Effectiveness of reactive oral cholera vaccination in rural Haiti: a case-control study and bias-indicator analysis

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Summary

Background Between April and June, 2012, a reactive cholera vaccination campaign was done in Haiti with an oral inactivated bivalent whole-cell vaccine. We aimed to assess the effectiveness of the vaccine in a case-control study and to assess the likelihood of bias in that study in a bias-indicator study.

Methods Residents of Bocozel or Grand Saline who were eligible for the vaccination campaign (ie, age ≥12 months, not pregnant, and living in the region at the time of the vaccine campaign) were included. In the primary case-control study, cases had acute watery diarrhoea, sought treatment at one of three participating cholera treatment units, and had a stool sample positive for cholera by culture. For each case, four control individuals who did not seek treatment for acute watery diarrhoea were matched by location of residence, enrolment time (within 2 weeks of the case), and age (1–4 years, 5–15 years, and >15 years). Cases in the bias-indicator study were individuals with acute watery diarrhoea with a negative stool sample for cholera. Controls were selected in the same manner as in the primary case-control study. Trained staff used standard laboratory procedures to do rapid tests and stool cultures from study cases. Participants were interviewed to collect data on sociodemographic characteristics, risk factors for cholera, and self-reported vaccination. Data were analysed by conditional logistic regression, adjusting for matching factors.

Findings From Oct 24, 2012, to March 9, 2014, 114 eligible individuals presented with acute watery diarrhoea and were enrolled, 25 of whom were subsequently excluded. 47 participants were analysed as cases in the vaccine effectiveness case-control study and 42 as cases in the bias-indicator study. 33 (70%) of 47 cholera cases self-reported vaccination versus 167 (89%) of 188 controls (vaccine effectiveness 63%, 95% CI 8–85). 27 (57%) of 47 cases had certified vaccination versus 147 (78%) of 188 controls (vaccine effectiveness 58%, 13–80). Neither self-reported nor verified vaccination was significantly associated with non-cholera diarrhoea (vaccine effectiveness 18%, 95% CI –208 to 78 by self-report and –21%, –238 to 57 by verified vaccination).

Interpretation Bivalent whole-cell oral cholera vaccine effectively protected against cholera in Haiti from 4 months to 24 months after vaccination. Vaccination is an important component of efforts to control cholera epidemics.

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Introduction

Cholera epidemics continue to cause major morbidity and mortality globally, and recent large outbreaks in Haiti, Zimbabwe, and Sierra Leone[1–3] show the urgent need for improved control measures to save lives and reduce human suffering. Two oral cholera vaccines are pre-qualified for use by WHO: a bivalent inactivated vaccine containing killed whole cells of *Vibrio cholerae* O1 and *V cholerae* O139 (bivalent whole-cell vaccine), marketed as Shanchol (Shantha Biotechnics, Hyderabad, India), and an inactivated vaccine containing killed whole cells of *V cholerae* O1 with recombinant B subunit of cholera toxin, marketed as Dukoral (Crucell, Stockholm, Sweden). Although oral cholera vaccines were safe and effective in large trials,[4–7] and WHO has recommended consideration of their use in epidemics, they are not routinely used in cholera outbreaks.[8] This is a result of several factors,[9] not least of which is the scarcity of data on the effectiveness of the vaccines in real-life settings, especially during the complex situation of a cholera epidemic.[10] In Guinea and Haiti in 2012, large-scale reactive oral cholera vaccine campaigns with bivalent whole-cell vaccine contributed to increased understanding of the use of oral cholera vaccines in epidemic settings.[11,12]

10 months after an earthquake near the capital city of Port-au-Prince resulted in a massive humanitarian disaster,[13] a major cholera epidemic began in central Haiti in October, 2010, and rapidly spread throughout the country within 1 month.[3] The Haitian National Public Health Laboratory identified *V cholerae* serogroup O1 biotype El Tor as the cause of the epidemic by culture of stool specimen.[3] By December, 2014, 720 524 people in Haiti were reported to have had cholera, of whom 407 147 were admitted to hospital and 8774 died, with unmeasured social and financial costs.[14,15] Cholera had never been reported in Haiti before this outbreak.

In response to this cholera epidemic, from April to June, 2012, we undertook an oral cholera vaccination campaign with bivalent whole-cell vaccine, in partnership with the Haitian Ministry of Health. By the time the vaccination campaign began, the cholera epidemic had been ongoing for 17 months in Haiti, and reported weekly case incidence remained as high as 123·5 cases per 10 000 population in some regions of the country.[14] 45 417 people were vaccinated in the campaign, 91% of whom received both doses of the two-dose vaccination schedule.[12,16] We subsequently undertook a case-control study to assess the effectiveness of the vaccine and a bias-indicator study to assess the likelihood of bias in the effectiveness study.

Methods

Study design and participants

We undertook two matched case-control studies. In the primary study, we aimed to examine the effectiveness of oral cholera vaccination. The second case-control study was a bias-indicator study in which we assessed the likelihood of bias in the primary case-control study by examining the relation between vaccination and non-cholera diarrhoea.[17]

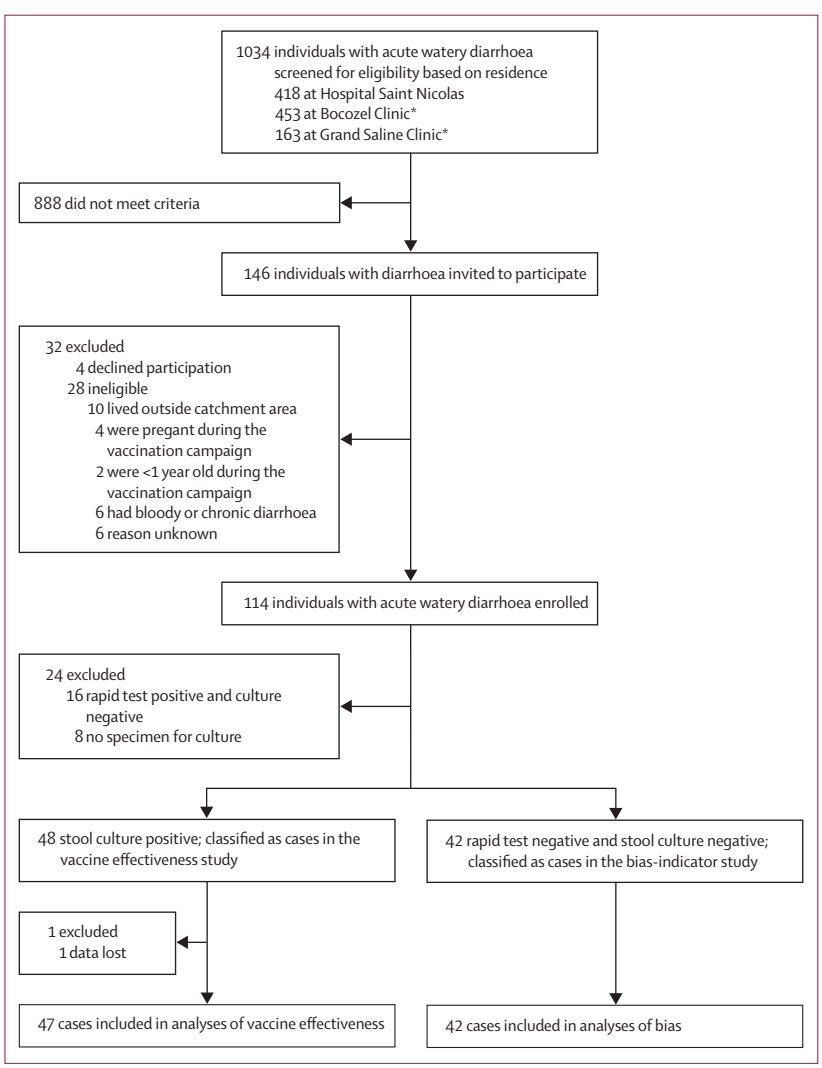

Figure 1: **Profile of study cases**
*Approximate, based on clinic reporting.

The studies were done in the Artibonite Department of Haiti, in three health centres that provide primary health services to the regions of Bocozel and Grand Saline. Bocozel and Grand Saline are rural, rice-growing regions of the country that are irrigated by branches of the Artibonite River, without which they are dry and desert like. Located about 120 km from Port-au-Prince, they have a combined population of about 55 000 people and were targeted by the oral cholera vaccine campaign between April and June, 2012. These regions are served by a 150-bed Ministry of Health hospital, L'Hôpital St Nicolas, which is supported by the non-governmental organisation Partners In Health and by two dispensaries, one in each of the isolated communities of Grand Saline and Bocozel. An estimated 77–93% of the Bocozel community and 63% of the Grand Saline community were vaccinated against cholera in the 2012 campaign.[12] The vaccination campaign is described in detail elsewhere.[12]

Enrolment into the studies began 4 months after the vaccination campaign ended. For both studies, eligible participants were residents of Bocozel or Grand Saline at the start of the studies who were eligible for the vaccination campaign (ie, age ≥12 months, not pregnant, and living in the region at the time of the vaccine campaign). Resident was defined as eating and sleeping in a household in the location over 50% of the time.

We recruited study participants at the three health centres, and we trained community health workers in the region to undertake surveillance and refer acute watery diarrhoea cases to the health centre, after initiating oral rehydration as appropriate. We enrolled individuals with acute watery diarrhoea—defined as three or more loose, non-bloody, liquid stools in a 24-h period with an onset of 3 days or fewer before presentation—who sought treatment at any of the three study sites and met all eligibility criteria. Participants were asked to provide a stool sample for testing by the Crystal VC rapid test (Span Diagnostics, Gujarat, India, hereafter referred to as the rapid test) and by culture. Cases were later classified as either cholera cases or non-cholera cases based on the results of the rapid test and culture.

Cases in the vaccine effectiveness study were individuals with a stool sample positive for *V cholerae* O1 by culture. Controls were individuals who did not seek treatment for diarrhoea between the first day of study enrolment and the date of onset of symptoms in their corresponding case. Four controls were matched to each case by location of residence, enrolment time (within 2 weeks of the case), and age (1–4 years, 5–15 years, and >15 years).[18] When more than one eligible control was available in a household, an individual of the same sex

was selected where possible. If more than one eligible control was available but they were both of different sex to the case, the one most closely matching the case in age was chosen. In rural Haiti, households are often grouped in a cluster of multigenerational families called "lakou".[19] In choosing controls, study workers approached the home nearest to the case's home, excluding homes within the same lakou because we anticipated that exposure to the cholera vaccine was likely to be highly correlated within the lakou. Study workers then approached the next closest residence and so on until four matched controls were enrolled.

Cases in the bias-indicator study were individuals with acute watery diarrhoea with a stool sample that tested negative for cholera by both the rapid test and culture. Controls were selected in the same manner as in the primary case-control study. Because the vaccine was not expected to provide protection against non-cholera diarrhoea, in the absence of bias we expected a null association between vaccination and non-cholera diarrhoea in the bias-indicator case-control study.[17,20,21]

Ethical approval for these studies was obtained from Partners Institutional Review Board (Boston, MA, USA) and the Haitian National Bioethics Committee (Port-au-Prince, Haiti). The vaccination campaign itself was a public health campaign directed by the Ministry of Health and Population of Haiti, implemented by Partners In Health and GHESKIO, and approved by the Haitian Bioethics Committee. Informed consent for vaccination was not required during the campaign, but all participants in the research studies signed informed consent before participation. For those participants who were unable to consent (eg, those who were too unwell), a health-care proxy was permitted to provide consent to participate. Consent from a parent or guardian was obtained for children under 18 years of age. Additionally, assent was sought from children aged 7–17 years.

Procedures

Trained staff used standard laboratory procedures to do rapid tests and stool cultures from study cases, and results were recorded in the study register. The stool samples were collected in sterile containers, and rapid tests were done immediately according to the manufacturer's protocol. An additional specimen was transported in Cary-Blair media to the Haitian National Public Health Laboratory in Port-au-Prince for subsequent culture on thiosulfate-citrate-bile salts-sucrose. Identification of *V cholerae* serogroup O1 at the serotype level was done using a standard slide agglutination method.[22]

To collect data on sociodemographic characteristics, risk factors for cholera, and self-reported vaccination, study workers interviewed participants at the cholera treatment unit at enrolment. For participants younger than 18 years and those who were unavailable for interview, guardians or a family member proxy responded to questions on behalf of the participant. Individuals who reported receipt of at least one dose of the vaccine were asked to produce their vaccine card as verification at a home visit within 2 weeks of enrolment. Vaccination registries were used to verify vaccination status for individuals who reported vaccination but could not produce a vaccine card or who reported no vaccination. A study worker reviewed the clinical charts of confirmed cholera cases.

	Cholera diarrhoea cases (n=48)	Non-cholera diarrhoea cases (n=41)*
Time from symptom onset to admission (days)	0 (0–1)	0 (0–1)
Serotype		
Ogawa	37 (77%)	NA
Inaba	11 (23%)	NA
Dehydration stage at presentation		
A (mild)	0 (0%)	10 (24%)
B (moderate)	22 (46%)	25 (61%)
C (severe)	26 (54%)	6 (15%)
Treatment received at clinic		
Oral rehydration solution	46 (96%)	39 (95%)
Intravenous fluids	46 (96%)	29 (71%)
Antibiotics	9 (19%)	2 (5%)
Volume of oral rehydration solution given in clinic (L)†	10 (6–14)	2 (2–5)
Volume of intravenous fluid given in clinic (L)‡	15 (9–20)	3 (2–6)
Admitted overnight to the cholera treatment unit	48 (100%)	29 (71%)
Duration of stay at cholera treatment unit (days)	3 (2–4)	1 (0–1)
Outcome		
Discharged	45 (94%)	38 (93%)
Transferred	1 (2%)	0 (0%)
Died	1 (2%)	0 (0%)
Left against medical advice	1 (2%)	3 (7%)

Data are median (IQR) or number (%). NA=not applicable. *Clinical data were missing for one of 42 non-cholera diarrhoea cases. †Among those given oral rehydration solution (46 cholera diarrhoea cases and 36 non-cholera diarrhoea cases). ‡Among those given intravenous fluids (46 cholera diarrhoea cases and 29 non-cholera diarrhoea cases).

Table 1: **Clinical presentation and treatment of cholera cases**

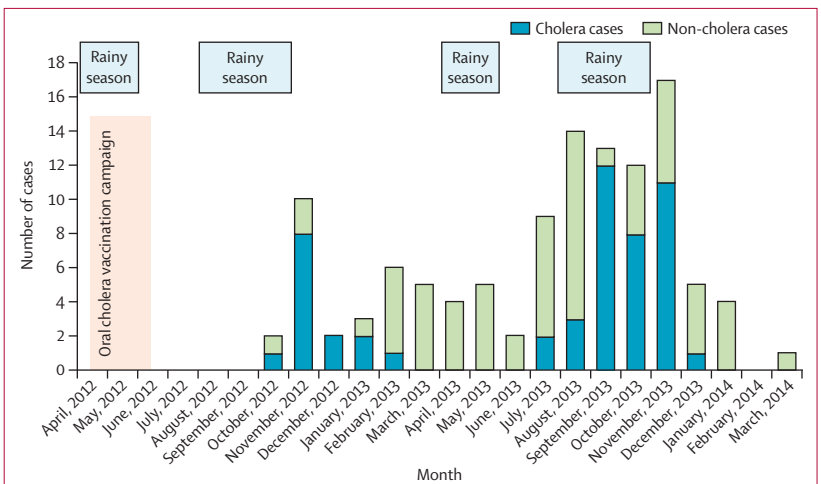

Figure 2: **Timeline of presentation of cases of cholera and non-cholera acute watery diarrhoea**
Cases were classified based on culture results; where culture results were not available (n=8), they were classified based on rapid test results. Depicted rainy seasons are based on historical mean rainfall, not actual rainfall.

	Cholera vaccine effectiveness case-control study			Bias-indicator case-control study		
	Cholera diarrhoea cases (n=47)	Controls (n=188)	p value*	Non-cholera diarrhoea cases (n=42)	Controls (n=168)	p value*
Age (years)	27 (13–43)	30·5 (9·5–44·5)	··†	31·5 (20–45)	34 (18·5–48)	··†
Sex						
Male	31 (66%)	91 (48%)	··	16 (38%)	66 (39%)	··
Female	16 (34%)	97 (52%)	0·010	26 (62%)	102 (61%)	0·82
Participant responded to interview (*vs* proxy)	30 (64%)	136 (72%)	0·012	35 (83%)	133 (79%)	0·26
Earthen floor in home (*vs* cement or wood)	36 (77%)	141 (75%)	0·77	35 (83%)	112 (67%)	0·021
Ever attended school	22 (47%)	112 (60%)	0·088	28 (67%)	110 (65%)	0·88
House has electricity	8 (17%)	19 (10%)	0·045	6 (14%)	23 (14%)	0·86
Number of people in household	5 (3–7)	5 (4–6)	0·42	5 (3–6)	5 (3–7)	0·88
Agriculture is the main income-generating activity	29 (62%)	109 (58%)	0·59	22 (52%)	100 (60%)	0·35
Main toilet is a latrine (*vs* unimproved or open defecation)	29 (62%)	90 (48%)	0·043	26 (62%)	95 (57%)	0·48
Ever admitted overnight to a cholera treatment unit‡	6 (17%)	20 (14%)	0·66	5 (13%)	19 (12%)	0·91
Household member with cholera in the past week	2 (4%)	3 (2%)	0·28	2 (5%)	2 (1%)	0·15
Household member ever spent a night in a cholera treatment unit	17 (36%)	50 (27%)	0·19	17 (40%)	57 (34%)	0·41
Household member with diarrhoea in the past week	8 (17%)§	18 (10%)	0·12	4 (10%)	11 (7%)	0·49

Data are median (IQR) or number (%). *Univariable conditional logistic regression adjusted for matching factors. †Cases and controls were matched by age; therefore, no p value is provided. ‡For the cholera case-control study, data were available for 35 cases and 140 controls. For the non-cholera diarrhoea case-control study, data were available for 39 cases and 160 controls. §Data were available for 46 cases.

Table 2: **Characteristics of cholera cases, non-cholera diarrhoea cases, and controls**

	Cases	Controls	Crude RR* (95% CI)	Adjusted RR (95% CI)	Vaccine effectiveness (95% CI)	p value
Cholera vaccine effectiveness case-control study						
Vaccinated, self-report	33/47 (70%)	167/188 (89%)	0·27 (0·12–0·61)	0·37 (0·15–0·92)†	63% (8 to 85)	0·031
Number of self-reported doses						
None	14/47 (30%)	21/188 (11%)	Reference	Reference	··	··
One	3/47 (6%)	19/188 (10%)	0·20 (0·05–0·87)	0·33 (0·07–1·62)†	67% (–62 to 93)	0·17
Two	30/47 (64%)	148/188 (79%)	0·28 (0·13–0·63)	0·38 (0·15–0·94)†	62% (6 to 85)	0·036
Proof of vaccination (card or registry record)	27/47 (57%)	147/188 (78%)	0·35 (0·17–0·72)	0·42 (0·20–0·87)‡	58% (13 to 80)	0·020
Bias-indicator case-control study						
Vaccinated, self-report	39/42 (93%)	158/168 (94%)	0·83 (0·22–3·09)	0·82 (0·22–3·08)‡	18% (–208 to 78)	0·77
Number of self-reported doses						
None	3/42 (7%)	10/168 (6%)	Reference	Reference		
One	7/42 (17%)	11/168 (7%)	2·50 (0·47–13·25)	2·53 (0·48–13·37)‡	–153% (–1237 to 52)	0·28
Two	32/42 (76%)	147/168 (88%)	0·73 (0·19–2·78)	0·72 (0·19–2·74)‡	28% (–174 to 81)	0·63
Proof of vaccination (card or registry record)	36/42 (86%)	137/168 (82%)	1·39 (0·52–3·70)	1·21 (0·43–3·38)§	–21% (–238 to 57)	0·72

Data are number (%), unless otherwise specified. Some percentages do not total 100 because of rounding. RR=relative risk. *Adjusted for matching factors. †Adjusted for matching factors, female sex, age (continuous), electricity in the home, main toilet type, and whether the participant completed the interview (*vs* a proxy). ‡Adjusted for matching factors, female sex, and age (continuous). §Adjusted for matching factors, female sex, age (continuous), and earthen floor in the household.

Table 3: **Effectiveness of the oral cholera vaccine in rural Haiti**

Statistical analysis

We analysed data by conditional logistic regression, adjusting for matching factors. Models included a measure of vaccination status: self-reported vaccination with at least one dose, number of self-reported doses, or documented vaccination with at least one dose per vaccine card or registry review. Multivariable models were adjusted for sex as a discrete variable and age as a continuous variable because we used broad age categories to match cases and controls according to age. We also adjusted for variables that were associated with both vaccination and cholera (or non-cholera diarrhoea in the bias-indicator study) at a p value of less than 0·20 (ie, potential confounders). Effectiveness of the vaccine was calculated using the vaccine

effectiveness formula: vaccine effectiveness=(1−relative risk).[23] We used a likelihood ratio test to examine whether there was a linear dose–response relation between the number of vaccine doses received and effectiveness. We examined whether cholera vaccine effectiveness varied by time since vaccination (before *vs* on or after July 1, 2013, about 1 year after the completion of the vaccination campaign), age group (<5 years *vs* ≥5 years), previous admission to a cholera treatment unit, and severity of dehydration. We included an interaction term between the potential modifier and any self-reported vaccination. Because of small sample sizes in subgroups, we reported ratios adjusted for matching factors only.

Role of the funding source

The funders of the studies had no role in study design, study execution, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the studies and had final responsibility for the decision to submit for publication.

	Cholera cases (n=47)	Controls (n=188)	Crude RR for self-reported vaccination* (95% CI)	Vaccine effectiveness (95% CI)	$p_{interaction}$
Age					
<5 years	9 (19%)	31 (16%)	0·50 (0·03 to 9·46)	50% (−850 to 97)	0·70
≥5 years	38 (81%)	157 (84%)	0·28 (0·12 to 0·64)	72% (36 to 88)	..
Dehydration stage at presentation					
B (moderate)	21 (45%)	NA	0·28 (0·08 to 0·97)	72% (3 to 92)	0·94
C (severe)	26 (55%)	NA	0·27 (0·09 to 0·77)	73% (23 to 91)	..
Time since vaccination					
<1 year	12 (26%)	49 (26%)	0·13 (0·02 to 0·68)	87% (32 to 98)	0·29
≥1 year	35 (74%)	139 (74%)	0·36 (0·14 to 0·90)	64% (10 to 86)	..
Previous admission to a cholera treatment unit†					
Yes	6 (17%)	20 (14%)	1·03 (0·08 to 12·61)	−3% (−1161 to 92)	0·35
No	29 (83%)	120 (86%)	0·29 (0·11 to 0·79)	71% (21 to 89)	..

Data are number (%), unless otherwise specified. NA=not applicable. RR=relative risk. *Adjusted for matching factors. †Data available for 35 cases and 140 controls.

Table 4: **Subgroup analyses of effectiveness of the oral cholera vaccine**

Results

From Oct 24, 2012, to March 9, 2014, 114 eligible individuals presented with acute watery diarrhoea and were enrolled (figure 1). Of these, 48 were confirmed to have cholera by culture and therefore were cases in the primary case-control study of cholera vaccine effectiveness. One participant with cholera was subsequently excluded from analysis of vaccine effectiveness when electronic interview data were lost because of a technology malfunction. 42 individuals were confirmed not to have cholera by a negative rapid test and culture and therefore were analysed as cases in the bias-indicator study. Participants with diarrhoea with and without cholera were geographically dispersed throughout the study area, with most recruited cases residing in Bocozel and southern Grand Saline.

Among the 48 participants with cholera, presentation to the clinic usually occurred within 1 day of symptom onset and more than half of cases had severe (grade C) dehydration (table 1). Median stay at the cholera treatment unit was 3 days (IQR 2–4). Figure 2 displays the timeline of presentation of cholera and non-cholera cases during the study period. Cholera cases seemed to be more frequent at times that corresponded to the rainy season.

Table 2 lists characteristics of cases and controls in both studies. In the primary case-control study, participants with cholera were less likely than controls to be female (p=0·010) and to have completed the interview themselves (p=0·012). Compared with controls, participants with cholera were more likely to have electricity in their home (p=0·045) and to have a latrine as their main toilet type (p=0·043).

70% of cholera cases and 89% of controls self-reported vaccination, and we verified vaccination in 57% of cholera cases and 78% of controls (table 3). Among those vaccinated, most received both vaccine doses (table 3). In univariate analyses adjusted for matching factors, both any self-reported vaccination (relative risk 0·27, 95% CI 0·12–0·61) and any vaccination verified through vaccine card or registry (0·35, 0·17–0·72) were associated with a significant reduction in the risk of cholera (table 3). In multivariable analyses, vaccine effectiveness was 63% (95% CI 8–85) by self-report and 58% (13–80) for vaccination verified through the card or registry. We examined whether protection increased with each dose of the vaccine. Although one dose of vaccine was not associated with a significantly lower rate of cholera than no vaccine, only a small number of individuals received a single dose and we could not rule out the possibility of a linear relation between the number of doses and effectiveness on the basis of the likelihood ratio test (likelihood ratio p value=0·67). We did not identify an interaction between the vaccine and age group ($p_{interaction}$=0·70), severity of dehydration ($p_{interaction}$=0·94), time since vaccination ($p_{interaction}$=0·29), or previous admission to a cholera treatment unit ($p_{interaction}$=0·35; table 4).

In the bias-indicator study, nearly all non-cholera diarrhoea cases (93%) and controls (94%) self-reported receipt of at least one dose of vaccine (table 3). Vaccination with at least one dose of vaccine was verified in 86% of cases and 82% of controls. Neither self-reported nor verified vaccination was significantly associated with non-cholera diarrhoea in univariate (relative risk 0·83, 95% CI 0·22–3·09 and 1·39, 0·52–3·70, respectively) or multivariable analyses (vaccine effectiveness 18%, 95% CI −208 to 78 and −21%, −238 to 57, respectively; table 3).

Discussion

The bivalent whole-cell vaccine was effective in reducing the rate of cholera among vaccine recipients in rural Haiti between 4 months and 24 months (ie, from April,

2012, to March, 2014) after vaccination began (panel). Vaccine effectiveness was similar to Sur and colleagues'[6] estimate of a 2-year effectiveness of the same vaccine of 67% in India, a historically cholera-endemic region. This similarity might be because the vaccine was administered in Haiti after many months of protracted transmission.

Our findings address the substantial knowledge gap surrounding the use of oral cholera vaccines in reactive vaccination in populations that have had limited endemic exposure to cholera.[8] Such populations are most at risk of explosive epidemics once cholera emerges. A study from the reactive oral cholera vaccination campaign in Guinea in 2012[11] showed that bivalent whole-cell vaccine offered significant early protection against cholera at 6 months (effectiveness 86·6%, 95% CI 56·7–95·7; p=0·001). The present findings suggest that reactive vaccination was effective in a population with no historical exposure or immunity to cholera and in the midst of the worst cholera epidemic of the past decade. Furthermore, our findings extend the findings of the Guinea study,[11] showing that the benefit of vaccination extends beyond 6 months to 2 years after vaccination. Our results are also consistent with our previous finding[29] that seroconversion rates among Haitian vaccine recipients were robust and comparable to those of Bangladeshis who had also received two doses of the vaccine.

Analysis of data from a placebo-controlled trial of recombinant cholera-toxin B subunit vaccine in Bangladesh[30] showed that vaccination provided significant herd protection to neighbouring non-vaccinated individuals. In our previous study,[12] community coverage in the region targeted by the vaccination campaign, which was also where the study sites were located, was between 62·5% and 92·7%. This coverage is more than is believed to be needed for significant herd immunity.[30] We also previously showed that the vaccination campaign in Haiti was associated with significant improvements in knowledge of cholera and practices related to waterborne disease,[31] suggesting additional indirect benefits associated with vaccination.

The present observational studies have some limitations. We assessed vaccine exposure through self-report, and we verified vaccination through documentation of the vaccine card or registration in the vaccine registry. Neither of these assessments is perfect: self-reported vaccination might be affected by a cholera episode and therefore might differ by case or control status, whereas lost vaccine cards and misspelled names might lead to underestimates of vaccination coverage. However, despite these limitations, we noted consistent, robust estimates of vaccine effectiveness in the order of 58–63% using two vaccination assessments with errors that are unlikely to be linked. The small number of cases in the vaccine effectiveness study limited the power for subgroup and dose–response analyses, which merit examination in larger studies. We assessed the likelihood of bias in the vaccine effectiveness case-control study and found no association between vaccination and non-cholera diarrhoea, which supports the validity of our findings.

Now in its fifth year, the cholera epidemic in Haiti has decelerated in terms of case incidence, but continues to cause substantial morbidity and mortality. More than 58 500 cases were registered in 2013 alone, and between Jan 8, 2014, and Dec 8, 2014, 22 668 cases and 240 deaths were reported.[14] The epidemic subsequently spread from Haiti to other countries in the region, including the Dominican Republic, Cuba, and Mexico.[32] The rapid evolution of this epidemic and its toll on human life and on the health system of Haiti have reinforced the need for improved methods for control of cholera in the country. Investment in water and sanitation infrastructure in Haiti will have a widespread effect on improving health and is the cornerstone of a binational plan to eliminate cholera from Hispaniola.[33] However, in

Panel: Research in context

Systematic review

Before planning the present studies, we searched PubMed on Dec 10, 2011, for articles with the search terms "oral cholera vaccine", "cholera", "vaccine effectiveness", "vaccine efficacy", and "case control". This search yielded 147 records, from which we identified 12 relevant studies, many of which were also included in a Cochrane review of oral cholera vaccine studies.[24] We also identified relevant articles and studies from agencies and resources such as WHO, the Haitian Ministry of Health website (articles in French), NIH RePORTER, and ClinicalTrials.gov. Three additional papers were published after our studies began.[4,10,11] Two case-control studies done in Mozambique[20] and Zanzibar[25] using a recombinant cholera-toxin B subunit vaccine showed 78% and 79% protection against cholera, respectively. In the Mozambique study,[20] vaccine effectiveness did not differ between those younger than 5 years or those aged 5 years or older.[20] In trials done in endemic settings, effectiveness of the same oral cholera bivalent whole-cell vaccine that we studied was 65% in India[5] and about 50% in Bangladesh[26] at 3 years of follow-up. In outbreak settings, a killed whole-cell vaccine produced in Vietnam (ORCvax) had 76% protection,[27] and a bivalent whole-cell vaccine had 86·6% protection at 6 months in Guinea.[11] In Peru, recombinant cholera-toxin B subunit oral cholera vaccine had 61–72% protective efficacy at 24-month follow-up, with better protection in those aged 15 years and older than in those younger than 15 years.[28] In a follow-up[4] of the Indian study,[5] the vaccine sustained a cumulative 65% protective efficacy at 5 years.

Interpretation

In our case-control studies of bivalent whole-cell oral cholera vaccine in a protracted epidemic in Haiti, vaccination was protective against cholera for up to 2 years of follow-up. Our studies show that oral cholera vaccine is effective in an epidemic setting; most previous evidence on oral cholera vaccine effectiveness has been collected in endemic settings such as India and Bangladesh. Our findings in the context of previously published work suggest that oral cholera vaccine can be used as an instrument to complement case finding, treatment, and clean water and hygeine initiatives in the response to cholera outbreaks and can reduce the burden of cholera in protracted epidemic settings. Continued follow-up should be done to ascertain longer-term vaccine effectiveness in epidemics, especially in populations, such as that in our studies, that do not have historic exposure to endemic cholera. Further research is also warranted to understand the effectiveness of one dose of vaccine, the safety and effectiveness of the vaccine in pregnancy, and the heat stability of the vaccine, all of which would improve the ease with which mass vaccination campaigns could be undertaken.

addition to intermediate-term and long-term water and sanitation interventions, new approaches to disease control are urgently needed. Our findings contribute to mounting evidence that oral cholera vaccines have an important part to play as a component of comprehensive, integrated cholera control efforts in Haiti.

Contributors

LCI conceived the studies, designed the protocol, contributed to analysis and interpretation of data, and drafted the first version of the manuscript. IJH collected data and contributed to data interpretation. JET contributed to the study design and data collection and interpretation. CPA, JGJ, RT, MBM, and JBH contributed to the study design and data interpretation. JBo and JBu contributed to the data analysis. MFF designed the protocol, analysed the data, contributed to data interpretation, and contributed to the writing of the first version of the manuscript. All authors contributed to manuscript revisions and approved the final version for publication.

Declaration of interests

We declare no competing interests.

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References

1 WHO. Outbreak news. Cholera, Sierra Leone. *Wkly Epidemiol Rec* 2012; **87:** 337–38.

2 WHO. Cholera outbreak, Zimbabwe. *Wkly Epidemiol Rec* 2009; **84:** 50–52.

3 Barzilay EJ, Schaad N, Magloire R, et al. Cholera surveillance during the Haiti epidemic—the first 2 years. *N Engl J Med* 2013; **368:** 599–609.

4 Bhattacharya SK, Sur D, Ali M, et al. 5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis* 2013; **13:** 1050–56.

5 Sur D, Kanungo S, Sah B, et al. Efficacy of a low-cost, inactivated whole-cell oral cholera vaccine: results from 3 years of follow-up of a randomized, controlled trial. *PLoS Negl Trop Dis* 2011; **5:** e1289.

6 Sur D, Lopez AL, Kanungo S, et al. Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2009; **374:** 1694–702.

7 van Loon FP, Clemens JD, Chakraborty J, et al. Field trial of inactivated oral cholera vaccines in Bangladesh: results from 5 years of follow-up. *Vaccine* 1996; **14:** 162–66.

8 WHO. Meeting of the Strategic Advisory Group of Experts on immunization, October 2009—conclusions and recommendations. *Wkly Epidemiol Rec* 2009; **84:** 517–31.

9 von Seidlein L, Jiddawi M, Grais RF, Luquero F, Lucas M, Deen J. The value of and challenges for cholera vaccines in Africa. *J Infect Dis* 2013; **208** (suppl 1)**:** S8–14.

10 Deen J, Ali M, Sack D. Methods to assess the impact of mass oral cholera vaccination campaigns under real field conditions. *PloS One* 2014; **9:** e88139.

11 Luquero FJ, Grout L, Ciglenecki I, et al. Use of *Vibrio cholerae* vaccine in an outbreak in Guinea. *N Engl J Med* 2014; **370:** 2111–20.

12 Ivers LC, Teng JE, Lascher J, et al. Use of oral cholera vaccine in Haiti: a rural demonstration project. *Am J Trop Med Hyg* 2013; **89:** 617–24.

13 Pape JW, Johnson WD Jr, Fitzgerald DW. The earthquake in Haiti—dispatch from Port-au-Prince. *N Engl J Med* 2010; **362:** 575–77.

14 Ministère de la Santé Publique et de la Population (MSPP). Rapport de cas, 8 decembre, 2014. http://mspp.gouv.ht/site/downloads/Rapport%20Web_08.12_Avec_Courbes_Departementales.pdf (accessed Jan 21, 2015).

15 Ministère de la Santé Publique et de la Population (MSPP). Rapport de cas, 1 janvier 2014. http://mspp.gouv.ht/site/downloads/Rapport%20Web_01.01_Avec_Courbes_Departementales.pdf (accessed Jan 21, 2015).

16 Ivers LC, Farmer PE, Pape WJ. Oral cholera vaccine and integrated cholera control in Haiti. *Lancet* 2012; **379:** 2026–28.

17 Shapiro ED. Case-control studies of the effectiveness of vaccines: validity and assessment of potential bias. *Pediatr Infect Dis J* 2004; **23:** 127–31.

18 Uyr H. Efficiency of case-control studies with multiple controls per case: continuous or dichotomous data. *Biometrics* 1975; **31:** 643–49.

19 Edmond Y, Randolph S, Richard G. The lakou system: a cultural, ecological analysis of mothering in rural Haiti. *JPAS* 2007; **2:** 19–32.

20 Lucas ME, Deen JL, von Seidlein L, et al. Effectiveness of mass oral cholera vaccination in Beira, Mozambique. *N Engl J Med* 2005; **352:** 757–67.

21 Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology* 2010; **21:** 383–88.

22 WHO. Manual for the laboratory identification and antimicrobial susceptibility testing of bacterial pathogens of public health importance in developing world. WHO/CDS/CSR/RMD/2003.6. Geneva: World Health Organization, 2003.

23 Halloran ME, Struchiner CJ, Longini IM Jr. Study designs for evaluating different efficacy and effectiveness aspects of vaccines. *Am J Epidemiol* 1997; **146:** 789–803.

24 Sinclair D, Abba K, Zaman K, Qadri F, Graves PM. Oral vaccines for preventing cholera. *Cochrane Database Syst Rev* 2011; **3:** CD008603.

25 Khatib AM, Ali M, von Seidlein L, et al. Effectiveness of an oral cholera vaccine in Zanzibar: findings from a mass vaccination campaign and observational cohort study. *Lancet Infect Dis* 2012; **12:** 837–44.

26 Clemens JD, Sack DA, Harris JR, et al. Field trial of oral cholera vaccines in Bangladesh: results from three-year follow-up. *Lancet* 1990; **335:** 270–73.

27 Anh DD, Lopez AL, Thiem VD, et al. Use of oral cholera vaccines in an outbreak in Vietnam: a case control study. *PLoS Negl Trop Dis* 2011; **5:** e1006.

28 Taylor DN, Cardenas V, Sanchez JL, et al. Two-year study of the protective efficacy of the oral whole cell plus recombinant B subunit cholera vaccine in Peru. *J Infect Dis* 2000; **181:** 1667–73.

29 Charles RC, Hilaire IJ, Mayo-Smith LM, et al. Immunogenicity of a killed bivalent (O1 and O139) whole cell oral cholera vaccine, Shanchol, in Haiti. *PLoS Negl Trop Dis* 2014; **8:** e2828.

30 Ali M, Emch M, von Seidlein L, et al. Herd immunity conferred by killed oral cholera vaccines in Bangladesh: a reanalysis. *Lancet* 2005; **366:** 44–49.

31 Aibana O, Franke MF, Teng JE, Hilaire J, Raymond M, Ivers LC. Cholera vaccination campaign contributes to improved knowledge regarding cholera and improved practice relevant to waterborne disease in rural Haiti. *PLoS Negl Trop Dis* 2013; **7:** e2576.

32 Pan American Health Organization. Epidemiologic update: Cholera, 27 June, 2014. Geneva: World Health Organization, 2014.

33 Ministère de la Santé Publique et de la Population. Direction Nationale de L'Eau Potable et de L'Assainissement. Plan d'elimination du cholera en Haiti 2013–2022, Port-au-Prince, Haiti, Novembre 2012. http://mspp.gouv.ht/site/downloads/Plan_elimination_du_cholera_2012_2022.pdf (accessed Jan 21, 2015).