BMJ Open

Effectiveness of case-area targeted interventions including vaccination on the control of epidemic cholera: protocol for a prospective observational study

Ruwan Ratnayake ,[1,2] Nicolas Peyraud,[3] Iza Ciglenecki,[3] Etienne Gignoux ,[2] Maria Lightowler,[2] Andrew S Azman,[3,4] Primitive Gakima,[5] Jean Patrick Ouamba,[5] Joseph Amadomon Sagara,[5] Rollin Ndombe,[5] Nana Mimbu,[2] Alexandra Ascorra,[2] Epicentre and MSF CATI Working Group, Placide Okitayemba Welo,[6] Elisabeth Mukamba Musenga,[7] Berthe Miwanda,[8] Yap Boum II,[9] Francesco Checchi,[1] W John Edmunds,[1] Francisco Luquero,[2,10] Klaudia Porten,[2] Flavio Finger[2]

To cite: Ratnayake R, Peyraud N, Ciglenecki I, *et al*. Effectiveness of case-area targeted interventions including vaccination on the control of epidemic cholera: protocol for a prospective observational study. *BMJ Open* 2022;**12**:e061206. doi:10.1136/bmjopen-2022-061206

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-061206).

Received 18 January 2022
Accepted 17 June 2022

For numbered affiliations see end of article.

Correspondence to
Ruwan Ratnayake;
ruwan.ratnayake@lshtm.ac.uk

ABSTRACT

Introduction Cholera outbreaks in fragile settings are prone to rapid expansion. Case-area targeted interventions (CATIs) have been proposed as a rapid and efficient response strategy to halt or substantially reduce the size of small outbreaks. CATI aims to deliver synergistic interventions (eg, water, sanitation, and hygiene interventions, vaccination, and antibiotic chemoprophylaxis) to households in a 100—250 m 'ring' around primary outbreak cases.

Methods and analysis We report on a protocol for a prospective observational study of the effectiveness of CATI. Médecins Sans Frontières (MSF) plans to implement CATI in the Democratic Republic of the Congo (DRC), Cameroon, Niger and Zimbabwe. This study will run in parallel to each implementation. The primary outcome is the cumulative incidence of cholera in each CATI ring. CATI will be triggered immediately on notification of a case in a new area. As with most real-world interventions, there will be delays to response as the strategy is rolled out. We will compare the cumulative incidence among rings as a function of response delay, as a proxy for performance. Cross-sectional household surveys will measure population-based coverage. Cohort studies will measure effects on reducing incidence among household contacts and changes in antimicrobial resistance.

Ethics and dissemination The ethics review boards of MSF and the London School of Hygiene and Tropical Medicine have approved a generic protocol. The DRC and Niger-specific versions have been approved by the respective national ethics review boards. Approvals are in process for Cameroon and Zimbabwe. The study findings will be disseminated to the networks of national cholera control actors and the Global Task Force for Cholera Control using meetings and policy briefs, to the scientific community using journal articles, and to communities via community meetings.

Strengths and limitations of this study

- ⇒ This is the first effectiveness study of case-area targeted interventions (CATIs) that includes oral cholera vaccination to respond to a cholera outbreak.
- ⇒ The prospective observational study design will provide rigorous measurement of exposures and outcomes whereas a randomised controlled trial would be logistically challenging to undertake during the early phase of a cholera outbreak, and ethically challenging given the need to withhold interventions that constitute the standard of care.
- ⇒ Multiple substudies are used to holistically evaluate the impact of CATI on community incidence and household transmission, and the coverage and uptake by communities.
- ⇒ The non-randomised design is a key limitation of this study.
- ⇒ Other limitations include the uncertainty: of community acceptance and uptake of CATI; in the adherence of the response team to the intervention standards; and in the course of the outbreak and in attaining adequate statistical power.

INTRODUCTION

Background and rationale

From 2018 to 2020, in the major focal areas for cholera transmission, the number of reported suspected cases has decreased (eg, in Democratic Republic of the Congo (DRC), Haiti), transmission has ceased (eg, in South Sudan), and in some settings, transmission has remained high (eg, in Ethiopia, Somalia, Yemen).[1 2] Within each of these scenarios, the risk of small outbreaks propagating and rapidly expanding remains substantial; in 2021, explosive cholera outbreaks have expanded during the rainy season in northern Nigeria, Niger and Cameroon.[3] This rapid spread is driven by inadequate access to water and sanitation, poor hygiene practices, population displacement from conflict and natural disasters, overcrowding in camps and slums, and disrupted surveillance and response systems; mortality risk is influenced by poor access to healthcare and high prevalence of acute malnutrition.[4–6]

Standard cholera response involves reinforcing surveillance and laboratory practices, water, sanitation and hygiene (WASH) interventions, case management and community engagement, and conducting oral cholera vaccination (OCV) campaigns.[7–11] Mass responses are delivered over large areas like towns and districts. To avoid delays in scaling responses, more agile control strategies have been proposed to target the foci of small outbreaks. The delivery of hygiene kits to households of patients of cholera treatment units, for example, has demonstrated reductions in cholera incidence among household contacts and in faecal contamination of drinking water.[12] Another strategy, case-area targeted intervention (CATIs), involves the early detection of primary outbreak cases and delivery of a rapid response to households in a 100—250 m 'ring' around the case's household to halt or substantially reduce transmission.[13 14] To increase the capacity to differentiate cholera from other diarrhoea, CATI can employ rapid diagnostic testing (RDT) with an enrichment step to substantially increase diagnostic performance.[15 16]

Cholera outbreaks are driven by household and community transmission via bacterial shedding from infected persons and contamination of water, food and fomites.[6] CATI's potential strength is its capacity to address person-to-person and environmentally-mediated transmission routes via synergistic interventions that act in the short term (ie, point-of-use water treatment, hygiene promotion with soap distribution and antibiotic chemoprophylaxis) and longer term (ie, vaccination). We conducted a scoping review to assess the effectiveness of the individual interventions delivered by CATI (and other targeted strategies) and the geographical risk zone for infection.[14] It suggested that the combination of household water treatment, hygiene promotion emphasising hand-washing with soap and antibiotic chemoprophylaxis adapted to household delivery shows promise for the rapid reduction of localised transmission.[14] A single dose of OCV can substantially extend the strength and duration of protection in the short term (the 2-month effectiveness is 89%, 95% CI 43 to 98).[17–20] A high-risk spatiotemporal zone of 100—250 m around case-households lasting for 7 days was supported by analyses of epidemic data.[21–23] A computational model also suggested that CATI including household WASH, OCV and antibiotic chemoprophylaxis distributed over a 100 m ring could reduce epidemic duration and size.[13]

CATI (without OCV) is currently used in numerous settings for outbreak control[24–26] and CATI (with OCV) has been harnessed to suppress sporadic clusters at the end of mass vaccination campaigns.[27 28] However, rigorous evaluation of its effectiveness is scarce. Seven evaluations of CATI (without OCV) were conducted in Bangladesh, Cameroon, DRC, Haiti, Nepal and two feasibility studies of CATI (with OCV) at the end of mass vaccination campaigns were conducted in South Sudan and Cameroon.[27–33] The most comprehensive evaluation was a retrospective observational study of CATI (without OCV) in Centre Department, Haiti from 2015 to 2017.[32] It demonstrated a relationship between the speed of implementation and reductions in incidence of suspected cholera and outbreak duration. Its detailed analysis was limited by its reliance on retrospective, routine data and incomplete documentation of the geographical extent and the population of the target areas, inconsistency in the exposure (ie, different combinations of interventions), lack of OCV and a lack of culture confirmation or rapid testing of suspected case clusters.

The Global Task Force for Cholera Control (GTFCC) has highlighted three main gaps in the understanding of CATI's effectiveness: its mix of interventions, the OCV delivery strategy, and the impact of CATI (with OCV) on transmission.[34] We report on a protocol for a prospective observational study on the effectiveness of a CATI strategy to be implemented by Médecins Sans Frontières (MSF). The study aims to evaluate CATI interventions which integrate household WASH, single-dose OCV and antibiotic chemoprophylaxis, and examine the impact on reduction in the cumulative incidence. Given that there is no policy option to obtain vaccines from the global OCV stockpile for CATI, MSF is obtaining a small quantity of OCV directly from the manufacturer to store in country in preparation for CATI.[35] We describe the generic study protocol with emphasis on the study in DRC, where ethical and administrative approvals have been obtained.

METHODS AND ANALYSIS

Study design and rationale

A prospective observational study is proposed. The gold-standard design, a cluster randomised trial, would require randomising communities to receive (or have withheld) commonly used and individually effective interventions that are the standard-of-care for cholera outbreaks, and is thus ethically challenging to implement during an outbreak.[36] In addition, randomisation would not be logistically-feasible during the acute phase of an emergency response.[37 38] To improve on the drawbacks of prior observational studies of CATI, we propose (1) prospective data collection of exposures and outcomes based on a scenario where CATI is administered using (2) a standardised intervention package which represents a standardised exposure (ie, a uniform intervention package and ring-radius) and (3) enriched RDT-testing of suspected cases to target the most likely cholera clusters.

The prospective observational study will run in parallel to the implementation of CATI during a cholera epidemic. The unit of analysis is the 'ring', which is defined as a

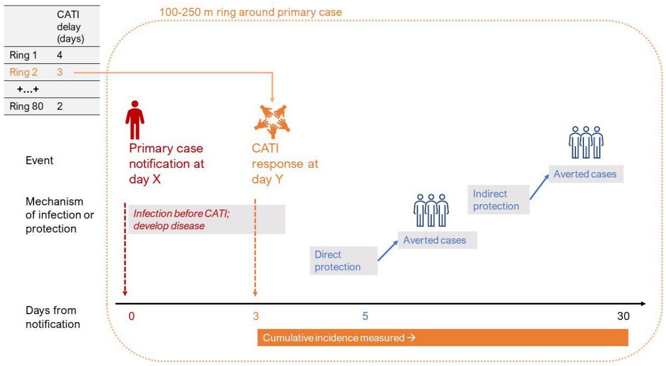

Figure 1 Infection, CATI response and measurement in a study ring, inspired by.[36] This figure describes the study design, events and interventions, mechanisms of infection and infection prevention, and measurements. In a set of rings (table in top left corner), a given ring has a first delay for the case to be detected by, and a second delay from detection to CATI response. After implementation, the effects of interventions occur after a third delay. This results in direct and indirect protection for persons in the ring. Incident cases occurring after 2–30 days postimplementation will contribute to the cumulative incidence. The cumulative incidence across rings is compared between rings as a function of delay to response. CATI, case-area targeted intervention.

geographically delineated cluster of a predefined radius around every primary case. The primary outcome measure is cumulative incidence in the ring 30 days after the start of CATI implementation (figure 1 depicts the implementation and study measurement). CATIs will be triggered immediately on notification of each primary outbreak case in a new area. As with most real-world interventions there will be delays to response as the strategy is rolled out due to the workload of the teams who are responding to multiple alerts in different communities and the distance between the CATI team and affected communities. This delay serves as a proxy for CATI's capacity to rapidly provide protection in a real-world scenario, based on the rationale that a prompt response can reduce the cumulative incidence.[32] To inform the range of potential delays, we conducted a meta-analysis of time to detection and response to cholera outbreaks in fragile states, and found that the median delay between symptom onset of the first-detected case to outbreak detection is 5 days (IQR 5—6).[39] Note that MSF aims to respond more rapidly with CATI, while the outbreak is still small.

As the time of infection cannot be captured, there is no means of estimating whether cases were infected between the end of incubation period of the primary case and the start of implementation. Therefore, cases detected in the ring will be counted toward incidence after a fixed delay of 2 days (ie, the upper limit of cholera's median incubation period (1–2 days)).[40]

In addition to the main study on effectiveness, three substudies will be undertaken:

1. Household coverage substudy: Cross-sectional surveys will be undertaken 21 days after the CATI implementation to measure coverage of interventions, uptake of WASH interventions, and outcome measures for water quality and quantity. Coverage estimates will be incorporated into the effectiveness analysis to account for variability in coverage across rings.
2. Household transmission substudy: A cohort study of household contacts in the primary case-households will be used to evaluate the effectiveness CATI in reducing intra-household transmission by measuring the incidence of symptomatic and asymptomatic cholera by positive enriched RDT.
3. Antimicrobial resistance (AMR) substudy: The potential for increasing AMR using azithromycin is greater than for doxycycline (see online supplemental information 1 for the rationale underlying this approach). If doxycycline is used, only routine AMR monitoring in *Vibrio cholerae* isolates will be undertaken.[41] If azithromycin is used, a cohort study of AMR will also be undertaken. Here, in a subset of rings, a description of AMR at baseline and post-administration of *Enterobacteriae* will be assessed among all persons receiving antibiotics.

Aims and objectives

1. We aim to evaluate the effectiveness of CATI on the reduction of cumulative incidence of suspected cases that are positive by enriched RDT in the rings ('main study').

The secondary objectives are:

1. To evaluate the effectiveness of CATI in reducing the cumulative incidence of deaths in the rings ('main study').
2. To estimate the coverage of individual components of CATI (household coverage substudy).
3. To evaluate the effectiveness of CATI in reducing the intrahousehold transmission (household transmission substudy).
4. If chemoprophylaxis is included in the CATI package, to describe the presence or changes of AMR in *V. cholerae* and/or indicator *Enterobacteriae* (AMR substudy).
5. To describe the overall spatiotemporal transmission patterns of the outbreak.
6. To document the resources and costs required.

Study setting and launch criteria: DRC as an example

A risk assessment will be undertaken in each country to highlight health zones with elevated incidence and persistence of transmission over the last 5 years (the GTFCC's definition for a hotspot).[42] In DRC, the hotspots include health zones near the Great Lakes with seasonal epidemics (eg, Ituri, Nord Kivu, Sud Kivu, Tanganyika, Haut Lomami, Haut Katanga) and cholera-free areas where outbreaks have recently appeared (eg, Kasai, Sankuru).[43 44] MSF has prepared to implement CATI where it has sufficient capacity for a robust response (ie, provinces of Haut Katanga, Ituri, Kasai Oriental, Nord and Sud Kivu, Tshopo). The MOH has undertaken preventive vaccination campaigns in hotspots in Nord and Sud Kivu, Haut Katanga, Tanganyika and Haut Lomani.[45] The national cholera elimination plan also contains a targeted

Table 1 Intervention package for CATI in the DRC

Domain and control target	Details on materials and delivery method
WASH to immediately reduce transmission via household water treatment, and to facilitate safe water storage, hand-washing, safe food handling and excreta disposal[29 77 78]	Hygiene kit that includes[12]: ► Jerrycan (10—20 L) for water collection and storage ► Point of use water treatment products (eg, chlorine/Aquatabs, flocculant if water has high turbidity) ► Soap ► Handwashing device (10 L bucket with tap) The kit will contain consumables sufficient for 1 month's use.
Antibiotic chemoprophylaxis to prevent or clear infection among household members and direct neighbours of cases (loses effect within 2 days due to its biological half-life)[13 79–81];	Single-dose, oral doxycycline delivered to members of primary case household and directly adjacent households. ► Adults (≥15 years): doxycycline, 300 mg, orally ► Children (1–12 years): doxycycline, 4 mg/kg, orally ► Infants (<1 year) and pregnant women will receive azithromycin instead
Oral cholera vaccination to prevent infection for a longer duration (taking effect several days after administration when an immune response is reached).[19 82]	Single-dose, OCV (Euvichol-Plus, Eubiologics, Seoul, South Korea) given to persons≥12 months of age In accordance with national guidelines and in collaboration with the MoH, the single dose of OCV will be followed by a second dose after CATI.[45]
Active case finding and case management	Referral mechanism to refer severely dehydrated cases to a cholera treatment unit and support to cholera treatment facilities.

CATI, case-area targeted intervention; DRC, Democratic Republic of the Congo; OCV, oral cholera vaccination; WASH, water, sanitation and hygiene.

WASH strategy ('quadrillage') to increase water supply and quality and hygiene promotion in a 500 m radius around clusters of suspected cholera cases.[31 45]

Intervention

MSF and the MOH will select an intervention strategy based on scientific evidence,[14] national policies[45] and operational considerations. RDTs and enrichment materials will be prepositioned in health facilities for rapid verification of alerts.[46] CATI will be implemented in rings of 100—250 m (or, rural settlements of a slightly larger size) surrounding the households of the primary case(s). A primary case is defined as the first case detected in a new ring that was previously cholera-free.

CATI will be launched in a health zone that is experiencing a new outbreak. A new outbreak is signalled by a single suspected case testing positive by enriched RDT. The RDT result will be confirmed by culture or PCR. The target is to implement CATI within a maximum 5–7 days from case presentation, corresponding to the period of highest risk.[21] The intervention package and criteria for launching and halting the strategy may differ slightly by country and the MSF mission. Table 1 shows the intervention package in the DRC.

Study population and sample size

The main outcome (cumulative incidence) is based on the collection of surveillance data from each ring, specifically the number of cases positive by enriched RDT (numerator), and the total enumerated population at-risk (denominator). Persons at-risk will include those who were resident in the ring at the start of the response.

The sample size was calculated using a statistical simulation (published in a separate article).[47 48] The simulation explicitly modelled the transmission dynamics and the effects of CATI within the first 30 days of a new outbreak in a set of rings. We then performed the study analysis of effectiveness (ie, the association between the delay to implementation (as a proxy for performance) across rings and the reduction in cumulative incidence (as a proxy for effectiveness) on these modelling results. The power was estimated for a range of sample sizes of rings (ie, 50—150 rings) with a mean size of 500 persons. This reflects the size of outbreaks where CATI was recently used in Haiti and Nepal.[32 33] Targeting 80–100 rings was estimated to achieve power ≥80%, using a basic reproduction number of 2.0 and a dispersion coefficient of 1.0—1.5.[48]

Study procedures

Recruitment

A schedule of the implementation and data collection is shown in table 2. On notification of a primary case, the study team led by a study coordinator will accompany the response team to the site. The approval process to carry out CATI will be conducted by the response team and is not covered here. The study team will seek a separate study approval verbally from the village leader using a formal process and informed consent from the primary case to collect case information. With these approvals, the team will take the coordinates of the primary case household using a tablet device. This will be used to automatically delineate a 100—250 m ring around the case-household, which is automatically visualised and can be adjusted

Table 2 Schedule of study interventions and data collection activities

Study intervention	Beginning of cholera season	Health zone(s) meets outbreak criteria	For each new RDT-positive case	Day 0 stool sample collection (substudies only)	Day 7 stool sample collection (substudies only)	Day 30 stool sample collection (substudies only)	21 days post-CATI implementation	End of epidemic
Routine surveillance by health facilities enriched RDTs, aided by CHWs	■	■	■	■	■	■	■	■
CATI response and study are launched		■						
Implementation and study teams visit village/neighbourhood			■					
Community leader approval for intervention/study			■					
GIS delineation of ring			■					
Enumeration of ring			■					
CATI delivered in ring			■					
Stool sample collection (substudies only)			■	■	■	■		
Coverage survey conducted							■	
Data analysis and reporting								■

CATI, case-area targeted intervention; CHWs, community health workers; GIS, geographic information system; RDT, rapid diagnostic testing;.

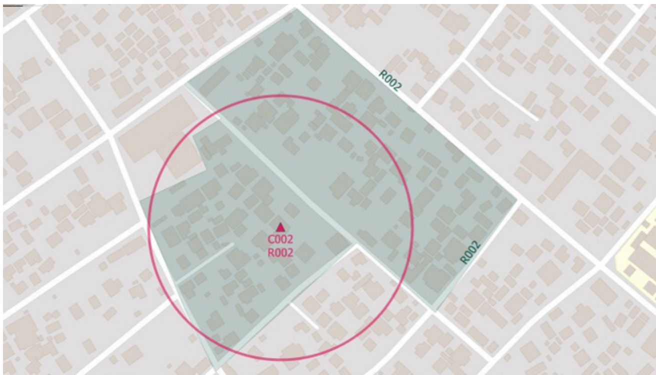

Figure 2 Screen capture of the ring estimation tool in input, as imagined in Goma, Nord Kivu, Democratic Republic of the Congo. The tool sketches a 100–250 m radius ring (in red) around the household of the primary case (triangle in red) and leads the operator through the steps to manually adjust the ring outline (shading in blue) and enumerate the households in the ring. OpenStreetMap contributors (https://www.openstreetmap.org/copyright).

manually for feasibility (figure 2). The team will geo-tag and enumerate the households within the ring and record the number of household members. The study team will collect data from the primary case and his or her household. For each of the substudies, an information note will be read to the household contacts (household and AMR substudies) and head of household (household coverage substudy) to explain the rationale, risks and benefits of participating in the studies. The respondent can consent to participate in the study or not, without any bearing on whether their household receives CATI.

Data collection and surveillance in the ring

Data will be collected from the primary case in each ring. Incident enriched RDT-positive cases (numerator) will be collected via a surveillance system set up for each ring at the closest health facility. Community health workers (CHWs) will be trained to use a community case definition to detect and immediately refer suspected cases to health facilities.[49] The population at-risk (denominator) will be determined during the initial geo-tagging and census of each household. Surveillance data will be recorded for 30 days after the last day of implementation.

CHWs and health facility staff will use a line-list to record new suspected cases in the ring. Each suspected case will trigger an enriched RDT carried out by trained staff.[15 16] However, if the enriched RDT is positive and the patient's household is not within a ring that previously received CATI, a new ring and CATI will be initiated and a questionnaire for the primary case will be filled out. The following information will be collected for all cases positive by enriched RDT: demographics, date of symptom onset, date of admission, provenance, vaccination status, month and year of last OCV dose, dehydration level at admission, duration of hospitalisation, outcome and test results.

Data on potential confounders at the ring level will be collected. This includes the distance to the nearest health facility (to account for the ability of cases to seek care and for response teams to reach sites); estimated population density to account for the capacity to achieve coverage rapidly (derived from the WorldPop database); and, average daily rainfall to account for the propensity for infection and ease of access for response teams (derived from satellite rainfall measurements from the Climate Hazards Group InfraRed Precipitation with Stations dataset).[50–52] In addition, the survey-based coverage of households by CATI to account for variability in uptake of interventions and incidence at the start of implementation to account for the initial outbreak severity will be included as confounders.

Fidelity to implementation guidelines in each ring will be documented through a set of process indicators including the delay to implementation and time to completion. Through the coverage survey, uptake and reasons for low uptake of individual interventions will be monitored. Direct and indirect costs of CATI will be documented.

Coverage substudy

Coverage will be estimated using individual coverage surveys in each ring 21 days after implementation. The minimum sample size for the household survey (600 or 30 randomly sampled households in at least 20 rings) is calculated to estimate mean vaccination coverage with a precision of ±10%, assumption of 70% one-dose vaccination coverage, alpha error of 5%, design effect of 2.5, finite population of 1000, mean household size of 5.5 persons, and non-response of 10%. Simple random sampling of the enumerated households will be used to select 30 households. The data collectors will interview the household heads to collect outcomes. These include the number of household members, receipt of CATI and its components, reasons for refusal, observations of remaining stocks (eg, chlorine tablets, soap, containers), observations of their placement as a proxy for uptake (eg, soap 1 m away from a kitchen and latrine) and individual uptake (vaccination coverage).[12 27 53 54] Drinking water will be tested for free residual chlorine concentration using a pool tester and for turbidity using a turbidity tube.[55] Absent households will be visited twice during the day, and if still absent, replaced with another randomly sampled household.

Household transmission and AMR substudies

The substudies will be undertaken in a subset of every fifth systematically sampled ring, based on attaining 80—100 rings. In the household transmission study, all household contacts of the primary case will be enrolled, interviewed for demographics and risk factors, and followed with self-collected stool samples and monitoring for cholera symptoms at days 0, 7 and 30 after notification of the primary case, following a protocol similar to Weil *et al*.[56] The presence of *V. cholerae* among symptomatic and asymptomatic cases will be detected by enriched RDT and compared on the basis of response delay.

The AMR substudy will only be conducted if azithromycin is used in the CATI interventions (see online supplemental information 1 for the rationale underlying this approach). Within each of the systematically sampled rings, the primary case household will be selected for the household transmission study, and an additional five adjacent households that received chemoprophylaxis will be included. From each of the six households for the AMR study, one adult per household will be randomly selected for monitoring presence of resistant *Enterobacteriae*.[41] Stool samples will be collected from each of these participants at days 0, 7 and 30 after notification of the primary case. The sample size for the AMR substudy is 120 adults, which is adequate for evaluating the difference between a change in AMR-prevalence of from 20% to 40% (95% confidence level, power of 80% and 50% inflation due to sample degradation and/or refusal). If doxycycline is used, only routine AMR monitoring in *V. cholerae* isolates will be undertaken.[41]

Laboratory outcomes and procedures

Given that running culture or PCR for each suspected case would be unfeasible, this study will use RDTs on enriched stool samples.[46] Whole stool samples will be incubated in alkaline peptone water for 4–6 hours at ambient temperature before RDT testing.[15 16] RDTs used will be Crystal VC, Arkray Healthcare, Surat, India and/or SD Bioline, Standard Diagnostics, Seoul, Korea. The rationale for using the enriched instead of a direct RDT is the high specificity (98.9%, 95% 97.8—99.6) and sensitivity (89.3%, 95% CI 71.8% to 97.7%).[46] The initial suspected cases and a subset of ≥5 cases per health facility each week will be culture confirmed. Wet filter paper or Cary Blair media will be used to transport stool samples at ambient temperature for culture and AMR testing.[57 58] For routine AMR monitoring of *V. cholerae* isolates against tetracycline, azithromycin, nalidixic acid and ciprofloxacin, the disk diffusion method will be used.[41] For the AMR substudy, AMR monitoring in *Enterobacteriae* will be done by selecting for resistant strains using antibiotic-enriched bacterial growth media.[41]

Data management and analysis

Data management

A tablet-based data collection system was developed using a secure REDCap tool hosted by Epicentre.[59] The system aims to link primary cases, ring linelists, testing results and substudy data using unique identification numbers for each ring, household and case. The ring delineation tool was developed in Quantum GIS (Open Source Geospatial Foundation Project) and Input/Mergin Maps (Lutra Consulting) and will be used by the study and response teams to facilitate the identification and follow-up of households. Data will be transferred to a local server every evening. Regular backups and data accuracy checks will be undertaken.

Effectiveness analyses (objectives 1 and 2)

Cumulative incidence is calculated using enriched RDT-positive cases in the numerator and the population census in the denominator. The main analyses will compare the 30-day cumulative incidence of enriched RDT-positive cases and deaths in each ring. The counterfactual is setup as rings with immediate CATI intervention versus rings with varying delays to CATI implementation, as has been done previously by Michel *et al*.[32] That is, every ring that receives CATI will be categorised into a separate control group based on the delay to receiving CATI. The measurement of cumulative incidence will be divided into two phases: (1) the number of cases in the 2 days after the start of implementation of CATI will be considered as already infected before implementation, and (2) the number of cases after these 2 days will be considered impacted by CATI.[32 36] A generalised linear mixed model (GLMM) with a negative binomial distribution will model the observed cumulative incidence of cholera in the rings (as a proxy for effectiveness at different levels of performance) associated with the time to response in days (as a proxy for performance).[60] It will include fixed effect terms for the exposure variable (ie, delay to CATI as a continuous variable) and potential confounder variables (ie, distance to health facility, population density, household coverage and rainfall), a random effect term that represents the location of the ring, and a term to offset the number of cases by the population, effectively modelling the cumulative incidence in the population in the CATI ring. A clinically meaningful effect would be a dose–response relationship between the delay to CATI implementation and cumulative incidence. The GLMM model formula is depicted in box 1.

Given the absence of the randomization of rings to the intervention, the differences in the outcome may reflect

Box 1 GLMM formula

$$y_{ij} \sim Neg.\ Binom.\ (\mu_{ij})$$

$$\log(\mu_{ij}) = \log(pop_{ij}) + \beta_0 + \sum_{p=1}^{P} \beta_p x_{pij} + (effect_{ring} + \in)$$

Where, observations i are nested in rings j;
y_{ij} is the count of cases and has a negative binomial distribution given the explanatory variables;
μ_{ij} is the exponential function of the explanatory variables;
P represents the explanatory variables, $x_1, \ldots, x_p$;
β_0 is an intercept parameter;
$\beta_p,\ p = 1, \ldots,$ P, are slope parameters associated with explanatory variables x_{pij} ; $\log(pop_{ij})$ is an offset term for the population density.
The explanatory variables include, per ring, ***time*** (delay to CATI implementation), ***dist*** (distance to nearest health facility), ***pop_dens*** (population density), ***cov*** (proportion of households who received CATI), and ***rain*** (average daily rainfall); ***effect_ring*** is the ring-specific random effect (deviation in cumulative incidence for a given ring), as an additional source of variance; $\in$ is the error that is assumed to be normally distributed with SD, σ.
GLMM, generalised linear mixed model.

differences in confounders rather than the intervention effect. This may be erroneously attributed to the intervention effect if unmeasured. Propensity score matching will be used to match the rings on a probability of the ring receiving the intervention conditioned on a set of confounders.[61] The set of confounders will include variables that are assumed to be strongly associated with the outcome or exposure (cumulative incidence in the ring and the delay to CATI response, respectively), including incidence prior to implementation (severity; as explored by Michel *et al*),[32] distance to site, population density, and prior OCV coverage (see data collection section above for a full set of confounders).[62] The generalised propensity score can be calculated by linear regression with the delay to response as the independent variable and the confounders as the covariates.[63] Rings will be grouped into a set of ≥5 strata. Balance between confounders among strata will be checked (eg, standardised mean difference >0.1 marking imbalance). A GLMM will be used to calculate the unbiased average treatment effect within each strata and the main unbiased estimator across weighted strata. Missing data will not be imputed for the analysis.

As the study takes place during an epidemic, its natural progression is difficult to predict and the sample size may fall short of the power requirements. Post hoc analytical techniques to address power for cRCTs can be applied, including pairwise matching on ring variables or changing the unit of analysis from rings to households.[64] A secondary analysis of the effect of CATI on reducing the spatiotemporal clustering of cases will be done. The tau statistic can be used to measure the relative risk (RR), compared with a reference value, of observing cases in a spatio-temporal window compared with a situation where the co-occurrence of cases is independent in space and time (using varying space-time windows from 15 to 250 m from primary cases and 1–7 days).[21 65 66] Finally, providing the intervention package remains relatively homogeneous between sites, a pooled analysis of rings across sites where CATI is used in DRC or other countries would increase the sample size.

Other analyses (objectives 3–7)

For the household coverage substudy (objective 3), mean coverage of CATI, its component interventions, and reasons for refusal or a missed CATI will be estimated with 95% CIs, accounting for the clustered design. Mean individual single-dose vaccination coverage and 95% CIs will be estimated for all persons. RRs for coverage by age and sex and 95% CIs will be estimated with a generalised linear model with a logarithmic link function. For the household transmission substudy (objective 4), the incidence of infection (asymptomatic and symptomatic) and 95% CIs will be calculated. A multivariate logistic regression using generalised estimating equations of predictors (eg, demographics, household characteristics, household size, delay from the primary case's symptoms onset to CATI implementation) of the incidence will be conducted, adjusting for household clustering. For the AMR substudy (Objective 5), the change in prevalence of carriers of azithromycin-resistant *Enterobacteriaceae* will be estimated for days 0, 7 and 30.[67 68] χ^2 or Fisher's exact tests will be used to compare prevalence between time points. For the analysis of surveillance trends (objective 6), the spatiotemporal diffusion of the epidemic will be described using time-trends and measurement of local and global case clustering through spatiotemporal scan statistics and tau statistics, respectively.[21 65] Direct and indirect costs will be analysed and prorated for the intervention period to derive cost-efficiency estimates (objective 7).[69]

Anticipated challenges and measurement biases

The study will be conducted in a very challenging context—cholera-affected areas of urban or rural and remote areas—where insecurity, poor road access, the rainy season and logistical issues with moving supplies are major concerns.[70] The level of community acceptance of the intervention is dependent on relationships between the community and implementers including MSF and the MOH. Some level of mistrust of government and partners regarding outbreak response are anticipated.[71–73] Given that CATI is limited to a small group of communities, similar to Ebola ring vaccination, this delivery approach may not always be an acceptable proposition to a community.[74] These challenges can be countered, to some extent, through preconsultation with communities. That MSF has a long history of collaboration with these MoHs and communities throughout historical cholera outbreaks is a strength in terms of community trust. Finally, CATI does not attempt to improve water supply or contamination at the community level (as compared with CATI approaches in Kinshasa where water was brought to the community).[31] Therefore, environment-to-human transmission via contaminated community water sources are not fully addressed in this model, and therefore, cannot be evaluated under this protocol. We do note that most likely in the context of outbreak, the initial primary infection from a water source is followed by extensive secondary person-to-person, faecal-oral transmission.[75]

Evaluating a complex intervention with multiple interacting components will be demanding. A holistic approach to understanding the pathway to impact through interrogation of multiple substudies (eg, importance of household vs neighbourhood and community transmission) has been included in the study. The coverage survey is a means of collecting information on the retention and uptake of interventions as well as uptake of vaccination which are needed to demonstrate a lasting and meaningful protective effect of CATI. To better complete the policy picture of implementing CATI (including OCV), the fidelity to implementation is captured through indicators reflecting process and community acceptance (via measuring refusal of interventions in the coverage survey), and by documenting direct and indirect costs.

Patient and public involvement

Before implementing CATI and the study, village leaders will be consulted to seek approval for the study. Implementation of any intervention and evaluation during an outbreak are critically dependent on developing a mutual understanding of objectives for control of the outbreak between citizens, community leaders and the response teams. MSF will hold community meetings including a discussion of the aims of CATI and the study, risks and benefits and needs to avoid stigmatisation of primary cases and their households.[76] The MSF health and hygiene promotion team supporting CATI will monitor community perceptions of the study over time and adjust the engagement strategy as needed.

ETHICS AND DISSEMINATION

This study has been designed to address evidence gaps in CATI's effectiveness. The study findings will be disseminated through networks of cholera control actors and the Ministries of Health in cholera-affected countries and the GTFCC.[14 34] The results will aid with the design of effective CATI strategies and their integration into national cholera preparedness and response plans and will provide evidence-based advocacy to fund and preposition CATI materials during the cholera season. At both a national and global level, we have presented the protocol to disease control programmes (eg, the DRC Programme National d'Elimination du Choléra et de Lutte contre les Maladies Diarrhéiques (PNECHOL-MD) and at GTFCC Working Groups). The study team will work with the MOH, local MSF, other nongovernmental organisations and affected communities to share the findings. This will include translating the science and communicating the findings with local communities via community meetings and posters in health facilities. We will communicate to the scientific and practitioner community using journal articles and policy briefs.

The ethics review boards of MSF and LSHTM have approved the generic protocol (MSF Protocol no 2074, LSHTM Protocol no 22976), a DRC-specific version of the protocol (MSF Protocol no 2074a, LSHTM Protocol no 22976-1). The DRC-specific protocol was approved by the MOH's ethics review board (Comité National d'Éthique de la Santé, Protocol no 249) and administrative approval was granted by the PNECHOL-MD and the Programme Élargi de Vaccination (PEV/EPI, Extended Programme of Immunisation). Approvals are being sought from provincial and local health authorities in high risk areas. In DRC, verbal approval for all data collection activities will be sought from village or neighbourhood leaders. Verbal informed consent for the primary case data, household and AMR substudies and household coverage substudy will be sought from adults (≥18 years) and parents or guardians of minors. Minors 8—17 years will be asked for verbal assent. Verbal rather than written informed consent is preferred given (1) the potential for the population in remote cholera-affected areas to have limited literacy and the compounded problem of finding a literate witnesses, (2) the collection of this data and stool samples are not considered to be invasive procedures and (3) the context of a fast-moving epidemic necessitating rapid data collection. For Cameroon, Zimbabwe and Niger, study protocols and informed consent procedures are being submitted for ethical review by the respective national, MSF and LSHTM ethics committees and for approval by health authorities.

Author affiliations
[1]Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
[2]Epicentre, Paris, France
[3]Médecins Sans Frontières, Geneva, Switzerland
[4]Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA
[5]Medecins Sans Frontieres, Kinshasa and Goma, Congo
[6]Programme National d'Elimination du Choléra et de lutte contre les autres Maladies Diarrhéiques, Kinshasa, Congo (the Democratic Republic of the)
[7]Programme Élargie de Vaccination, Kinshasa, Congo (the Democratic Republic of the)
[8]Institut National de Recherche Biologique, Kinshasa, Congo (the Democratic Republic of the)
[9]Epicentre, Yaoundé, Cameroon
[10]GAVI the Vaccine Alliance, Geneva, Switzerland

Twitter Ruwan Ratnayake @ruwanepi

Collaborators Epicentre and MSF CATI Working Group : Médecins Sans Frontières (MSF), Spain: Miriam Alia. Epicentre, Niger: Bachir Assao, Abdoul-Moumouni Issa-Soumana, Oumar Touré. Médecins Sans Frontières (MSF), Belgium: Catherine Bachy, Rob D'hondt, Isabella Panunzi. London School of Hygiene & Tropical Medicine (LSHTM): Lauren D'Mello-Guyett. Epicentre, Cameroon: Karl Njuwa Fai, Rodrigue Ntone. Médecins Sans Frontières (MSF), Switzerland: Caroline Henry-Ostian. Médecins Sans Frontières (MSF), Zimbabwe: Danish Malik, Herbert Mutubuki. Epicentre, France: Issaka Soumana, Mamady Traore.

Contributors RR, FF, FL, FC, JE, NP, IC, EG, ML, ASA, PG, PO, JAS, RN, NM, AA and KP conceived of and led the design of the study. RR and FF led the writing of the protocol and the article. RN and AA provided specific advice on laboratory methods. The CATI and MSF Working Group contributed to the design of the study. All other authors (including PO, EMM, BM, YBII) and all working group members (MA, BA, CB, RdH, LDG, KNF, CH, AI, DM, HB, RN, IP, IS, OT, MT) contributed to the design of the study. All authors and working group members revised the draft and approved the final manuscript. RR and FF are the guarantors of the overall content of the protocol and the article. RR, FF, EG, ML, NM,and YBII will lead the planning of the study and will oversee study implementation and data acquisition. RR and FF will lead the statistical analysis and interpretation, and the reporting of the results.

Funding This research is internally funded by Médecins Sans Frontières and therefore received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. RR is funded by a Doctoral Foreign Study Award from the Canadian Institutes of Health Research (award number DFS-164266). FC and WJE are funded by UK Research and Innovation as part of the Global Challenges Research Fund (grant number ES/P010873/1).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Ruwan Ratnayake http://orcid.org/0000-0003-4978-6668
Etienne Gignoux http://orcid.org/0000-0003-3930-2770

REFERENCES

1 WHO. Cholera, 2019. *Weekly Epidemiologic Record* 2020;37:441–8.
2 WHO. Cholera. *Weekly Epidemiological Record* 20202021;96:445–54.
3 WHO Regional Office for Africa. *Weekly Bulletin on Outbreaks and Other Emergencies (Week 34: 16 - 22 August 2021*, 2021.
4 Connolly MA, Gayer M, Ryan MJ, *et al*. Communicable diseases in complex emergencies: impact and challenges. *Lancet* 2004;364:1974–83.
5 Shannon K, Hast M, Azman AS, *et al*. Cholera prevention and control in refugee settings: successes and continued challenges. *PLoS Negl Trop Dis* 2019;13:e0007347.
6 Kanungo S, Azman AS, Ramamurthy T, *et al*. Cholera. *The Lancet* 2022;399:1429–40.
7 Centers for Disease Control and Prevention (CDC). Cholera outbreak among Rwandan refugees--Democratic Republic of Congo, April 1997. *MMWR Morb Mortal Wkly Rep* 1998;47:389–91.
8 Centers for Disease Control and Prevention (CDC). Update: cholera outbreak --- Haiti, 2010. *MMWR Morb Mortal Wkly Rep* 2010;59:1473–9.
9 Abubakar A, Azman AS, Rumunu J, *et al*. The first use of the global oral cholera vaccine emergency stockpile: lessons from South Sudan. *PLoS Med* 2015;12:e1001901.
10 Kapata N, Sinyange N, Mazaba ML, *et al*. A Multisectoral emergency response approach to a cholera outbreak in Zambia: October 2017-February 2018. *J Infect Dis* 2018;218:S181–3.
11 Ngwa MC, Wondimagegnehu A, Okudo I, *et al*. The multi-sectorial emergency response to a cholera outbreak in internally displaced persons camps in Borno state, Nigeria, 2017. *BMJ Glob Health* 2020;5:e002000.
12 D'Mello-Guyett L, Cumming O, Bonneville S, *et al*. Effectiveness of hygiene kit distribution to reduce cholera transmission in Kasaï-Oriental, Democratic Republic of Congo, 2018: a prospective cohort study. *BMJ Open* 2021;11:e050943.
13 Finger F, Bertuzzo E, Luquero FJ, *et al*. The potential impact of case-area targeted interventions in response to cholera outbreaks: a modeling study. *PLoS Med* 2018;15:e1002509.
14 Ratnayake R, Finger F, Azman AS, *et al*. Highly targeted spatiotemporal interventions against cholera epidemics, 2000-19: a scoping review. *Lancet Infect Dis* 2021;21:e37–48.
15 Mwaba J, Ferreras E, Chizema-Kawesa E, *et al*. Evaluation of the SD Bioline cholera rapid diagnostic test during the 2016 cholera outbreak in Lusaka, Zambia. *Trop Med Int Health* 2018;23:834–40.
16 Ontweka LN, Deng LO, Rauzier J, *et al*. Cholera rapid test with enrichment step has diagnostic performance equivalent to culture. *PLoS One* 2016;11:e0168257.
17 Bi Q, Ferreras E, Pezzoli L, *et al*. Protection against cholera from killed whole-cell oral cholera vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2017;17:1080–8.
18 Qadri F, Wierzba TF, Ali M, *et al*. Efficacy of a single-dose, inactivated oral cholera vaccine in Bangladesh. *N Engl J Med* 2016;374:1723–32.
19 Azman AS, Parker LA, Rumunu J, *et al*. Effectiveness of one dose of oral cholera vaccine in response to an outbreak: a case-cohort study. *Lancet Glob Health* 2016;4:e856–63.
20 Ferreras E, Chizema-Kawesha E, Blake A, *et al*. Single-Dose cholera vaccine in response to an outbreak in Zambia. *N Engl J Med* 2018;378:577–9.
21 Azman AS, Luquero FJ, Salje H, *et al*. Micro-Hotspots of risk in urban cholera epidemics. *J Infect Dis* 2018;218:1164–8.
22 Debes AK, Ali M, Azman AS, *et al*. Cholera cases cluster in time and space in Matlab, Bangladesh: implications for targeted preventive interventions. *Int J Epidemiol* 2016;45:2134-2139.
23 Ali M, Debes AK, Luquero FJ, *et al*. Potential for controlling cholera using a ring vaccination strategy: Re-analysis of data from a cluster-randomized clinical trial. *PLoS Med* 2016;13:e1002120.
24 Ramos M. *Global Review of Water, Sanitation and Hygiene (WASH) Components in Rapid Response Mechanisms and Rapid Response Teams in Cholera Outbreak Settings - Haiti, Nigeria, South Sudan and Yemen*. New York, NY, USA: UNICEF, 2019.
25 Rebaudet S, Bulit G, Gaudart J, *et al*. The case-area targeted rapid response strategy to control cholera in Haiti: a four-year implementation study. *PLoS Negl Trop Dis* 2019;13:e0007263.
26 Sikder M, Altare C, Doocy S, *et al*. Case-area targeted preventive interventions to interrupt cholera transmission: current implementation practices and lessons learned. *PLoS Negl Trop Dis* 2021;15:e0010042.
27 Parker LA, Rumunu J, Jamet C, *et al*. Neighborhood-targeted and case-triggered use of a single dose of oral cholera vaccine in an urban setting: feasibility and vaccine coverage. *PLoS Negl Trop Dis* 2017;11:e0005652.
28 Ouamba JP, Peyraud N, Mbarga NF. *Case-area targeted interventions for cholera control: experience from tail of cholera outbreak in Kribi, Cameroon. MSF scientific days*. London, UK, 2021.
29 George CM, Monira S, Sack DA, *et al*. Randomized controlled trial of hospital-based hygiene and water treatment intervention (CHoBI7) to reduce cholera. *Emerg Infect Dis* 2016;22:233–41.
30 Guévart E, Noeske J, Sollé J, *et al*. [Large-scale selective antibiotic prophylaxis during the 2004 cholera outbreak in Douala (Cameroon)]. *Sante* 2007;17:63–8.
31 Bompangue D, Moore S, Taty N, *et al*. Description of the targeted water supply and hygiene response strategy implemented during the cholera outbreak of 2017-2018 in Kinshasa, DRC. *BMC Infect Dis* 2020;20:226.
32 Michel E, Gaudart J, Beaulieu S, *et al*. Estimating effectiveness of case-area targeted response interventions against cholera in Haiti. *Elife* 2019;8:e50243.
33 Roskosky M, Acharya B, Shakya G, *et al*. Feasibility of a comprehensive targeted cholera intervention in the Kathmandu Valley, Nepal. *Am J Trop Med Hyg* 2019;100:1088–97.
34 Global Task Force for Cholera Control. *Cholera roadmap: research agenda*. Geneva, Switzerland: WHO, 2021.
35 WHO. Cholera vaccines: who position paper – August 2017. *Wkly Epidemiol Rec* 2017;92:477–98.
36 Ebola ça Suffit Ring Vaccination Trial Consortium. The ring vaccination trial: a novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola. *BMJ* 2015;351:h3740.
37 Ager A, Burnham G, Checchi F, *et al*. Strengthening the evidence base for health programming in humanitarian crises. *Science* 2014;345:1290–2.
38 Falb K, Laird B, Ratnayake R, *et al*. The ethical Contours of research in crisis settings: five practical considerations for academic institutional review boards and researchers. *Disasters* 2019;43:711–26.
39 Ratnayake R, Finger F, Edmunds WJ, *et al*. Early detection of cholera epidemics to support control in fragile states: estimation of delays and potential epidemic sizes. *BMC Med* 2020;18:397.
40 Azman AS, Rudolph KE, Cummings DAT, *et al*. The incubation period of cholera: a systematic review. *J Infect* 2013;66:432–8.
41 Global Task Force for Cholera Control. Antimicrobial susceptibility testing for treatment and control of cholera, 2021. Available: https://www.gtfcc.org/wp-content/uploads/2021/04/gtfcc-job-aid-antimicrobial-susceptibility-testing-for-treatment-and-control-of-cholera.pdf
42 Global Task Force for Cholera Control. *Guidance and tool for countries to identify priority areas for intervention*, 2021.
43 Ingelbeen B, Hendrickx D, Miwanda B, *et al*. Recurrent cholera outbreaks, Democratic Republic of the Congo, 2008-2017. *Emerg Infect Dis* 2019;25:856–64.
44 Ratnayake R, Finger F. *Évaluation Du Risque d'épidémie de choléra en République démocratique Du Congo, 2021-2022*. Paris, France: Epicentre, 2021.
45 Plan MD, Congo RDD. Multisectoriel d'Elimination Du Choléra En République Démocratique Du Congo 2018–2022, 2020. Available: https://www.plateformecholera.info/attachments/article/554/PMSEC%202018_2022_30032018.pdf
46 Debes AK, Ateudjieu J, Guenou E, *et al*. Clinical and environmental surveillance for Vibrio cholerae in resource constrained areas: application during a 1-year surveillance in the far North region of Cameroon. *Am J Trop Med Hyg* 2016;94:537–43.
47 Halloran ME, Auranen K, Baird S, *et al*. Simulations for designing and interpreting intervention trials in infectious diseases. *BMC Med* 2017;15:223.

48 Ratnayake R, Checchi F, Jarvis CI, *et al*. Inference is bliss: simulation for power estimation for an observational study of a cholera outbreak intervention. *PLoS Negl Trop Dis* 2022;16:e0010163.
49 Ratnayake R, Tammaro M, Tiffany A, *et al*. People-centred surveillance: a narrative review of community-based surveillance among crisis-affected populations. *Lancet Planet Health* 2020;4:e483–95.
50 Tatem AJ. WorldPop, open data for spatial demography. *Sci Data* 2017;4:170004.
51 Funk C, Peterson P, Landsfeld M, *et al*. The climate hazards infrared precipitation with stations--a new environmental record for monitoring extremes. *Sci Data* 2015;2:150066.
52 ClimateSERV. *Climate hazards group IR precipitation with stations (chirps*, 2021. https://climateserv.servirglobal.net
53 WHO/UNICEF. *Joint monitoring programme (JMP) for water supply, sanitation and hygiene*. 4th ed.. Geneva: WHO/UNICEF, 2017.
54 WHO. *Guidelines for drinking water quality*. 4th ed. Geneva, Switzerland, 2017: 631.
55 Médecins Sans Frontières. *Management of a cholera epidemic: practical guide for doctors, nurses, laboratory technicians, medical auxiliaries, water and sanitation specialists and logisticians*. 2018 Edition. ed. Paris, France, 2018.
56 Weil AA, Begum Y, Chowdhury F, *et al*. Bacterial shedding in household contacts of cholera patients in Dhaka, Bangladesh. *Am J Trop Med Hyg* 2014;91:738–42.
57 Global Task Force for Cholera Control. Specimen packaging and domestic transportation for laboratory confirmation of Vibrio cholerae O1/O139, 2019. Available: https://www.gtfcc.org/wp-content/uploads/2020/09/gtfcc-job-aid-specimen-packaging-domestic-transportation-for-laboratory-confirmation-of-vibrio-cholerae.pdf
58 Page A-L, Alberti KP, Guénolé A, *et al*. Use of filter paper as a transport medium for laboratory diagnosis of cholera under field conditions. *J Clin Microbiol* 2011;49:3021–3.
59 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
60 Berridge DM, Crouchley R. *Multivariate generalized linear mixed models using R*. Boca Raton, FL: CRC Press, 2011.
61 Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399–424.
62 Brookhart MA, Schneeweiss S, Rothman KJ, *et al*. Variable selection for propensity score models. *Am J Epidemiol* 2006;163:1149–56.
63 Zhao S, van Dyk DA, Imai K. Propensity score-based methods for causal inference in observational studies with non-binary treatments. *Stat Methods Med Res* 2020;29:709–27.
64 Leyrat C, Morgan KE, Leurent B, *et al*. Cluster randomized trials with a small number of clusters: which analyses should be used? *Int J Epidemiol* 2018;47:321–31.
65 Lessler J, Salje H, Grabowski MK, *et al*. Measuring spatial dependence for infectious disease epidemiology. *PLoS One* 2016;11:e0155249.
66 Pollington TM, Tildesley MJ, Hollingsworth TD, *et al*. Developments in statistical inference when assessing spatiotemporal disease clustering with the tau statistic. *Spat Stat* 2021;42:100438.
67 Liu H, Wu T. Sample size calculation and power analysis of time-averaged difference. *Journal of Modern Applied Statistical Methods* 2005;4:434–45.
68 Hanley JA, Negassa A, Edwardes MDdeB, *et al*. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol* 2003;157:364–75.
69 Tulloch C. Taking intervention costs seriously: a new, old toolbox for inference about costs. *J Dev Effect* 2019;11:273–87.
70 Gallandat K, Jeandron A, Ross I, *et al*. The impact of improved water supply on cholera and diarrhoeal diseases in Uvira, Democratic Republic of the Congo: a protocol for a pragmatic stepped-wedge cluster randomised trial and economic evaluation. *Trials* 2021;22:408.
71 Mobula LM, Samaha H, Yao M, *et al*. Recommendations for the COVID-19 response at the National level based on lessons learned from the Ebola virus disease outbreak in the Democratic Republic of the Congo. *Am J Trop Med Hyg* 2020;103:12–17.
72 Vinck P, Pham PN, Bindu KK, *et al*. Institutional trust and misinformation in the response to the 2018-19 Ebola outbreak in North Kivu, DR Congo: a population-based survey. *Lancet Infect Dis* 2019;19:529–36.
73 Amani A, Fouda AAB, Nangmo AJ, *et al*. Reactive mass vaccination campaign against cholera in the COVID-19 context in Cameroon: challenges, best practices and lessons learned. *Pan Afr Med J* 2021;38:392.
74 Bausch DG. The need for a new strategy for Ebola vaccination. *Nat Med* 2021;27:580–1.
75 Miller CJ, Feachem RG, Drasar BS. Cholera epidemiology in developed and developing countries: new thoughts on transmission, seasonality, and control. *Lancet* 1985;1:261–2.
76 Médecins Sans Frontières. *Involving communities: guidance document for approaching and cooperating with communities*, 2013.
77 Fewtrell L, Kaufmann RB, Kay D, *et al*. Water, sanitation, and hygiene interventions to reduce diarrhoea in less developed countries: a systematic review and meta-analysis. *Lancet Infect Dis* 2005;5:42–52.
78 Roberts L, Chartier Y, Chartier O, *et al*. Keeping clean water clean in a Malawi refugee cAMP: a randomized intervention trial. *Bull World Health Organ* 2001;79:280–7.
79 Reveiz L, Chapman E, Ramon-Pardo P, *et al*. Chemoprophylaxis in contacts of patients with cholera: systematic review and meta-analysis. *PLoS One* 2011;6:e27060.
80 Peyriere H, Makinson A, Marchandin H, *et al*. Doxycycline in the management of sexually transmitted infections. *J Antimicrob Chemother* 2018;73:553–63.
81 Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including Glycylcyclines. *J Antimicrob Chemother* 2006;58:256–65.
82 Akhtar M, Qadri F, Bhuiyan TR, *et al*. Kinetics of antibody-secreting cell and fecal IgA responses after oral cholera vaccination in different age groups in a cholera endemic country. *Vaccine* 2017;35:321–8.