

Generic protocol for vaccine effectiveness post implementation of a reactive mass vaccination campaign with oral cholera vaccine

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Table of Contents

- 1. Background..... 3
- 2. Rationale..... 3
- 3. Objectives..... 3
 - 3.1 Overall Objective 3
 - 3.2 Specific Objective 3
- 4. Methods 4
 - 4.1 Study Definitions 4
 - 4.2 Case control study of an indicator group 4
 - 4.3 Surveillance, detection, and interview of cases 5
 - 4.4 Laboratory procedures 6
 - 4.5 Identification and interview of controls 6
 - 4.6 Statistical considerations..... 6
 - 4.7 Ethical considerations 7
 - 4.8 Timeline 8
- 5. Annexes 9
 - Annex 1: INFORMED CONSENT FORM: 9
 - Annex 2: QUESTIONNAIRES FOR CHOLERA CASE-CONTROL STUDY 10

1. Background

Cholera is an infection of the intestines caused by the bacterium *vibrio cholerae*. The infection is usually transmitted by consumption of contaminated food or water. In many cases, it can lead to severe watery diarrhea, dehydration and in extreme cases, death. Two safe and effective oral vaccines are currently recommended by the World Health Organization to reduce the risk of outbreaks of the disease in vulnerable populations, or can also serve to limit the spread of an existing outbreak. Consequently, mass vaccination campaigns will likely be carried out in many places where cholera is a risk. Vaccination campaigns can take place to prevent or quickly stop large outbreaks. Additional background on cholera and vaccines can be found in the World Health Organization website.

Many factors influence the degree of protection offered by vaccines. Therefore, in addition to estimating the proportion of the population who were vaccinated (i.e. vaccination coverage), it is also important to determine how well protected they are. Biological tests can provide some of this information, but monitoring rates of infection in a vaccinated population provide a more complete picture. Understanding vaccine effectiveness helps to determine the actual risk cholera poses to a population at risk and helps health authorities better plan health activities.

2. Rationale

There is a need to identify effective strategies to prevent or quickly stop large cholera epidemics. The use of oral cholera vaccines in high-risk populations may offer one such solution. In combination with other studies, such as vaccine coverage, this protocol enables the assessment of whether the reactive cholera vaccine intervention in a selected, high-risk area is an effective strategy to reduce the consequences of cholera outbreaks.

3. Objectives

3.1 Overall Objective

- To evaluate the effectiveness of a mass vaccination campaign using oral cholera vaccine.

The overall objective will be accomplished through achieving the following specific objectives

3.2 Specific Objective

- Assess vaccine effectiveness through a case control study of cholera infection following a mass vaccination campaign
- Assess the presence of selection bias related with health seeking behavior through a case control study of an indicator group

4. Methods

4.1 Study Definitions

- *Date1* will be defined as the date at which the cholera mass vaccination campaign started for a defined catchment area.
- *Date2* will be defined as the last day of the mass vaccination campaign.
- *Date3* will be defined as the official end of the cholera season, as defined by the respective Ministry of Health, or in its absence, based on expert advice and epidemiological evidence.
- A *Cholera Treatment Center (CTC)* will be defined as a health center set up or otherwise adapted for treating cholera cases in a defined catchment area.
- A *Suspected Case* will be defined as an individual who present to the CTC for treatment of acute watery diarrhea
 - whose onset of diarrhea was any time from *date1* to the end of the cholera season
 - and
 - who present to the CTC for diarrhea for the first time since *date1*
 - and
 - who are residents of the target area of the vaccination campaign since *date1*
 - and
 - who were eligible for vaccination (i.e. not pregnant or under 2 years of age from *date1* to *date2*).
- A *Confirmed Case* will be defined as a probably case with stool culture results positive for *V. cholerae*.
- *Controls* will be defined as individuals
 - who did not present the CTC for treatment of diarrhea
 - and
 - who would have sought care at the CTC for treatment of severe diarrhea from *date1*
 - and
 - who were residents of the target vaccinated area since *date1*.
 - and
 - who were eligible for the vaccine (i.e. not pregnant or under 2 years of age from *date1* to *date2*).

4.2 Case control study of an indicator group

Additionally, an *indicator group* case-control study will be carried out to help rule out potential biases resulting from differential health seeking behavior between vaccinated and unvaccinated individuals. The assumption is that similar vaccination status among cases and controls would imply absence of significant health seeking behavior bias.

For the indicator case-control study, cases will be defined as individuals who present for treatment of acute watery diarrhea to the CTC but confirmed as not cholera diarrhea cases. Ideally, the indicator case control study should be started at least four months after vaccination (*date3*) if the rBS-WC vaccine is used considering the short-term protection offered by this vaccine against *Escherichia coli*.

- Cases will include only individuals:
 - whose onset of diarrhea was any time starting from *date3*
 - and
 - who present to the CTC for diarrhea for the first time since *date3*
 - and
 - who are residents of the target vaccinated area since *date1*
 - and
 - who were eligible for vaccination (i.e. not pregnant or under 2 years of age from *date1* to *date2*)
 - and
 - who are fecal sample negative for *V. cholerae*.

- Controls will consist of individuals:
 - who did not seek treatment for diarrhea at the CTC with symptoms starting from *date3* to the focal time for the matched case
 - and
 - who are residents of the target vaccinated area since *date1*
 - and
 - who were eligible for vaccination (i.e. not pregnant or under 2 years of age from *date1* to *date2*)
 - and
 - who would have sought treatment at the CTC if they had developed severe watery diarrhea.

4.3 Surveillance, detection, and interview of cases

For both the primary case-control study and indicator group case-control study, surveillance and detection of potential cases will be done at the CTC. Individuals coming from the target vaccinated area of the selected locale will be identified at the CTC triage area. A log book will be maintained to list cases. Once the initial assessment and rehydration is completed, each case will be requested to participate in the study. Informed consent will be obtained (see Annex 1). A stool sample will be collected for rapid testing from all individuals with diarrhea coming from the target vaccinated area of the defined locale. The eligibility criteria will be applied (i.e. check that the answer is “no” to all the screening questions in the questionnaire), then the questionnaire will be completed (see Annex 2). Information about

oral cholera vaccination and details from the vaccination card will be collected only at the end of the interview. Completed questionnaires will be computerized in real time.

4.4 Laboratory procedures

A dipstick test for *vibrio cholerae* O1 developed by the Institute Pasteur will be performed on a stool sample (200 µl) from individuals presenting to the CTC from the target vaccinated area in selected locale. The appearance of two pink lines (upper control line and lower LPS positive line) indicates a positive result, and a single upper pink control line indicates a negative result.

For those patients with a positive result to the RDT, a filter paper disc will be dipped into fresh stool and placed into a microtube with 2 to 3 drops of normal saline solution (NaCl 0.9%). The tubes will be kept at room temperature and sent to the lab for isolation of *V. cholerae* according to standard methods¹. PCR can be also performed on the specimens sent to confirm the presence of *V. cholerae*

4.5 Identification and interview of controls

For both studies, four individually matched neighborhood controls will be recruited per case. Matching will be based on sex and age range (0 to 1, 2 to 4, 5 to 14, or 15 years and above) and reside in the same township as the respective case. Controls will be selected through a walk around procedure starting from every third house to the right of the case's house (right hand side while facing the house).

An assembly log for controls will be maintained. This log will be an ordered list of all age-sex- eligible with their names; addresses; whether they were found; if found, whether they agreed; and, if they agreed, whether they were otherwise eligible. This log will have the information needed to go back to vaccination logs for both participating and non-participating potential controls, to check for biased selection.

For each control, after informed consent is obtained and the eligibility criteria applied, the questionnaire will be completed (see Annex 2). Information about oral cholera vaccination and details from the vaccination card will be collected only at the end of the interview. The completed questionnaires will be computerized in real time.

4.6 Statistical considerations

- **Endpoints:** The odds (OR) of having been fully vaccinated (2 complete doses) will be compared with the odds of not being vaccinated between the cases and controls through the odds ratio.

¹ Dodin JFA. Diagnosis of the cholera vibrio. In: Paris IP, editor. Laboratory methods for the diagnosis of cholera vibrio and other vibrios. Paris: 1992. p. 59-82.

- **Sample size calculation:** Using the following assumptions: 0.05 1-tailed p value, 0.2 Beta error, 80% coverage and a conservative estimate of 50% protective effect, 90 cases and 360 controls would be necessary. A similar sample size will be needed for the indicator case-control study.

- **Ascertainment and definition of vaccination:** Vaccination status will be ascertained through information collected during the interview (recall and from vaccination cards) and from the computerized vaccination logs.

The categories for documentation of vaccination for cases and controls will be as follows.

- written documentation of vaccination in vaccination card, vaccination log, or both;
- vaccination by recall only as orally reported by the participant;
- written documentation of non-vaccination in vaccination card, vaccination log, or both;
- no vaccination by recall as orally reported by the participant;
- unknown vaccination status by recall as orally reported by the participant

The definition of “fully vaccinated” for the primary analysis of the cases and controls is: written documentation in the vaccination log of intake of most or all of two doses of vaccine.

- Analysis Plan

The odds ratio for vaccination with two completely (or nearly completely) swallowed doses, separated by at least 10 days, with the second dose having been received at least 14 days before focal time (focal time is the date of onset of diarrhea for the cases) will be compared between the cases and controls. Confounding variables will be adjusted by using conditional logistic regression models.

The vaccine effectiveness (VE) equation can be expressed in the form of relative risk (RR), which in a case control study can be approximated by the OR. The VE will be calculated as follows:

$$VE (\%) = (1 - OR) \times 100$$

All p -values and 95% confidence intervals will be two-sided. Statistical significance will be determined as a p -value less than 0.05. Data will be analyzed using appropriate statistical analysis packages (e.g. STATA, SAS, SPSS, etc)

4.7 Ethical considerations

This study will adhere to the principles that govern biomedical research involving human subjects as delineated in The Declaration of Helsinki² in order to provide assurance that the rights, integrity, and confidentiality of trial subjects are protected.

² World Medical Association. <http://www.wma.net/e/policy/b3.htm>

Information about cholera, the vaccine, and the study will be provided at community level, just prior to the first round of vaccination and during the campaign.

Written informed consent will be obtained from the participants or their parents / guardians prior to inclusion in the study (Annex 1).

The privacy and confidentiality of participants will be protected during and following data collection.

Before initiating of the study, the final protocol and the written consent form will be submitted for clearance and approval to the medical Ethics Review Committee of the Country.

There are no direct benefits for participation in the case control study to determine vaccine effectiveness. The results of this study however will benefit all populations at risk of cholera infection by improving understanding of the protection offered by vaccination.

There are no anticipated risks for participation in the vaccine efficacy study.

4.8 Timeline

- Each of two case-control studies is estimated to take 44 days to complete
 - Preparation and training: 14 days
 - Field data collection: 30 days

5. Annexes

Annex 1: INFORMED CONSENT FORM:

I (or my child/ward) have been invited to take part in the research on cholera. I have read the information letter concerning the study, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate (or for my child/ward to participate) as a subject in this study and understand that I have the right to withdraw from the study at any time without in any way affecting my (or my child/ward's) medical care.

Print Name of Subject

Date and Signature of Subject

 / / (dd/mm/yy)

If illiterate

Print Name of Independent Literate Witness

(if possible, this person should be selected by the participant and should have no connection to the research team)

Date and Signature of Witness

 / / (dd/mm/yy)

Print Name of Researcher

Date and Signature of Researcher

 / / (dd/mm/yy)

Annex 2: QUESTIONNAIRES FOR CHOLERA CASE-CONTROL STUDY

A. QUESTIONNAIRE FOR INDIVIDUALS PRESENTING TO THE CTC WITH DIARRHOEA STARTING AFTER THE VACCINATION CAMPAIGN

Screening questions: Include only cases from the target area and if he/she answers “no” to ALL the following questions.

Did this diarrhea episode start before *date1* (starting day of the vaccination campaign)?

Did he/she seek treatment for diarrhea at the CTC anytime from *date1* but BEFORE this current episode?

Was he/she living in a place other than the target area from *date1* to the present?

If female, was she pregnant from *date1* to the *date2* (end of the campaign)?

If child, was he/she under 2 years of age from *date1* to *date2*?

A: IDENTIFICATION

A1 Name A2 Age A3 Sex F[] M[]

A4 How many people are living in your household?

1 to 5 ₁[] 6 to 14 ₂[] More than 15 ₃[]

B: RESIDENCE DURING THE LAST WEEK

URBAN ZONE:

B1 City B2 Constituency B3 Township

B4 Street B5 No B6 Other references

RURAL ZONE

B7 Province..... B8 Constituency..... B9 Village

B10 Street..... B11 No..... B12 Other references.....

B14 GPS COORDINATES: S..... E..... Nom

C: SYMPTOMS

C1 Diarrhea: No ₂[] Yes ₁[] Date of onset/...../..... C2 Frequency: times/day.....

C3 Type:

C4 Vomiting: No ₂[] Yes ₁[] Date of onset...../...../..... C5 Dehydration: No ₂[] Yes ₁[]

C6 ADMISSION TO THE CTC Date/...../.....

C7 STOOL SAMPLE Date of collection/...../.....

C8 Did you take: Antibiotics: No ₂[] Yes ₁[] If yes, date/...../.....

Specify:

C9: CLINICAL DIAGNOSIS: CHOLERA [] SIMPLE DIARRHOEA []

OTHER [] SPECIFY

D: HISTORY OF CHOLERA & HOUSEHOLD CONTACTS)

D1 VISITORS LIVING IN YOUR HOUSE DURING THE PAST 5 DAYS

Name where now?

Name where now?

Name where now?

D2 Did you ever have cholera during the previous years? No ₂[] Yes ₁[] If yes, when

D3 Did any member of your family have cholera during the previous years? No ₂[] Yes ₁[]

D4 If yes, how many? < 5 ₁[] 5 a 14 ₂[] 15 or more ₃[] when

Other cases of diarrhea during the last week:

D5 Family members: No ₂[] Yes ₁[] D6 Neighbors or friends: No ₂[] Yes ₁[] Don't know ₃[]

E: WATER SUPPLY

E1 Normally, what is your usual source for drinking water?

Piped into the house ₁[] Stand pipe/public tap ₂[] Individual well ₃[] Community well ₄[]

Purchased ₅[] Collected directly from a lake or other source ₆[] Other ₇[]

E2 During the last five days, what was the source of your drinking water?

.....

E3 Approximately how many persons utilize the same water source?

1 ₁[] 2-5 ₂[] 6-15 ₃[] 51-200 ₄[] > 200 ₅[]

E4 Describe your water source: Concrete well with pump ₁[] Concrete well – manual, covered ₂[]

Concrete well - open Well without concrete - open Piped

E5 Is the water from the source visibly contaminated? No Yes No Obs

E6 GPS Coordinates: S..... Nom

E7 MAIN SOURCE: Chlorine more than 0.3 MG/L No Yes

E8 HOUSE WATER: Chlorine more than 0.3 MG/L No Yes

E9 Do you treat your water now?

F: WATER STORAGE AND TREATMENT

F1 What type of container do you use for storing your DRINKING WATER?

Plastic bucket Metal bucket Clay pot Tank or cistern

Motor oil container Metallic pot 200-litre metal container 20-litre bottle

Other

F2 During the last 5 days, how do you ensure that your water is safe for drinking?

Boil Cover Filter Treat with chlorine Use other chemicals

No answer Other

G: FOOD CONSUMED DURING THE PAST 5 DAYS

G1 Type of uncooked food:

G2 Milk products: No Yes What

G3 Fresh fish: No Yes What

G4 Dried fish: No Yes What

G5 Fresh seafood: No Yes What

G6 Dried seafood: No Yes What

G7 Did you eat cooked food from the market? No Yes

If yes, what kind?

G8 Where did you eat during the last 5 days?

Residence Outside your residence If outside, where?

H: TOILET

H 1 Do you have a toilet in your house? None Yes

He Normally, where do you defecate? No mato Toilet inside the house Communal toilet
 Individual latrine (covered with concrete) Simple latrine (no cement) Communal
latrine (with cement) Anywhere Other

J: SOCIO-ECONOMIC STATUS

J1 How many animals does your household have? Goats Pigs Ducks
Chickens Other (*Specify*)

J2 How many of these does your household have: Bicycles Radios Metal pots Working
watches/clocks Electricity in the house Cars Television Cellular phone Mosquito
nets Soap

J3 Do you have a field for planting? No Yes

J4 Other than working in the field, how many members of your family have sources of income? []

J5 Who is the main source of household income? What is this household member's job?
Fisherman Selling goats along the road Farmer Small scale farmer
Laborer Other service worker Technician

Professional Other (*specify*)

J6 Is there anybody sick in the household?

J7 Do you know to write and read?

K: LABORATORY RESULTS

K1 Negative Positive Date/...../..... Antibiotic susceptibility.....

K3 HEALTH UNIT

K4 Date of data collection/...../.....

Other important comments:

By observation: Toilet in the house No Yes Don't know

L. Did he/she come directly to the CTC to seek treatment for this episode of diarrhea? No Yes
If no, list (in order) where he/she sought treatment prior to coming to the CTC:

.....

M. RESULT OF RAPID TEST

L1 Negative Positive Data/...../.....

N. CHOLERA VACCINATION

Did you receive the cholera vaccine given in *date1* – *date2*? No ₂[] Yes ₁[] Don't know ₃[]

If yes, how many doses? Two ₂[] One ₁[] Don't know ₃[]

If his/her vaccination card is available, copy the following information from the card.

Vaccination card serial number:

Received dose 1? No ₂[] Yes ₁[] Was dose 1 ingested? Incompletely ₂[] Completely ₁[]

Received dose 2? No ₂[] Yes ₁[] Was dose 2 ingested? Incompletely ₂[] Completely ₁[]

B. QUESTIONNAIRE FOR CONTROLS

Screening questions: Include only controls from the target area and if he/she answers “no” to ALL the following questions.

Did he/she seek treatment at the CTC for diarrhea which started from *date1* ----/-----/----- (date of onset of diarrhea of the case)?

Was he/she living in a place other than the target area *date1* to the present?

If female, was she pregnant from *date1* to *date2*?

If child, was he/she under 2 years of age from *date1* to *date2*?

In case he/she develops severe watery diarrhea, would he/she go to a treatment facility other than the CTC?

A: IDENTIFICATION

A1 Name A2 Age A3 Sex F[] M[]

A4 How many people are living in your household?

1 to 5 ₁[] 6 to 14 ₂[] More than 15 ₃[]

B: RESIDENCE DURING THE LAST WEEK

URBAN ZONE:

B1 City B2 Constituency B3 Township

B4 Street B5 No B6 Other references

RURAL ZONE

B7 Province..... B8 Constituency..... B9 Village

B10 Street..... B11 No..... B12 Other references.....

B14 GPS COORDINATES: S..... E..... Nom

D: HISTORY OF CHOLERA & HOUSEHOLD CONTACTS)

D1 VISITORS LIVING IN YOUR HOUSE DURING THE PAST 5 DAYS

Name where now?

Name where now?

Name where now?

D2 Did you ever have cholera during the previous years? No ₂[] Yes ₁[] If yes, when

D3 Did any member of your family have cholera during the previous years? No ₂[] Yes ₁[]

D4 If yes, how many? < 5 ₁[] 5 a 14 ₂[] 15 or more ₃[] when

Other cases of diarrhea during the last week:

D5 Family members: No ₂[] Yes ₁[] D6 Neighbors or friends: No ₂[] Yes ₁[] Don't know ₃[]

E: WATER SUPPLY

E1 Normally, what is your usual source for drinking water?

Piped into the house ₁[] Stand pipe/public tap ₂[] Individual well ₃[] Community well ₄[]

Purchased ₅[] Collected directly from a lake or other source ₆[] Other ₇[]

E2 During the last five days, what was the source of your drinking water?

.....

E3 Approximately how many persons utilise the same water source?

1 ₁[] 2-5 ₂[] 6-15 ₃[] 51-200 ₄[] > 200 ₅[]

E4 Describe your water source: Concrete well with pump ₁[] Concrete well – manual, covered ₂[]

Concrete well - open ₃[] Well without concrete - open ₄[] Piped ₅[]

E5 Is the water from the source visibly contaminated? No ₂[] Yes ₁[] No Obs ₃[]

E6 GPS Coordinates: S..... Nom

E7 MAIN SOURCE: Chlorine more than 0.3 MG/L No ₂[] Yes ₁[]

E8 HOUSE WATER: Chlorine more than 0.3 MG/L No ₂[] Yes ₁[]

E9 Do you treat your water now?

F: WATER STORAGE AND TREATMENT

F1 What type of container do you use for storing your DRINKING WATER?

Plastic bucket ₁[] Metal bucket ₂[] Clay pot ₃[] Tank or cistern ₄[]

Motor oil container ₅ [] Metallic pot ₆ [] 200-litre metal container ₇ [] 20-litre bottle ₈ []

Other ₉ []

F2 During the last 5 days, how do you ensure that your water is safe for drinking?

Boil ₁ [] Cover ₂ [] Filter ₃ [] Treat with chlorine ₄ [] Use other chemicals ₅ []

No answer ₆ [] Other ₇ []

G: FOOD CONSUMED DURING THE PAST 5 DAYS

G1 Type of uncooked food:

G2 Milk products: No ₂ [] Yes ₁ [] What

G3 Fresh fish: No ₂ [] Yes ₁ [] What

G4 Dried fish: No ₂ [] Yes ₁ [] What

G5 Fresh seafood: No ₂ [] Yes ₁ [] What

G6 Dried seafood: No ₂ [] Yes ₁ [] What

G7 Did you eat cooked food from the market? No ₂ [] Yes ₁ []

If yes, what kind?

G8 Where did you eat during the last 5 days?

Residence ₂ [] Outside your residence ₁ [] If outside, where?

H: TOILET

H 1 Do you have a toilet in your house? None ₂ [] Yes ₁ []

He Normally, where do you defecate? No ₁ [] Toilet inside the house ₂ [] Communal toilet ₃ [] Individual latrine (covered with concrete) ₄ [] In the sea ₅ [] Simple latrine (no cement) ₆ [] Communal latrine (with cement) ₇ [] Anywhere ₈ [] Other ₉ []

J: SOCIO-ECONOMIC STATUS

J1 How many animals does your household have? Goats ₁ [] Pigs ₂ [] Ducks ₃ []

Chickens ₄ [] Other ₅ [] (*Specify*)

J2 How many of these does your household have: Bicycles [] Radios [] Metal pots [] Working watches/clocks [] Electricity in the house [] Cars [] Television [] Cellular phone [] Mosquito nets [] Soap []

J3 Do you have a field for planting? No [] Yes []

J4 Other than working in the field, how many members of your family have sources of income? []

J5 Who is the main source of household income? What is this household member's job?

Fisherman ₁[] Selling goats along the road ₂[] Farmer ₃[] Small scale farmer ₄[]

Labourer ₅[] Other service worker ₆[] Technician ₈[]

Professional ₈[] Other ₉[] (*specify.*)

J6 Is there anybody sick in the household?

J7 Do you know to write and read?

K. HEALTH UTILIZATION BEHAVIOR FOR DIARRHOEA

When you have SEVERE diarrhea what do you do to treat it?

Go to a health unit ₁[] specify..... Take ORS ₂[] Go to the pharmacy ₃[]

Consult a traditional healer ₄[] Other ₄[] specify.....

L. CHOLERA VACCINATION

Did you receive the cholera vaccine given in ____ (vaccination dates)?

No ₂[] Yes ₁[] Don't know ₃[]

If yes, how many doses? Two ₂[] One ₁[] Don't know ₃[]

If his/her vaccination card is available, copy the following information from the card.

Vaccination card serial number:

Received dose 1? No ₂[] Yes ₁[] Was dose 1 ingested? Incompletely ₂[] Completely ₁[]

Received dose 2? No ₂[] Yes ₁[] Was dose 2 ingested? Incompletely ₂[] Completely ₁[]