conferred direct protection to recipients, and the outbreak likely occurred due to gaps in population immunity rather than vaccine failure(3).

A critical finding pertains to the comparison of single-dose versus two-dose regimens. While the single-dose regimen was associated with a statistically significant risk reduction, the two-dose regimen demonstrated superior efficacy. The combined analysis revealed that the odds of cholera infection were five times higher among individuals who received only one dose compared to those who completed the two-dose series, yielding a VE of 97.2% for the full regimen. This is consistent with global evidence indicating that while a single dose offers short-term protection, the two-dose schedule provides more durable and robust immunity(13, 18, 22). The World Health Organization's recent shift to a single-dose strategy due to global supply constraints may therefore have implications for long-term outbreak prevention in endemic settings(9).

Furthermore, the study identified significant environmental risk factors, notably the consumption of lake water among cases. Approximately 70% of cases reported to consuming lake water, compared with none among controls, highlighting that despite vaccination efforts, ongoing exposure to unsafe water sources perpetuates transmission. This underscores a key limitation of relying solely on vaccination; OCVs are a crucial complement to, but not a substitute for, basic water, sanitation, and hygiene (WASH) interventions(19). The persistence of cholera in the study districts, despite achieving herd immunity thresholds, can thus be attributed to the convergence of incomplete vaccination (single-dose coverage) and continued high-risk environmental exposures(20, 21).

Strengths and Limitations of the Study

- This study used a matched case-control design with a 1:1 ratio, providing a robust assessment of oral cholera vaccine effectiveness in a real-world outbreak setting.
- The study achieved a 100% response rate and included 254 participants from three districts and six health facilities, enhancing representativeness.
- Both single-dose and two-dose regimens were compared, contributing critical evidence for vaccination policy in resource-limited settings.
- Limitations included retrospective data collection with potential incomplete records, sparse data at the District level leading to wide confidence intervals, lack of laboratory confirmation for all cases, and

limited adjustment for confounding factors such as sanitation access and socioeconomic status.

- Findings may not be generalizable beyond the 2023 outbreak or to other provinces in Zambia.

CONCLUSION

The oral cholera vaccine remains highly efficacious in preventing cholera in Luapula Province. However, the sustained occurrence of outbreaks is likely driven by a combination of suboptimal two-dose coverage and persistent environmental contamination. To enhance cholera control, Zambia must prioritize the completion of the two-dose OCV schedule and strengthen integrated WASH interventions, particularly ensuring access to safe drinking water(21, 22). Future research should focus on long-term vaccine durability and strategies to improve vaccine uptake in hard-to-reach endemic communities.

Abbreviations

OCV	Oral Cholera Vaccine
CI	Confidence Interval
W.H.O	World Health Organization
P-value	Probability value
OR	Odds ratio
EOR	Exposure odds ratio
SEM	standard Error of the mean
PHO	Provincial Health Office
DHO	District Health Office
RR	Relative risk
WASH	Water Sanitation and Hygiene
SBC	Social Behavior Change
EHT	Environmental health technologist
PHS	Public Health Specialist
UNILUS	University of Lusaka
MOH	Ministry of Health
VBC	Vibrio Cholerae

Et al	and others
MAX	Maximum
MIN	Minimum
Dr.	Doctor
H/H	household
VIP	ventilated improved pitratrine
CLTS	Community Led Total Sanitation
IPC	Infection Prevention and Control
EPC	Epidemic Preparedness and Control
HIMS	Health information management system
UNILUS	University of Lusaka

Declarations

Competing interests

The authors declare that no competing interests exist.

Clinical trial number

Not applicable.

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki and followed applicable national guidelines for research involving human participants. Ethical approval was obtained from the University of Lusaka Research Ethics Committee (Reference No: IORG0092) and the National Health Research Authority (Reference No: NHRAR-R-3017/18/07/2025). Additional permissions were secured from the Luapula Province Provincial Health Office and the respective District Health Offices. As this was a retrospective review of routinely collected, de-identified medical records, a waiver of individual informed consent was granted by the reviewing ethics committees. All data were anonymized, and confidentiality was maintained by assigning unique study identifiers and storing personal identifying information separately from analytical datasets, accessible only to the research team.

Consent to Participate

This retrospective study analyzed de-identified data from routine medical records. No direct participant contact occurred. A waiver of individual informed consent was granted by the University of Lusaka Research Ethics Committee and the National Health Research Authority (Reference Nos: IORG0092 and NHRAR-R-3017/18/07/2025) due to the retrospective, anonymized nature of the data and the public health importance of the research during an outbreak setting.

Consent for publication

Not applicable

Funding

Declaration: No Funding

Author Contribution

CM and AB conceptualized the study. CM, HM, MC, CMy, and AK developed the methodology. CM, KB, CMu, and CS curated the data. CM, CMy, AB, and CS performed the formal analysis. CS, HM, and KB conducted the investigation. CM, AB, and CMy handled visualization. CM wrote the original draft. CM, AK, HM, MC, KB, AB, CMu, and CMy reviewed and edited the manuscript. AB, CMy, and AK supervised the study. All authors read and approved the final manuscript.

Acknowledgement

The authors acknowledge the Ministry of Health, Luapula Province Provincial Health Office, and the District Health Offices of Nchelenge, Mwansabombwe, and Chiengi for granting permission to conduct this study and access to routine health facility medical records. We are grateful to the management and staff of Kashikishi Hospital Affiliated Health Centre, Nchelenge Urban Clinic, Kalambwe Rural Health Centre, Puta Rural Health Centre, Mbereshi Rural Health Centre, and Mukamba Rural Health Centre for their support during data collection. Special thanks go to the Health Information Management System (HIMS) teams for their assistance with data management and reporting. We also extend our appreciation to the University of Lusaka Research Ethics Committee for reviewing and approving the study protocol, and to the National Health Research Training Institute (NHRTI) for their institutional support. Finally, we thank Ms Yilan Gao for the insights contributed and all study participants whose medical records contributed to this research.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available due to patient confidentiality and restrictions imposed by the Zambian Ministry of Health, but are available from the

corresponding author (Cephas Mulenga, mulengacephas896@gmail.com, National Health Research Training Institute) on reasonable request and with institutional permission.

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Figures

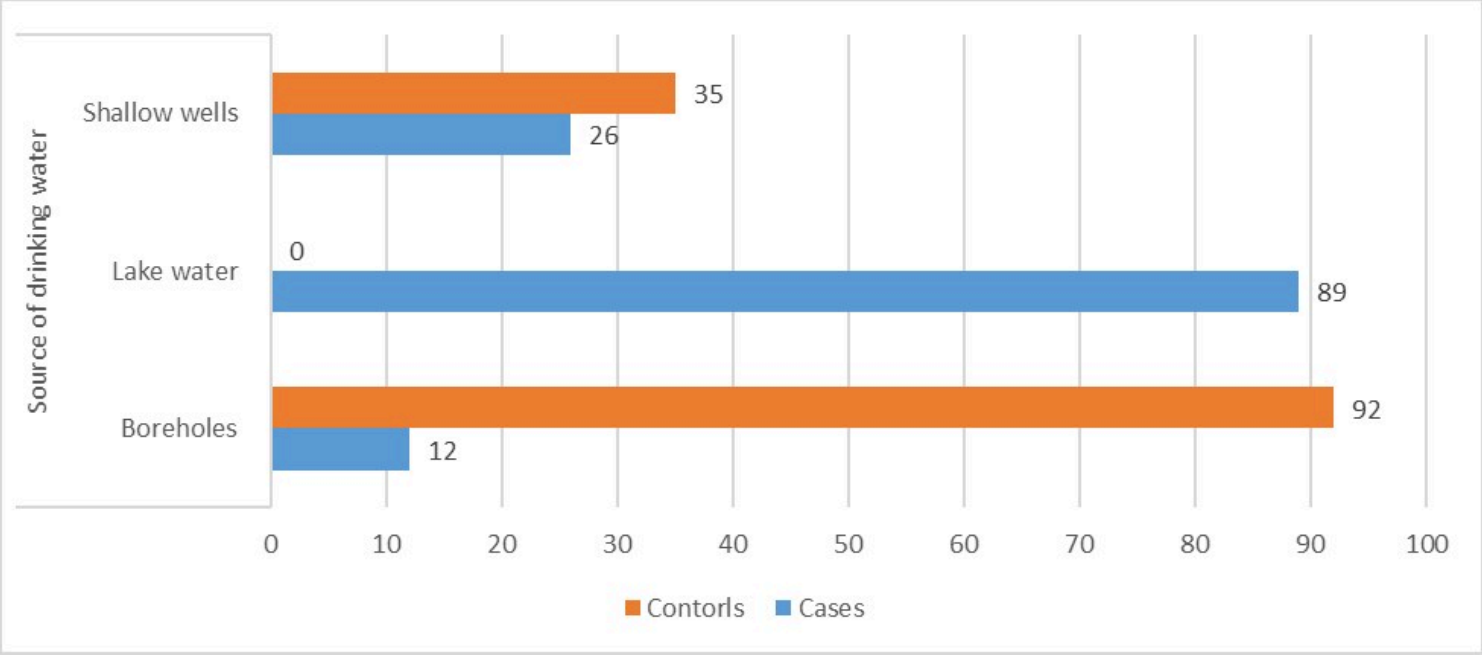


Figure 1

Source of drinking water among cases and controls

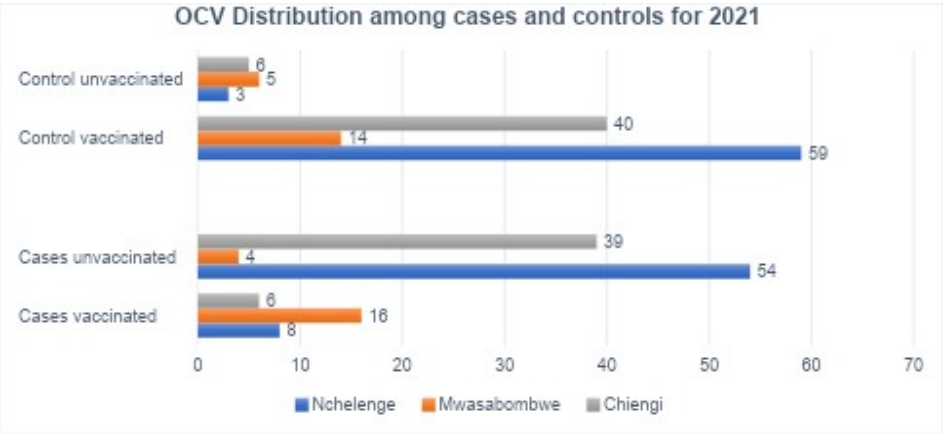


Figure 2

Sample distribution of oral cholera vaccine

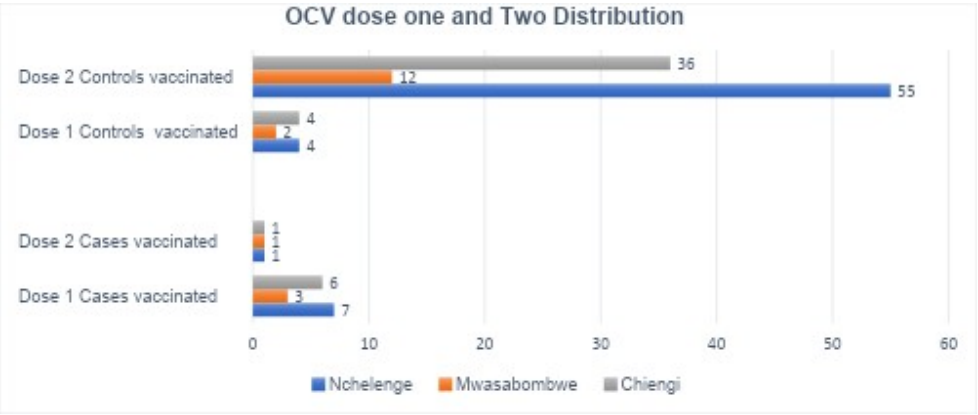


Figure 3

Oral cholera dose distribution