Case-Area Targeted Intervention for the Control of Cholera Epidemics in Crises: From Spatial Mathematical Modelling to Field Evaluation

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DECLARATION

Statement of Own Work

I, Ruwan Ratnayake, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, this has been indicated in the thesis. I have read and understood the school's definition of plagiarism and cheating given in the Research Degrees Handbook.

Ruwan Ratnayake

April 2024

ABSTRACT

Cholera transmission is rising globally in 2023, in the most deprived communities in Africa, Asia, the Middle East and in Haiti. Containment strategies for small outbreaks may be an efficient use of currently scarce vaccine doses and water and sanitation interventions usually delivered through mass campaigns. Case area-targeted intervention (CATI) aims to control small outbreaks with multiple interventions in 'rings' of 100–250m around case households. Currently, there is little evidence of CATI's impact and delivery. In this thesis, I used evidence review, spatial analyses and mathematical modelling to investigate CATI's potential impact in containing or reducing cholera transmission during outbreaks.

Using a scoping review, I found moderate evidence that antibiotic chemoprophylaxis, single-dose vaccination, hygiene promotion, and water treatment can rapidly limit transmission in the household and surrounding 100m radius for 7 days following case presentation. To investigate whether CATI can be implemented within 7 days in fragile settings where cholera emerges, I conducted a statistical review of milestones in 76 cholera outbreaks in 34 countries. Median delay to outbreak detection and response were 5 and 10 days, respectively, revealing an opportunity for CATI. Localized event-based surveillance, rapid diagnostic testing, and integration of alert and response functions among local teams were qualitatively linked to early detection and response.

Next, I analysed the spatiotemporal clustering of cholera in Uvira, Democratic Republic of Congo, where it is endemic. This suggested a 1000m zone of infection risk around a case within 5 days of presentation, and the timing and locations of 26 recurring clusters. To quantify CATI's potential control in the first 60 days of an outbreak, I developed a spatially explicit dynamic model driven by a spatial force of infection around new cases. This showed that prompt implementation of CATI with vaccination, antibiotics, and water treatment in a 150m radius around new cases is potentially effective in containing cholera within the first 60 days of an outbreak and requires <6% of the population that would have been addressed in a mass campaign.

Overall, this thesis demonstrates the potential speed and impact of CATI, when vaccination is included, on containing cholera outbreaks in their earliest phase. While CATI is inherently reactive and cannot achieve long-lasting protection for a larger population, it may be able to contain outbreaks with fewer resources in order to reduce cases and strain on case management. In an era of vaccine scarcity, this thesis provides rationale to procure small vaccine stocks (and other interventions) for district-level activation of CATI. This work has also informed the development of a now-concluded observational study to measure CATI's impact.

ACKNOWLEDGEMENTS

I am grateful to the Canadian Institutes of Health Research not only for making my PhD financially feasible, but also for seeing the promise of this research on an ancient disease that remains devastating for a large proportion of the population.

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TABLE OF ABBREVIATIONS

ACP	Antibiotic chemoprophylaxis
AIC	Akaike information criterion
AMR	Antimicrobial resistance
AWD	Acute watery diarrhoea
CATI	Case-area targeted intervention(s)
CHW	Community health worker
CTC	Cholera treatment centre
CTU	Cholera treatment unit
DEWS	Disease Early Warning System
DRC	Democratic Republic of the Congo
EWARS	Early Warning Alert and Response System
FCAS	Fragile and conflict-affected state
GAM	Generalised additive model
GEE	Generalised estimating equations
GLMM	Generalised linear mixed model
GTFCC	Global Task Force for Cholera Control
kOCV	Killed oral cholera vaccine
LOESS	Locally estimated scatterplot smoothing
MOH	Ministry of Health
MSF	Médecins Sans Frontières
NGO	Non-governmental organization
OCV	Oral cholera vaccination
ORP	Oral rehydration point
ORS	Oral rehydration solution
PCR	Polymerase chain reaction
PNECHOL-MD	Programme National d'Élimination du Choléra et de Lutte contre les Maladies Diarrhéiques
POUWT	Point of use water treatment
RDT	Rapid diagnostic test
RE	Effective reproduction number
R0	Basic reproduction number
RR	Relative risk
SDG	Sustainable Development Goal
SEIR	Susceptible, exposed, infected, recovered model
UNICEF	United Nations Children's Fund
WASH	Water, sanitation, and hygiene
WHO	World Health Organisation

SUMMARY OF THE THESIS

CHOLERA CONTINUES TO FLARE IN AFRICA, ASIA, MIDDLE EAST AND HAITI

Cholera is an ancient disease which, despite the available methods of prevention and control, persists as a major public health issue primarily affecting the most deprived communities in Africa, Asia, the Middle East and in Haiti. While it has been eliminated in North America and Europe after the widespread installation of piped water and sewage systems, the lack of these advancements globally means that 126 million persons live in hotspots where cholera recurs. Conflict, disaster, and displacement continue to amplify the risks of explosive cholera outbreaks.

DETECTION OF SMALL CHOLERA OUTBREAKS PROVIDE OPPORTUNITIES FOR RAPID CONTROL

In the 2010s, a global commitment to improving water, sanitation, and hygiene infrastructure, well-practised multisector cholera control and a novel vaccine together made inroads to reducing cholera morbidity and mortality. Currently, improvements in the delivery of vaccines and other interventions to communities most at-risk hold promise for reducing the risk of large epidemics that become difficult to control. Case-area targeted intervention (CATI) with vaccination remains one such untested strategy.

WHAT IS IN THIS THESIS?

In this thesis, I explore the potential impact of CATI on the rapid containment of cholera outbreaks. I conducted a scoping review of CATI and its interventions (vaccines, antibiotic chemoprophylaxis, and water treatment), a statistical review of the timeliness of outbreak detection and response in fragile settings and estimation of the impact of early detection, modelling of the spatiotemporal risk of infection in a cholera hotspot (Uvira, Democratic Republic of the Congo), and spatially-explicit mathematical modelling to investigate the potential impact of CATI on the containment of outbreaks. In parallel, I used the findings from these studies to inform the development of a prospective observational study of CATI with vaccination in the Democratic Republic of the Congo and Cameroon (please see Appendix D and E as this does not form the core of this thesis).

LIST OF PUBLICATIONS AND PRESENTATIONS

PUBLICATIONS AND MANUSCRIPTS SUPPORTING THIS THESIS

1. Ratnayake R, Finger F, Azman AS, Lantagne D, Funk S, Edmunds WJ, Checchi F. **Highly targeted spatiotemporal interventions against cholera epidemics, 2000-19: a scoping review.** The Lancet Infectious Diseases. 2021;21(3):e37-e48.

2. Ratnayake R, Finger F, Edmunds WJ, Checchi F. **Early detection of cholera epidemics to support control in fragile states: estimation of delays and potential epidemic sizes.** BMC Medicine. 2020;18(1):397.

3. Ratnayake R, Knee J, Cumming O, Mufitini Saidi J, Bashige Rumedeka B, Finger F, Azman AS, Edmunds WJ, Checchi F, Gallandat G. **Spatiotemporal modelling of cholera and implications for its control, Uvira, Democratic Republic of the Congo.**

   Submitted to Emerging Infectious Diseases. Preprint available through medRxiv 2023.08.22.23294124.

4. Ratnayake R, Funk S, Gallandat K, Knee J, Cumming O, Mufitini Saidi J, Bashige Rumedeka B, Finger F, Brady O, Edmunds WJ, Checchi F. **Case-area targeted intervention with vaccination to rapidly control cholera outbreaks: a spatial modelling study.**

   Draft paper prepared for submission.

PUBLICATIONS SUPPORTING BUT NOT CORE TO THE THESIS

1. Ratnayake R, Checchi F, Jarvis CI, Edmunds WJ, Finger F. **Inference is bliss: Simulation for power estimation for an observational study of a cholera outbreak intervention.** PLoS Neglected Tropical Diseases. 2022;16(2):e0010163.

2. Ratnayake R, Peyraud N, Ciglenecki I, Gignoux E, Lightowler M, Azman AS, 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(7):e061206.

3. Ouamba JP, Mbarga NF, Ciglenecki I, Ratnayake R, Tchiasso D, Finger F, et al. **Implementation of targeted cholera response activities, Cameroon.** Bulletin of the World Health Organization. 2023;101(3):170-178.

4. Ratnayake R, Tammaro M, Tiffany A, Kongelf A, Polonsky JA, McClelland A. **People-centred surveillance: a narrative review of community-based surveillance among crisis-affected populations.** The Lancet Planetary Health. 2020; 4(10): 483-495.

PRESENTATIONS

I made the following presentations at conferences and scientific forums:

1. **Highly-targeted spatiotemporal interventions against cholera epidemics, 2000-2018 (poster).** Epidemics7: International Conference on Infectious Disease Dynamics, Charleston, SC, USA, Oct. 2019.

2. **Early detection of cholera epidemics to support control in fragile states: estimation of delays and potential epidemic sizes (oral).**
   European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE), online, Nov. 2020

   UNICEF's Integrated Outbreaks Analytics seminar, Sept. 2022

3. **Inference is bliss: simulation for power estimation of a cholera outbreak intervention study (poster).** Epidemics8: International Conference on Infectious Disease Dynamics, online, Oct. 2021.

4. **Effectiveness of case-area targeted interventions including vaccination on the control of epidemic cholera: protocol for an observational study (oral).**
   Global Task Force for Cholera Control: WASH, OCV, case management working groups

   Médecins Sans Frontières, throughout 2020

   Canadian Conference on Global Health (poster), Toronto, ON, Canada, Nov. 2022

   Consultation with the Ministry of Health of Cameroon, Yaoundé, Cameroon, Apr. 2023.

5. **Case-area targeted interventions (CATI) to rapidly contain the spread of cholera: updates from the study in the Democratic Republic of the Congo (oral).**
   Global WASH Cluster and Tufts University, online, Apr. 2023

   Global Task Force for Cholera Control, Annual Research Session, Veyrier-du-Lac, France, Jun. 2023.

6. **Spatiotemporal modelling of cholera and its implications for control, Uvira, Democratic Republic of the Congo (oral).**
   Consultation with DRC Ministry of Health on the Uvira Impact Evaluation, Kinshasa, DRC, Jan. 2023

   Accepted to Epidemics9: International Conference on Infectious Disease Dynamics (poster), Bologna, Italy, Dec. 2023.

7. **Case-area targeted interventions (CATI)** in the WHO African Regional Progress towards the Global Roadmap to 2030: New Strategies (oral). Consultation with WHO AFRO Region and Member States, Congo-Brazzaville, Oct, 2023.

Chapter 1: Introduction

1 INTRODUCTION

"The data gathered during the month after the influx of Rwandan refugees into Zaire describe a public health disaster of major proportions. Between 6 and 10% of the refugee population died during the month after arrival in Zaire, a death rate two to three times the highest previously reported rates among refugees in Thailand (1979), Somalia (1980), and Sudan (1985). This high mortality was due almost entirely to the epidemic of diarrhoeal diseases…we estimate that between 58 000 and 80 000 cases of cholera occurred in the first month after the [refugee] influx, giving an attack rate between 7.3% (58 000 cases in 800 000 refugees) and 16.0% (80 000 cases in 500 000 refugees)."

"Mass vaccination would not have altered the course of this cholera epidemic. Of the two newer and potentially effective vaccines available, one requires two doses and does not induce immunity until 7-10 days after the second dose. The other, a single-dose, oral, live vaccine, has not been subjected to testing under field conditions and its use in refugee populations would be questionable. In any event, it is unlikely that the vaccine could have been given rapidly enough to affect the progression of the epidemic. Clearly, by the time vaccine could have been obtained, administered, and provided immunity, the epidemic would have already run its course."

Goma Epidemiology Group, *Public health impact of Rwandan refugee crisis: what happened in Goma, Zaire, in July, 1994?* [1]

This chapter establishes the global burden of cholera, advances in its control and, the rationale for evaluating targeted interventions for its outbreaks that formed this thesis.

1.1. PUBLIC HEALTH BURDEN AND SURVEILLANCE

Cholera is an epidemic-prone disease that presents with severe diarrhoea and dehydration and can be rapidly fatal if rehydration is not provided immediately. [2] It has the potential to cause explosive epidemics of severe and fatal disease among extremely-vulnerable populations, as described above in relation to the 1994 Rwandan refugee crisis in Nord Kivu, Democratic Republic of the Congo (DRC) (then called Zaire). [1] Descriptions of epidemics that are highly suggestive of cholera, exist from both from the times of Hippocrates and in Indian texts, the latter which point to an origin in the Bay of Bengal prior to 1817. [3] Since the 19th century, seven cholera pandemics have unfolded from its origin in South Asia, with the last pandemic beginning in Indonesia in 1961 and persisting for the last 62 years. [4] Elimination in North American and Europe was achieved in the 1900s due to the widespread establishment of water and sanitation

systems which made it difficult for *V. cholerae* to survive in the local environment.[5] Since 1971, the current pandemic has affected Africa in an unprecedented way, and the continent now features endemic cholera transmission hotspots that trigger epidemic-like propagation of cholera to surrounding populations (Figure 1-1).[6,7] The last three decades have seen large cholera epidemics in previously-cholera free countries including in Peru (1991-1992, 1 million suspected cases, 10,000 deaths), DRC (July-August 1994, 50—80,000 suspected cases, 50,000 deaths), Zimbabwe (2008, 100,000 suspected cases, 4400 deaths), Haiti (2010-2011, 820,000 suspected cases, 10,000 deaths), and Yemen (2016-2021, 2.5 million suspected cases, 4,000 deaths).[1,8-11] Throughout this period, the threat of cholera was downplayed due to a lack of reporting from endemic countries (i.e., Ethiopia, India) and global concern over non-cholera diarrhoea among children.[12] In 2015, cholera's annual burden was estimated as 2.9 million cases, 95,000 deaths, and 1.3 billion persons at-risk.[13] Incidence continues to be poorly estimated due to all-cause diarrhoea being pervasive, little reporting of asymptomatic and mild cholera cases, weak specificity of rapid diagnostic testing (RDT), and the continued lack of reporting by some endemic countries.[14,15]

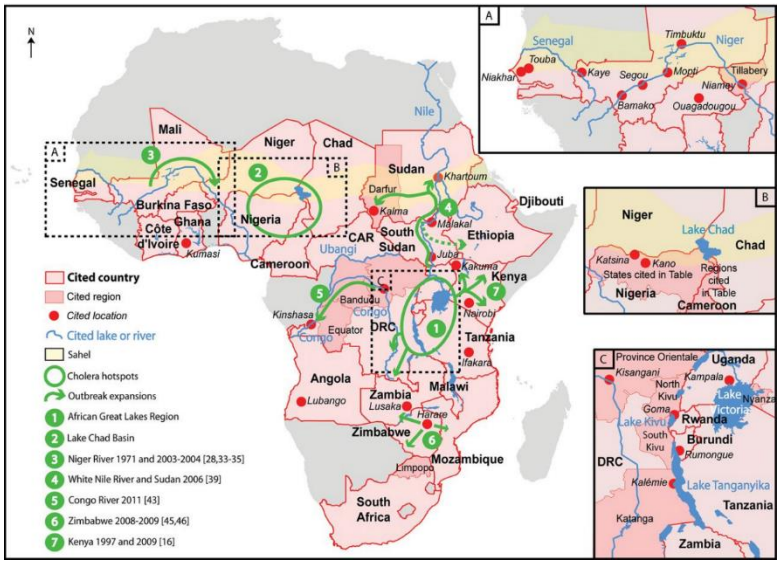

Figure 1-1. "Main cholera hotspots and outbreak expansions. Abbreviations: DRC, Democratic Republic of the Congo; CAR, Central African Republic." (produced in 2013) Source: Rebaudet et al, 2013[6]

Since mid-2022, cholera transmission has been rising globally, and particularly in countries in Africa and the Middle East that have been cholera-free for many years (i.e., Haiti, Lebanon, South Sudan, Syria), and those experiencing flooding and/or drought (i.e., Malawi, Mozambique, Pakistan, Somalia, and Yemen) and conflict-related displacement (DRC) (see Figure 1-2). [16,17] Other hypotheses for increased transmission include an increase in susceptible populations in endemic areas in Africa where vaccination had been used previously, due to the waning of vaccination and the difficulty in applying control measures during the COVID-19 pandemic. [18,19] Some outbreaks have resulted in very high case fatality ratios, indicating challenges in providing access to timely health care for vulnerable populations. [17]

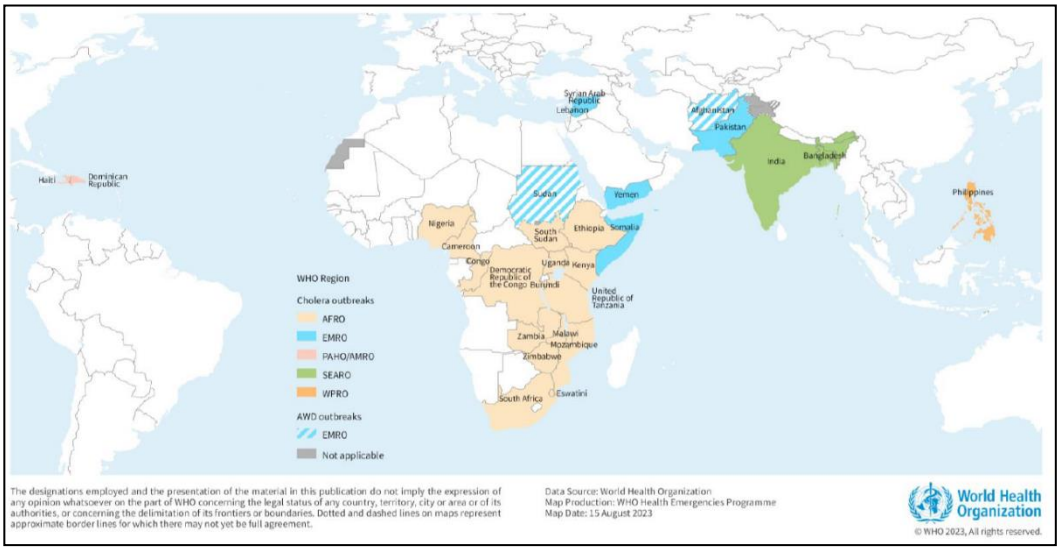

Figure 1-2. "Global situation of epidemics of cholera and acute watery diarrhoea reported in 2023, as of 15 August 2023". Source: WHO, 2023[20].

Cholera is now endemic in at least 47 countries in Africa and Asia, and in Haiti. [13,21] This is widely lauded as a failure of global public health; despite having adequate means of controlling cholera with the establishment of community-wide water and sanitation systems and timely access to health care, countries suffer from the lack of these systems and hence, cholera persists. Moreover, in addition to societal deprivation, large epidemics frequently coincide with humanitarian crises, as exemplified by recurrent outbreaks in the DRC, Somalia, South Sudan, and Yemen (Figure 1-3). [22-25] Humanitarian crises are typified by excess morbidity and mortality during the acute and protracted phases, with three quarters of deaths caused by endemic diarrheal diseases, acute respiratory infection, measles, and malaria. [25] Drivers of the emergence

and persistence of cholera epidemics in crises include inadequate water, sanitation and hygiene (WASH) and health care access, poor surveillance and response, underlying malnutrition, food insecurity, and displacement and overcrowding. [25]

Figure 1-3. A Rapidly-implemented outbreak response during a concurrent cholera outbreak and humanitarian crisis in South Sudan, 2014 (source: author's photo)

1.2. MICROBIOLOGY AND TRANSMISSION OF *VIBRIO CHOLERAE*

Cholera is caused by *Vibrio cholerae*, a gram-negative bacterium found in aquatic environments.[4] *V. cholerae* has over 200 serogroups, of which O1 and O139 cause outbreaks in humans. The O1 serogroup has two biotypes; El Tor currently dominates over the classical biotype. [26] Each biotype is divided into three serotypes (Inaba, Ogawa, and Hikojima). In 1992, the O139 serogroup emerged as a variant of the El Tor biotype through genetic exchange with

environmental bacteria.[4] O139 displaced O1 and efficiently caused epidemics across Asia as populations lacked O139-specific immunity.[4]

Vibrios thrive in coastal and brackish waters and estuaries; these typically coincide with known 'hotspots' for endemic transmission in Africa and Asia, but surprisingly less is known about the permanence of environmental reservoirs of *V. cholerae* in these waters (and what can be done for their elimination).[6,27] Ingestion of vibrios results in colonisation of the small intestine for a short period (12-72 hours) before symptoms appear.[26]

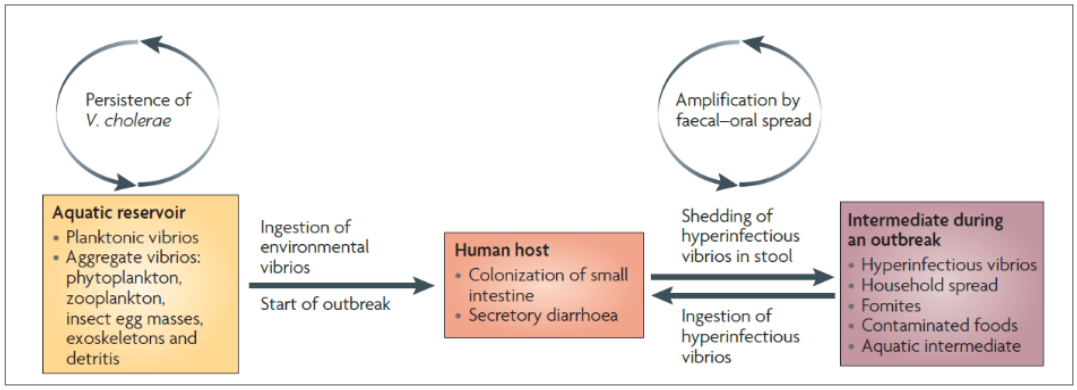

Figure 1-4. **"**Life cycle of pathogenic *V. cholerae*". This figure demonstrates how *V. cholerae can persist in aquatic reservoirs, become ingested by humans at the start of an outbreak, and lead to gut colonization and diarrhoea, shedding of vibrios in stool and ingestion by humans through contaminated drinking water, food, and fomites.* Source: Nelson, 2009, Figure 2.[26]

During an outbreak, transmission routes are hypothesized to change from environmentally mediated sources to intermediate sources in the household (direct transmission) (Figure 1-4).[26] Transmission is rapid; the mean serial interval (i.e., time between symptom onset in successive cases) is 3 to 4 days.[28] The infectious period is 2 to 14 days with the highest transmission coinciding with profuse diarrhoea during the first 2 days.[4,29] Human and animal models together with mathematical modelling suggest that freshly shed stool has a lower infectious dose and a higher capacity for infection.[30,31] Hartley et al theorized that early exponential growth of outbreaks is driven by the shedding of this hyperinfectious stool in close-contact settings (e.g., households).[32] High secondary attack rates may also be a function of critical masses of cases shedding simultaneously, i.e., multiple exposures.[33] It follows that interrupting transmission among contacts in the household and any other close contacts remains critical for outbreak control.

1.3. CHOLERA OUTBREAK CONTROL AND GLOBAL PREVENTION AND CONTROL STRATEGIES

There is consensus that to control cholera outbreaks, practitioners must apply a multisector response integrating case management, WASH, community engagement, surveillance, oral cholera vaccination (OCV) (where appropriate), with coordination of the response, as recommended in two key guidelines produced by WHO's Global Task Force for Cholera Control (GTFCC) and Médecins Sans Frontières (MSF) in the 2000s. [34,35] The objective of multisector response is to go beyond a strictly medical response through cholera treatment centres (which aims to reduce mortality) and to integrate interventions to reduce community transmission. [36] Inadequate preparedness of these sectors and lack of access to treatment in the early phase is thought to have driven transmission and mortality in recent large epidemics in crisis-affected settings (i.e. Angola, Zimbabwe, Haiti and Yemen). [11,22] Building on experience with large epidemics and the identification of hotspots in Asia and Africa, in 2019 the GTFCC revitalized its commitment to reducing the threat of cholera by adopting ambitious goals to eliminate transmission in up to 20 countries and reduce cholera deaths by 90% by 2030. [21,36] Part of this effort has involved support to Ministries of Health to develop national cholera preparedness and response plans, as well as preparedness efforts (i.e., stockpiling supplies and training health workers) to avoid outbreaks escalating out of control. [35]

Figure 1-5. Cholera outbreak response in Haiti, 2011, demonstrating the lack of piped water systems in one of Haiti's largest cities. Source: author's photo.

1.4. CHOLERA CONTROL INTERVENTIONS

In cholera-prone countries, structural interventions (i.e., water and sanitation infrastructure) to prevent infection are difficult to implement at scale at the timeline of an unfolding epidemic. In the following section, I outline the main interventions to control cholera outbreaks, noting that the scoping review in Chapter 2 describes the effectiveness, delivery mechanisms, and uptake of these interventions in detail. It is critical to note that the sanitary revolution that brought widespread piped water and sanitation systems to North America and Europe in the 19th century led to the prevention of cholera in the Global North but has not reached the Global South.[3,5] Progress with the adoption of universal safe water and sanitation remains inadequate with 2 billion persons lacking safe drinking water and 3.6 billion lacking safe sanitation in 2021 (coverage increased from 70 to 74% and 47 to 54% since 2015, respectively (Figure 1-5)).[2,37] Thus, the prevention of exposure to *V. cholerae* in water is critical to breaking its contact with susceptible individuals. WASH interventions aim to reduce contact with faeces and contaminated water, food, fly vectors and fomites.[38] While no cholera-specific estimates are available, Wolf et al estimated that household point of use water treatment (POUWT) via chlorination reduced diarrhoea among children by 66% (95% CI 56—77) (compared to an untreated water source), safe disposal of faeces (without a sewer connection) reduced diarrhoea non-significantly by 79% (95% CI 61—110.3), and water treatment of community water sources (where chlorination is not done on premises) reduced diarrhoea by 81% (95% CI 70—94).[39] Promotion of hygienic behaviour (i.e., handwashing with soap and safe food handling practices) was estimated to reduce diarrhoea by 30% (95% CI 24—36). The challenge is that these practices must be sustained throughout the outbreak and thus require logistical and financial support, hygiene promotion, and positive community uptake to sustain their effects.[40]

Once persons are infected, their isolation in cholera treatment units removes infectious sources from the community, while they receive treatment and rehydration.[2] Antibiotic chemoprophylaxis (ACP, commonly with doxycycline or azithromycin) of household contacts of known cases may prevent onward transmission by 66% (95% CI 34—82).[41] However, it must be given as soon as possible. The GTFCC does not recommend ACP in community settings due to a lack of evidence of the effectiveness of currently used antibiotics and concerns about antimicrobial resistance.

Cholera surveillance is also a core intervention given that detection of suspected cases and deaths across the community is key to detecting and responding to the outbreak, monitoring its propagation, its eventual end, and more broadly, verifying elimination status for a country. It is integrated across routine health facility surveillance, and community-based surveillance and immediate, event-based surveillance for immediate detection and reporting of suspected outbreaks.[42] The suspected case definition in areas without a current outbreak is challenging as it lacks specific symptoms and is of low-specificity: *any person aged two years and older with acute watery diarrhoea and: - severe dehydration or - dying from acute watery diarrhoea with no other specific cause attributed to this death*.[42] Community deaths are routinely missed, as cholera may occur in areas where baseline mortality is high, and access to care is poor. Mortality in health facilities is commonly tracked but does not represent potential deaths in the community.[43] Improvements in the use and dissemination of enriched RDTs hold promise for local ascertainment of alerts which can trigger investigation.[44]

1.4.1. CHOLERA DISEASE MANAGEMENT WITHIN THE TREATMENT UNIT

Oral rehydration solution (ORS) and antibiotics, when accessible, should reduce case fatality to zero.[12] ORS, an electrolyte solution delivered by mouth and not intravenously, works to replenish lost fluids, and was first used during the Bangladeshi War of Independence in 1971 among refugees in West Bengal, India.[45] The poor management of rehydration of Rwandan refugees during the explosive cholera outbreak in 1994 was another turning point which indicated a lack of understanding of rehydration among health actors.[1] Oral antibiotics were introduced as a complement to rehydration in the 1960s and 1970s and can reduce the duration of diarrhoea and shedding.[46,47]

1.4.2. VACCINATION FOR REACTIVE CONTROL OF CHOLERA OUTBREAKS

Oral cholera vaccination (OCV) has recently been established as a key intervention for both prevention and control to offer medium-term protection against infection.[48] Its mechanism of action is the reduction of susceptibility of individuals, risk of infection, and the infectiousness of vaccinated individuals who are infected.[49] The development of live attenuated vaccines against cholera dates back to the 1970s, but the first killed OCV (kOCV) whole cell monovalent (O1) vaccine with a recombinant B subunit of cholera toxin (Dukoral) was prequalified by WHO in 2001.[50] It was used in 1997 for the mass vaccination of South Sudanese refugees in Uganda with high coverage, but its use is in general logistically complicated as it requires a buffer and

water for administration.[51] Two biologically identical killed whole-cell bivalent (O1 and O139) OCVs, Shanchol and Euvichol, were prequalified by WHO in 2001 and 2015 respectively.[48] An identical precursor, mORC-Vax, is licensed in Vietnam only.[52] These three kOCVs do not have a B subunit and thus do not require a buffer and water for administration. Two doses are given 14 days apart. Antibodies are developed 7 to 11 days after administration of the first dose.[53,54] Individuals ≥1 year are eligible, as are pregnant women.[48] Tracking of pregnancy outcomes among pregnant women who received two doses during mass campaigns in Guinea and Malawi has shown no association with foetal loss or malformation.[55,56] Both kOCVs have been shown to be stable at ambient temperature up to 40°C for 14 days.[57] Lack of a buffer, use of a controlled cold chain, and the availability of Euvichol in a plastic vial (Euvichol Plus) makes these OCVs preferable for use in campaigns during outbreaks.[50]

Other vaccines are being developed but are not ready for prequalification. VaxChora (also known as CVD 103-HgR) is a live attenuated vaccine that was licensed by the US Food and Drug Administration in 2006.[50] Live vaccines have the distinct advantage of generating a rapid immune response that does not require repeat dosing.[50,58] Several other live attenuated vaccines are in development including HaitiV, which can induce immunogenicity within 24 hours.[59] However, they may be less effective among persons with prior exposure to cholera in endemic areas, as antibodies may block gut colonisation.[58] They may cause shedding in stool and potential infection of household contacts, though this has not yet been observed.[50] Finally, live vaccines have strict cold chain requirements and require a buffer for administration, both detriments for mass administration during outbreaks.

kOCVs confer protection through a combination of direct protection and herd immunity. Two dose average efficacy through meta-analysis was 58% (95% CI 42—69) with continued protection in the second year (59%, 95% CI 49—67) and third year (39%, 95% CI 13—57).[60] Direct effectiveness, measured through observational studies, was 76% (95% CI 62—85).[60] When delivered reactively against outbreaks, two-dose and single-dose effectiveness at 12 months is similar, with the single-dose contributing most of the public health benefit at very short time periods (i.e., the 2-month effectiveness was 87% (70—100) during an outbreak among a cholera-exposed population in South Sudan and 89% (95% CI 43—98) in a cholera-naïve population in Zambia).[60-62]

On top of direct protection, increased protection through herd immunity (i.e., protection of unvaccinated neighbours of vaccinated individuals) is conferred. In an analysis of trial data in Kolkata, India, a lower risk of cholera among placebo recipients was inversely related to high vaccine coverage at the neighbourhood level.[49] Herd protection was also invoked in a mathematical model of a vaccine trial in Matlab, Bangladesh, which showed that with an OCV coverage of 50%, a 93% reduction in cholera cases would occur.[63]

The Global OCV Stockpile, established in 2013, has supported 104 mass vaccination campaigns using 36 million doses in 22 countries (as of 2018).[64] With limited stocks, OCV is delivered on a case-by-case basis to extremely vulnerable populations to reactively control ongoing cholera outbreaks or prevent infection in crisis-affected populations. By 2022, OCV stocks have become severely restricted, an ongoing issue projected to last into 2026 which has necessitated the use of single-doses.[17]

Single-dose delivery to highly-prone city neighborhoods[65,66] and for outbreak control (sometimes with a delayed-second dose) has been documented already.[62] The GTFCC's *Ending Cholera Roadmap* focuses on finding the most efficient cholera control strategies involving vaccination, as referenced in 3 of the first 5 ranked research priorities (Box 1).[21,67]

Box 1: **The Cholera Roadmap Research Agenda's key priorities for vaccination strategy research[67]**

Priority 2: What are potential delivery strategies to optimise oral cholera vaccine coverage in hard-to-reach populations (including during humanitarian emergencies and areas of insecurity)?

Priority 3: Is there additional benefit to adding WASH packages, for example household WASH kits, to an oral cholera vaccine campaign?

Priority 4: Can the impact of oral cholera vaccine on disease transmission, morbidity and mortality be maximized by targeting specific populations and/or targeted delivery strategies?

...

Priority 12: What is the effectiveness and impact of different vaccination strategies for rapid response to cholera outbreaks (e.g., ring vaccination, case-area targeted interventions, etc.)?

1.4.3. CASE-AREA TARGETED INTERVENTION (CATI)

An ideal scenario for cholera control is a containment strategy for small outbreaks that target people at the highest risk of infection. This may be a more efficient use of vaccine doses (and other interventions) compared with campaigns that aim to cover large geographical areas but are comparatively more delayed and produce more community transmission.[68] Case-area targeted intervention (CATI) aims to control outbreaks while they are still small by interrupting transmission with multiple interventions that address multiple routes of transmission (antibiotic chemoprophylaxis, WASH, and OCV) in geographic 'rings' of 100–250m around the household of the index case.[68-71] CATI may be able to reduce intra-household transmission and secondary transmission among neighbouring households before spatial propagation occurs. The approach is akin to that used for the targeted surveillance and containment strategy for close contacts of smallpox cases in the 1970s and for ring vaccination for Ebola.[72,73] CATI using WASH interventions is currently a key pillar of UNICEF-supported cholera control strategies in Haiti, Yemen, Zimbabwe, and Mozambique.[70,74] Different configurations for CATI used during cholera epidemics for early containment, routine reactive control, and late containment are displayed in Figure 1-6.

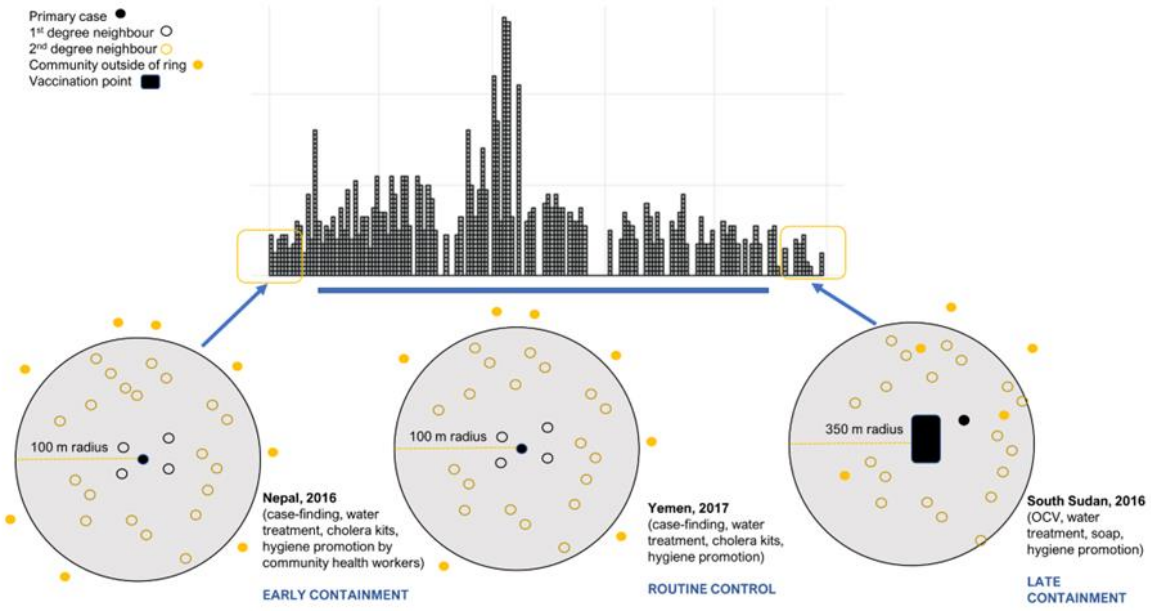

Figure 1-6. Diagrammatic representation of CATI implemented during recent epidemics in Nepal, Yemen, and South Sudan, by their timing and aims (source: created by author based on[66,74,75])

1.5. MATHEMATICAL MODELLING OF CHOLERA

In this section, I describe recent developments in the mathematical modelling of cholera with an emphasis on the assumptions made, and the challenges these assumptions bring. The aim is to explain the choices that I made for the model structures that I used in this thesis.

In 1979, Capasso and Paveri-Fontana published the first cholera model documented in the literature which evaluated the progression of a 1973 cholera epidemic across the Mediterranean region to shape a strategy for cholera control.[76] Cholera models have since gained traction in the scientific discourse and have often been influential as evidence for public health decision-making, particularly in the late 2000-era of large-scale cholera epidemics in Angola, Haiti, and Zimbabwe.[77] Milestones in the modelling of cholera have included estimation of cholera incidence based on the incorporation of, a water reservoir as an infectious source[78], asymptomatic/inapparent infections[79], hyperinfectivity of *V. cholerae* and human-to-human transmission during outbreaks[32,33], human mobility and river networks[80,81], multisector interventions during the Haiti epidemic[80,82], herd immunity[63], and the impact of single-dose vaccination.[54,83]

Given the multifactorial nature of cholera transmission (e.g., relating to co-circulating strains, prior immunity due to infection or vaccination, climate, spatial heterogeneity, etc.) and multiple routes of transmission, cholera modelling is necessarily complex. Uncertainty in biological parameters can greatly reduce the predictive value of a model.[77] Ten years ago, Grad et al and Fung reviewed the challenges to cholera modelling, most of which remain relevant today.[77,83] Chao has updated these challenges based on modelling cholera in the era of vaccination.[84]

1.5.1. TRANSMISSION DUE TO PARAMETER UNCERTAINTY AND MODEL MISSPECIFICATION

There are gaps in the accurate parameterisation of environmental parameters for waterborne transmission.[77,83] Eisenburg et al have noted that the persistence of *V. cholerae* in water sources and its concentration would be essential for estimating the waterborne transmission pathway.[85] Contact rate between humans and the contaminated water source(s) and rate of water contamination by infectious persons are also required.[83] The challenge is that these parameters are largely unmeasured and unknown, dynamic, and contextual. Therefore, such models suffer from parameter uncertainty (i.e., parameter values are impossible or difficult to estimate accurately). Moreover, there exists no quantifiable biological process to link these water parameters to a rate of infection.[77,83] Parameter uncertainty is also an issue for measuring

average shedding intensity over time and the level of underreporting of cases to the surveillance system.

1.5.2. TRANSMISSION ROUTES: DIRECT, ENVIRONMENTALLY MEDIATED, OR BOTH?

Hyperinfectivity (discussed above) via intense human-to-human transmission in households, is thought to drive transmission more than environmentally mediated transmission during an outbreak.[33,83] Freshly shed stool with a lower infectious dose will primarily affect household contacts sharing water, food, and fomites. For parsimony, and to capture this close-contact dynamic, some models have focused only on direct transmission which should incorporate the sharing of contaminated water and food among household members. In this way, even the provision of safe water can be modelled to reduce direct transmission.[82,83]

1.5.3. REALISTIC IMPACTS OF NON-PHARMACEUTICAL INTERVENTIONS AND VACCINATION

Assumptions must be made about how to capture cholera interventions, and in particular non-pharmaceutical interventions such as household water treatment and hygiene promotion. The effectiveness (i.e., as measured in randomized trials) of these interventions are determined by the relationships between coverage of the population, and both the short-term and sustained uptake of the interventions by the communities affected.[83,84] For example, we know that there is variable uptake of household water treatment methods during cholera outbreaks, particularly among communities living in endemic areas.[40] Some authors have proposed integrating this information into individual-based models with sensitivity analyses to examine plausible ranges of uptake over time.[86] While this approach would be computationally expensive, it is plausible that valid data inputs are available (i.e., knowledge, attitude, and practice surveys of cholera prevention and control conducted during an outbreak).

Dynamic models can capture complicated components of disease control, such as direct and indirect protection of vaccinated and unvaccinated individuals (who live close to vaccinated neighbours).[49,63] Effectiveness of vaccination is lower in younger age groups, meaning that even universal coverage would not lead to 100% effectiveness among all individuals[87] However, vaccinating individuals 0—14 years of age may prevent onward transmission to their family members as young persons may have higher incidence than other age groups, even though vaccine effectiveness is lower in this group.[84] Taken together, this means that to assumptions about vaccination coverage should consider incidence among different age groups and various strategies to provide indirect protection. Cholera-affected populations in camps, slums, and

resource-poor settings experience influx and efflux and a change in the susceptible population. Therefore, thoughtfulness around the intended impact of reactive and preventative vaccination, demographic groups most susceptible, expected population change and re-seeding of outbreaks is needed when attempting to model the impacts of vaccination. [84]

1.5.4. VARIABILITY OF CHOLERA OVER GEOGRAPHICAL SPACE

Cholera transmission can be highly heterogeneous over space due to differences in exposure to *V. cholerae*, existing control measures, and prior immunity. [69,77] The estimation of transmission rates at the province or state level may not represent local transmission where communities have heterogeneous dynamics. Grad et al surmise that in Zimbabwe in 2008—2009, multiple epidemic peaks represented the contribution to overall transmission of the neighbourhood and province levels, and heterogeneously mixed populations. [77] Use of finer geographical scales through spatially-explicit individual-based models or metapopulation/patch models can allow for the exploration of spatial dynamics. [69] Taking into account differences in population density, structure, and intervention coverage over space may be important when understanding the progression of an outbreak. [69,80,81]

1.5.5. MODELS RELEVANT FOR THIS THESIS

In tandem with field evaluation, increasingly mathematical modelling has been used to simulate outbreak response and the potential impact of new interventions. Two examples of such models are relevant to this thesis:

- Azman et al used a model to explore potential strategies and impacts of single-dose vaccination[54], and then tested this empirically in South Sudan. [61]
- Finger et al used a spatially explicit, individual-based model of the 2011 cholera outbreak in N'Djamena, Chad to estimate the potential impact of CATI when applied at day 50 after the first notified case (Figure 1-7). [69] This is currently being followed by an empirical evaluation of CATI, using a similar structure, in the DRC. [68]

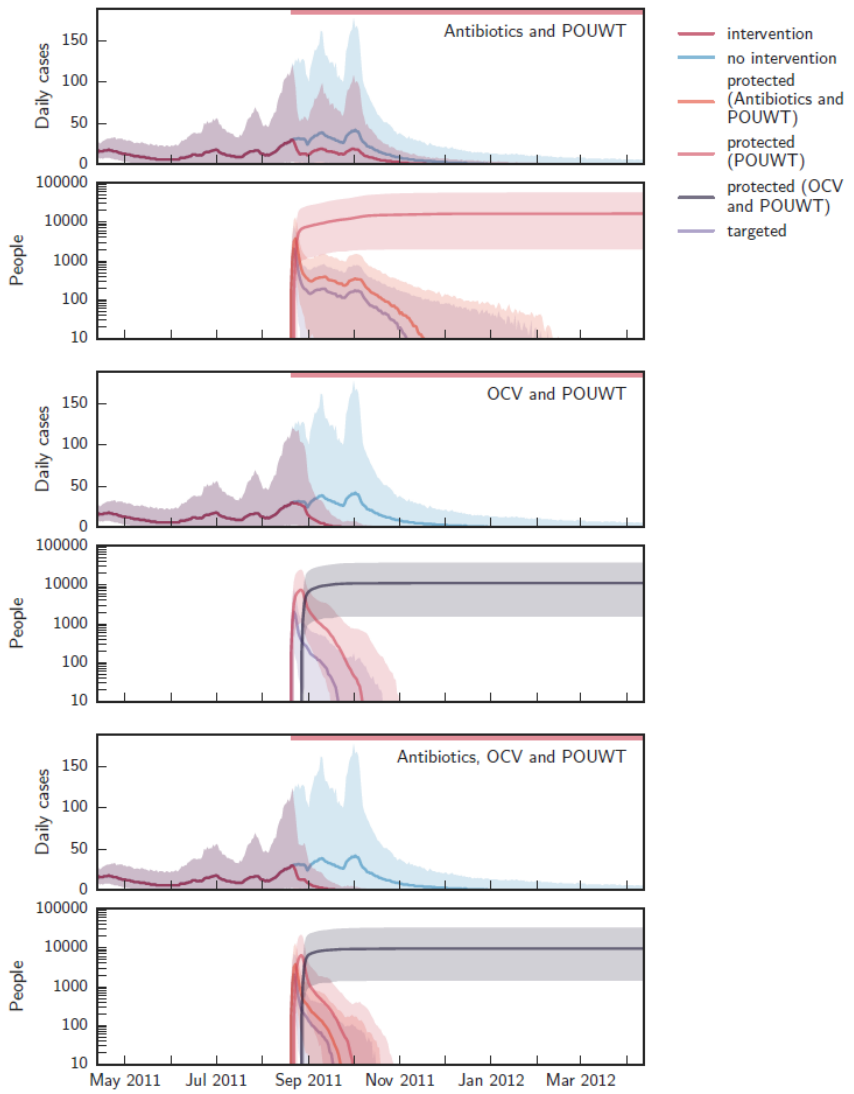

Figure 1-7. "Simulated evolution of the epidemics without intervention and with case-area targeted allocation of combinations of the 3 main intervention types within a 100-m radius starting around the epidemic peak". This model uses data from the 2011 cholera outbreak in N'Djamena, Chad. Source: Finger, 2018, Figure 3. [69].

The lower panels in each pair of panels show the number of people targeted during each timestep and the number of people protected by the interventions. Solid lines show the median over all simulations, shaded areas the 2.5th and 97.5th percentiles. The red bar at the top of each panel marks the period during which interventions are applied".

1.6. RATIONALE FOR THIS THESIS

From Malawi to Syria, cholera epidemics continue to occur in resource-poor settings and humanitarian crises where control options are severely constrained. Once outbreaks have been allowed to escalate to region-wide threats affecting large populations, the application of a multi-sector strategy is logistically complex, resource-intensive, and interferes with other critical public health priorities.[11] The rapid detection and control of small clusters is thus increasingly recognized as being important for efficient control. To substantially reduce transmission globally by 2030, the GTFCC has proposed to countries a rapid response mechanism through the *Ending Cholera* roadmap (i.e., WASH and health rapid response teams for investigation and early response).[21] However, the data to support this policy are at-present insubstantial (see Chapter 2). Rigorous evaluation of the effectiveness of CATI is scarce. The most comprehensive evaluation is a retrospective observational study of CATI (without vaccination) in Haiti from 2015 to 2017.[70]

My thesis therefore aims to evaluate the scope and potential impact of this emergent approach, specifically for the containment of cholera outbreaks in their early phase.

1.6.1. HYPOTHESIS

The hypothesis of my research is that CATI, so as long as single-dose vaccination is included, will be able to achieve control and containment during the early phase of a cholera outbreak.

1.6.2. SPECIFIC RESEARCH AIMS

In this thesis, I aimed to evaluate the effectiveness of CATI with or without vaccination for the rapid containment of case-clusters in the early phase of an outbreak. I outlined the scope of its potential impact and the capacity for rapid detection and response needed to trigger CATI, estimated outbreak detection capacity and spatiotemporal dynamics of high-risk zones to target CATI, and carried out a spatial model to estimate its potential impact on rapid control.

1.6.3. RESEARCH QUESTIONS

I sought to answer the following questions:

- **What is known about the effectiveness of interventions included in the CATI package, CATI's optimal spatiotemporal scale, and its effectiveness in reducing transmission?**

These results are presented in the first article: Highly targeted spatiotemporal interventions against cholera epidemics, 2000-19: a scoping review.

- **What is the timeliness of response to small cholera outbreaks in fragile states, and to what extent does this support the potential utility of CATI?**

These results are presented in the second article: Early detection of cholera epidemics to support control in fragile states: estimation of delays and potential epidemic sizes.

- **How can spatiotemporal clustering approaches be used to identify spatiotemporal zones of increased cholera risk around incident cases in an endemic setting?**

These results are presented in the third article: Spatiotemporal modelling of cholera and implications for its control, Uvira, Democratic Republic of the Congo.

- **What is the potential impact of CATI for containment of outbreaks in a cholera-endemic setting?**

These results are presented in the fourth article: Case-area targeted intervention with vaccination to rapidly control cholera outbreaks: a spatial modelling study.

1.7. ETHICAL APPROVAL

Chapters 2 and 3 used publicly available data and simulated data and did not require ethical approval. Ethical approval for the modelling of Uvira data in Chapters 4 and 5 was provided by the LSHTM (Reference no. 10603-5) and the University of Kinshasa School of Public Health (Reference no. ESP/CE/173B/2022) (see Appendix F).

1.8. PROSPECTIVE OBSERVATIONAL STUDY ON CATI EFFECTIVENESS

Whilst I originally planned to include in this thesis an observational study of CATI's effectiveness with vaccination, run by Epicentre, Médecins Sans Frontières (MSF) and myself, the study implementation in the DRC was delayed by 2 years due to COVID-19. While it was completed by April 2023, the analysis is ongoing. In parallel with this thesis, I worked as a co-investigator on the study in DRC and a lead investigator for a proposed study in Cameroon. This involved co-designing a study protocol and using modelling and simulation to estimate the sample sizes of rings required, both of which I have published and are found in Appendix D and E. [88,89] The scoping review aided in developing the strategy, standards, and interventions for the actual CATI with vaccination for MSF. I also made several trips to Cameroon to work with the Epicentre, MSF and Ministry of Health teams and implement the study. I presented the interim results to the GTFCC in June 2023 and we will report to the DRC Ministry of Health in September 2023. [90] In the Discussion, I interpret the preliminary results and how they compare to modelling results to date.

1.9. FUNDING

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Chapter 2: Highly-targeted spatiotemporal interventions against cholera epidemics, 2000-19: a scoping review

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Student ID Number	071663	**Title**	Mr.
First Name(s)	Ruwan		
Surname/Family Name	Ratnayake		
Thesis Title	Case-area targeted intervention for the control of cholera epidemics in crises: from spatial mathematical modelling to field evaluation		
Primary Supervisor	Prof. Francesco Checchi		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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Where was the work published?	The Lancet Infectious Diseases		
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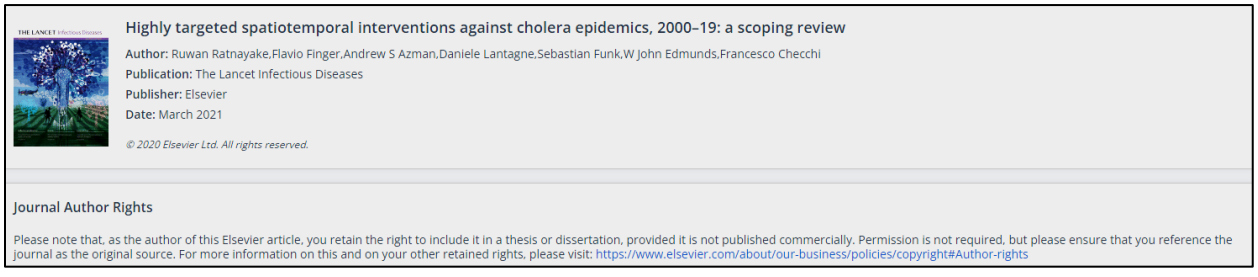

Highly targeted spatiotemporal interventions against cholera epidemics, 2000–19: a scoping review

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BRIDGING PASSAGE

Rationale for study: As of 2020, case-area targeted intervention (CATI) was still a novel strategy without sufficient empirical study and little documentation of its implementation during cholera epidemics. At the same time, it was being used by UNICEF and Ministries of Health to direct cholera control in Haiti and Yemen.

I started the doctoral work by compiling the available data, information, and evidence on the effectiveness of each component intervention delivered through CATI, routes of delivery, optimal spatiotemporal scale and studies of the effectiveness of CATI in reducing transmission at the start or end or during an ongoing cholera outbreak.

Overview of methods: As I established early on that there were no effectiveness studies suitable for systematic review and meta-analysis, I carried out a scoping review of the scientific literature to understand the size and scope of available evidence. I also contacted representatives in cholera control (including those from World Health Organization, Médecins Sans Frontières, University of the Philippines, Johns Hopkins University) to source any unpublished reports of CATI implementation or effectiveness studies.

Main conclusion: "*Although case-area targeted intervention shows promise for outbreak control, it is critically dependent on early detection capacity and requires prospective evaluation of intervention packages*". The supplementary section contains information on the search strategy, a risk of bias assessment, and detailed tables of effectiveness indicators for interventions and spatiotemporal ring sizes.

Role: I developed the concept for the review, searched the literature, extracted and synthesized the data, and wrote the original draft. I was supported by experts in CATI (F Finger), vaccination (A Azman), and water, sanitation, and hygiene (D Lantagne).

Use of findings in Ph.D. and beyond: I used this review to help to develop an evidence-based CATI intervention for MSF, to find an optimal study design for the CATI effectiveness study with Epicentre, and to source parameters for the effectiveness of interventions and size of CATI radii for modelling studies. MSF and Epicentre have used the review to inform their preparedness and response using CATI. It has been cited in *The Lancet's* seminar article on cholera.

Highly targeted spatiotemporal interventions against cholera epidemics, 2000–19: a scoping review

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ABSTRACT

Globally, cholera epidemics continue to challenge disease control. Although mass campaigns covering large populations are commonly used to control cholera, spatial targeting of case households and their radius is emerging as a potentially efficient strategy. We did a Scoping Review to investigate the effectiveness of interventions delivered through case-area targeted intervention, its optimal spatiotemporal scale, and its effectiveness in reducing transmission. 53 articles were retrieved. We found that antibiotic chemoprophylaxis, point-of-use water treatment, and hygiene promotion can rapidly reduce household transmission, and single-dose vaccination can extend the duration of protection within the radius of households. Evidence supports a high-risk spatiotemporal zone of 100 m around case households, for 7 days. Two evaluations separately showed reductions in household transmission when targeting case households, and in size and duration of case clusters when targeting radii. Although case-area targeted intervention shows promise for outbreak control, it is critically dependent on early detection capacity and requires prospective evaluation of intervention packages.

KEY MESSAGES

- Case-area targeted intervention (CATI) for cholera is based on the premise that early cluster detection can trigger a rapid, localised response in the high-risk radius around one or several households to reduce transmission sufficiently to extinguish an outbreak or reduce its spread
- There is moderate evidence that antibiotic chemoprophylaxis, single-dose oral cholera vaccination, intensive hygiene promotion, and point-of-use water treatment present effective mechanisms of action for rapidly limiting transmission in the household and its high-risk radius
- A high-risk spatiotemporal ring of 50–100 m across 7 days in urban and rural contexts specifies an appropriate implementation radius, probably due to intense household transmission and shared risk factors among neighbouring households
- Two controlled evaluations of CATI showed a reduction in the size of case-clusters (Haiti) and infection among household contacts (Bangladesh), and uncontrolled evaluations in Cameroon and the Democratic Republic of the Congo suggested reductions in transmission following CATI
- Although CATI shows promise for outbreak control, it is critically dependent on early detection capacity and requires further evaluation to evaluate the effectiveness of different packages of interventions

INTRODUCTION

In Africa and the Middle East, 126 million people live in cholera hotspots where outbreaks often recur.[1,2] From 2017 to 2018, the largest epidemics (16000 to 1.3 million reported cases) occurred during humanitarian crises in Yemen, Democratic Republic of the Congo, Somalia, northern Nigeria, and South Sudan.[3,4] Rapid spread is driven by inadequate access to water, sanitation, and health services; poor hygiene practices; weak surveillance and response systems; population displacement and overcrowding; and compromised immunity due to malnutrition.[5-8] These factors result in large at-risk populations and challenging epidemic responses.

Mass, community-wide campaigns, in which multi-sector interventions cover large administrative areas thought to be at risk for infection (e.g., cities), are commonly used to control cholera outbreaks. To prevent spatial propagation, control strategies could focus on containing clusters. Case-area targeted intervention (CATI) is based on the premise that early cluster detection can trigger a rapid, localised response in the high-risk radius around one or several households to reduce transmission sufficiently to extinguish the outbreak or reduce its spread. Similar logic underpinned ring vaccination of close contacts to control smallpox in the 1970s and Ebola more recently.[9,10] Comparatively, cholera containment must address both person-to-person and environmentally mediated transmission routes. Outbreaks are driven by a rapid cycle of household transmission, due to a short incubation period (estimated median 1.4 days), bacterial shedding that lasts from several days to 2 weeks, and resulting contamination of water, food, and fomites.[11-14] Estimates of the proportion of the effective reproduction number (R_E, the average number of secondary infections per case) due to person-to-person transmission as compared with environment-to-human transmission were 45.4% in Haiti and 82.7% in Zimbabwe.[15] CATI's ability to rapidly interrupt both routes is key to reducing R_E.

In 2017, the Global Task Force on Cholera Control proposed a strategy, which emphasised the use of rapid response teams who use CATI together with early detection, to substantially reduce transmission by 2030.[1] However, the key parameters for CATI implementation (e.g., intervention mix, timeliness, and geographical scale) are not well studied. We did a Scoping Review to identify the evidence available and critically review the potential for CATI to reduce transmission during outbreaks. We had three objectives. First, we investigated evidence on the effectiveness and feasibility of interventions to rapidly limit transmission between people and through the

environment. Second, we investigated the spatiotemporal dimensions of transmission to outline CATI's appropriate spatial scale and timing. Finally, we evaluated CATI's feasibility and effectiveness during epidemics.

METHODS

Search strategy and selection criteria

We searched the PubMed, Embase, and Cochrane databases for studies published in English or French between Jan 1, 2000, and April 24, 2020. Unpublished reports on CATI were sought using searches of agency websites and by emailing 40 experts in cholera response (appendix A.2). For objective 1 (interventions), meta-analyses, systematic reviews, and studies of the impact of health and water, sanitation, and hygiene (WASH) interventions that primarily aim to reduce transmission at the household or community level were retrieved (table 2.1). For objective 2 (spatiotemporal risk), studies providing estimates of spatiotemporal scales of transmission were found. For objective 3 (feasibility and effectiveness of CATI), reports and evaluations of CATI implementation during outbreaks were sought. We defined CATI as any control strategy where upon detection of a cholera case(s), a team immediately targeted interventions to people or households living within a geographic area (often based on distance) around these cases. For objective 1, if effect estimates from a meta-analysis were unavailable, we used experimental, quasi-experimental, or observational studies describing a reduction in incidence using relative risk (RR). For objective 3, we included evaluations with effect estimates, population coverage (measured through a household survey or administrative data), or both values.

Table 2.1 *Health and WASH interventions to reduce Vibrio cholerae transmission, by place of delivery*

	Household or community	Health facilities
WASH	Point-of-use water treatment;* community water treatment; safe water storage;* household spraying;* hygiene promotion and handwashing; disinfection of corpses	Hygiene kit distribution
Health	Antibiotic chemoprophylaxis of household contacts; oral cholera vaccination	Supportive care; isolation and admission to treatment facility; antibiotic treatment of mildly and moderately dehydrated cases

WASH=water, sanitation, and hygiene. *These interventions are often delivered through hygiene kits which might include chlorine tablets, soap, bleach for disinfection, and hygiene promotion materials.

Table 1: **Health and WASH interventions to reduce *Vibrio cholerae* transmission, by place of delivery**

We searched using the following terms in the title or abstract: “cholera”, “Vibrio cholerae”, or “acute watery diarrhoea”. We also used terms describing specific interventions and their effectiveness (i.e., antibiotic chemoprophylaxis [ACP], oral cholera vaccination [OCV], hygiene promotion, water treatment, household spraying and disinfection, and safe burial for objective 1; dimensions of transmission for objective 2; and the feasibility and effectiveness of CATI for objective 3). A full list of the terms is provided in the appendix (A.1). This Scoping Review followed the Preferred Reporting Items for Systematic Review and Meta-Analyses Extension for Scoping Reviews guidelines. [16]

DATA ABSTRACTION

For objective 1, RR (and 95% CIs) of infection or exposure were extracted and converted to a RR reduction (1–RR). Information on the feasibility of rapid application at the household and community level was documented. For objective 2, spatial dimensions (in metres) and temporal dimensions (in days) and RR (and 95% CIs) were extracted. For objective 3, operational data on resources, procedures, and costs were extracted (appendix A.3). For evaluations of CATI where its effectiveness in reducing cholera incidence, population coverage, or delay to implementation were assessed, study objectives, study design, sample size, RR or odds ratios (ORs and uncertainty intervals), and coverage indicators were extracted. The quality of evaluations was assessed using the Cochrane Collaboration Risk of Bias tool (e.g., selection bias, confounding, spill over and contamination, incomplete outcomes, and selective reporting; appendix A.5). [17]

CONCEPTUAL FRAMEWORK

We developed a conceptual framework to integrate the findings into a pathway for rapidly reducing transmission within a spatio-temporal zone around the primary case-household (herein, the ring). We integrated evidence on the optimal spatiotemporal window and positioned interventions at the primary-case household(s), adjacent households, and ring according to the speed and magnitude of biological effect, and the logistical burden.

RESULTS

Across searches, 3601 studies were retrieved. After deduplication, 2698 records remained. After screening titles for relevance, 56 records remained. Screening by abstract yielded 41 articles. After reviewing reference lists and reports sent from experts, 12 studies were added (nine articles from reference lists, two abstracts, and one UNICEF report). In total, 53 articles met the inclusion criteria for objective 1 (n=28),[18-45] objective 2 (n=10),[46-55] and objective 3 (n=15; appendix A.4).[56-70]

Table 2.2 *Theoretical effects on transmission of case-area targeted interventions*

	Intervention description, objectives, and potential delivery approach through case-area targeted interventions	Theoretical effect (host)
ACP	ACP acts to rapidly clear *Vibrio cholerae* among infected people and protect against infection among uninfected people; ACP can therefore achieve multiple goals by addressing multiple hosts: rapidly protecting uninfected household contacts at risk of infection, and reducing symptom development and shedding among infected people; ACP has been delivered as single-dose doxycycline;[21,62,63] the GTFCC only recommends selective ACP for closed populations at high risk of infection (eg, prisons);[71] doxycycline is recommended as first line and azithromycin as second line due to resistance to multiple antibiotics[71]	Reduce susceptibility (uninfected host); reduce infectiousness (infected host)
OCV	Two kOCVs, specific to O1 and O139 *V cholerae*, are available from the global OCV stockpile (Shanchol [Shantha Biotechnics] and Euvichol [Eubiologics]); given the limited stock of OCV, a single dose of kOCV can be used strategically during outbreaks to achieve rapid protection among a large population;[72] one dose of OCV delivered to the ring* could protect against further generations of disease in the ring, thus preventing community transmission; Shanchol can be kept in a controlled cold chain (or at ambient temperature on the day of vaccination) without affecting safety or effectiveness;[73] kOCVs do not require a buffer; OCV requires substantial logistical inputs and campaigns are frequently supported by non-governmental organisations[28]	Reduce susceptibility (uninfected host)
POUWT delivered to the household	POUWT, in the form of disinfectant (eg, chlorine) tablets or liquid, aims to reduce the concentration of *V cholerae* in water; one tablet can treat a container of water which can be used after 30 min;[40] POUWT could be routinely delivered to households before the outbreak begins, as a preventative measure against a wide spectrum of diarrhoeal diseases; POUWT requires education on appropriate use and promotion given taste and odour changes and difficulties in achieving an appropriate concentration	Reduce bacterial concentration (household water)
Water treatment of local collection sources	Water treatment of local collection sources aims to reduce the bacterial concentration of *V cholerae* at the source of collection; some sources (eg, wells) have shown a poor ability to maintain chlorine concentration;[36,38] water from a treated local source is at risk of re-contamination; therefore, where possible, providing a narrow-necked container for safe transportation and storage is optimal	Reduce bacterial concentration (local collection source)
Safe storage of treated water	Safe storage and transport of water using narrow-neck containers aims to prevent faecal contamination of treated water by soiled hands during transport from the source or storage in the household;[36] a container can be delivered with POUWT or at the site of treatment of local water sources, as biofilms shielding cholera are difficult to remove[74]	Facilitate reduction of bacterial concentration (household water)
Household spraying	Household spraying aims to reduce contamination on surfaces; although this intervention lacks evidence for reducing contamination or reducing transmission, household spraying is often carried out during outbreaks;[36] an alternative to household spraying is distribution of a hygiene kit wherein the household members can use the bleach to repeatedly disinfect surfaces	Reduce bacterial concentration (household surfaces and fomites)
Hygiene promotion	Hygiene promotion aims to improve knowledge of infection prevention, and encourages behaviour change to facilitate handwashing, use of safe water and safe food-handling measures, and safe excreta disposal practices; intensive hygiene promotion at case households can be done by a hygiene promoter once or repeatedly over a short time period; it is optimally facilitated by providing people with access to treated water, safe storage, and soap to facilitate actions;[60] mass messaging in the community can be done through hygiene promoters delivering messages on water treatment, safe food handling and sanitation, and infection prevention through community events and radio messages[67]	Reduce susceptibility (uninfected host)
Disinfection of corpses	The corpses of infected people who died are disinfected with chlorine to prevent leakage of infectious fluids;[45] additional measures should be done to promote safe food handling and handwashing during funeral gatherings	Facilitate reduction in susceptibility through safe corpse management and food handling (uninfected host)

ACP=antibiotic chemoprophylaxis. GTFCC=Global Task Force on Cholera Control. kOCV=killed OCV. OCV=oral cholera vaccination. POUWT=point-of-use water treatment. *The ring comprises the spatiotemporal zone around the primary-case household.

Table 2: **Theoretical effects on transmission of case-area targeted interventions**

EFFECTIVENESS OF INTERVENTIONS AND THEIR POTENTIAL DELIVERY THROUGH CATI

We summarised the potential for interventions to rapidly limit transmission, their estimated effectiveness, and potential delivery approaches through CATI (table 2.2). We extracted estimates of effect sizes, delay to onset of effects, and duration of effects for interventions (appendix A.6). For ACP, a 2011 meta-analysis of different antibiotics (tetracycline, doxycycline, ciprofloxacin, and sulfadoxine) administered to contacts estimated its effectiveness against culture-confirmed infection as 66% (95% CI 34–82).[19] During an outbreak in Nairobi, Kenya in 2015, a cohort study of doxycycline given to household contacts found a similar effectiveness estimate against diarrhoea (68%, 95% CI 29–87).[21] The effectiveness of ACP in preventing symptoms among those who are infected has been estimated as 96% (95% CI 70–99), with a 2.74 day (95% CI 2.4–3.1) mean reduction in shedding duration.[18-20,57,75,76] ACP's effects are short-lived. Doxycycline's half-life is estimated as 20 h and a single-dose of azithromycin can maintain a concentration adequate to eliminate *Vibrio cholerae* for 2 days.[18,77,78] *V cholerae's* antibiotic resistance patterns change frequently. Circulating strains from recent epidemics in Democratic Republic of the Congo, Haiti, Nepal, Tanzania, Yemen, and Zambia have shown susceptibility (doxycycline,[62,79,80] azithromycin,[79] and tetracyclines[80,81]), fluctuating resistance (ciprofloxacin,[80,82,83], cotrimoxazole,[80,82] and ampicillin[81,82]), and complete resistance (nalidixic acid)[81-84] to common antibiotics. When ACP was delivered through CATI in Cameroon (2004) and Haiti (2015–17) doxycycline resistance was not detected among cholera cases.[61,63,66] Although no updated trial using a particular antibiotic class is available, meta-analysed evidence across classes suggests that ACP can provide immediate protection among household contacts. Antibiotics can be stockpiled locally, and a single, oral dose can be administered by non-clinical staff.

WHO recommends using a single dose of killed-OCV during outbreaks where the supply of OCV is constrained and resources limited to cover a larger proportion of the population in the short-term.[29,72] 12-month effectiveness is similar for single-dose (69%, 95% CI 35–85) and two-dose (83%, 79–91) regimens, but neither show adequate protection for children aged under 5 years.[24,26,27,31,33] High single-dose effectiveness at 2 months was found during outbreaks among an immunologically naive population in Lusaka, Zambia (89%, 95% CI 43–98) and among a population exposed to cholera 1 year before in Juba, South Sudan (87%, 95% CI 70–100; includes indirect effects), where a single dose might have acted as a booster after exposure.[24,25,30] Peak vibriocidal antibody response occurs 7–11 days after administration.[24,85] Although

single-dose killed-OCV might prevent transmission minimally during the first week, it could offer longer protection during subsequent generations of transmission in the ring than other interventions. The vaccine Shanchol (Shantha Biotechnics, Hyderabad, India) is approved to be kept out of the cold chain for up to 14 days without exceeding 40°C, allowing vaccinators to reduce their use of cold boxes on the day of vaccination and carry additional vaccines to cover more people per day. The vaccine Euvichol (Eubiologics, Seoul, South Korea) is expected to be approved soon for out of cold chain use. [73,86,87]

Concerns are commonly raised about the equitable distribution of limited vaccines, feasibility of campaigns during humanitarian crises, and of offsetting WASH activities, as shown by delays in use of vaccines in Haiti (2011), South Sudan (2014), and Yemen (2017). [22,23,28,29,34] However, with the addition of Euvichol and increased manufacturing capacity, vaccine supply is expected to triple current levels by 2030. [88,89] In 2017, rapid recognition of the outbreak in Lusaka and a detailed epidemiological assessment led to the initiation of a one-dose reactive campaign within 2 months of the first reported case. [32] From 2013 to 2018, the median time from approval of vaccination by the global OCV stockpile and arrival in-country was 13 days (range 4 to 24) and from arrival to the start of campaign was 15 days (−2 to 87). [90] To support CATI's rapid response, these timelines emphasise the need to have accessible OCV stocks already in-country, and preparedness plans. [29]

WASH interventions reduce the risk of exposure to *V cholerae* by increasing water quantity and quality, isolating faeces, promoting hygiene awareness, and disinfecting surfaces. [38] Two systematic reviews of WASH interventions for cholera cited few studies and low-to-moderate evidence of impact. [36,38] In a meta-analysis of WASH interventions for diarrhoea, the effectiveness of point-of-use water treatment (POUWT) in preventing diarrhoea was estimated as 26% (95% CI 15 to 35), whereas that of treating the water source was estimated as 11% (−90 to 58), while noting the probable attenuation of uptake outside of an outbreak. [35] Use of POUWT for cholera was highly variable (range 7% to 87%) in DR Congo, Haiti, Kenya, Nepal, South Sudan, and Zimbabwe, with previous familiarity with products and hygiene promotion by community health workers (CHW) influencing uptake. [40] Water treatment at collection sources could prevent recontamination during transport. To maintain protection of treated water in the household, the use of narrow-neck containers is optimal. [40] A randomised controlled trial (RCT) of narrow-neck containers without POUWT showed inconclusive protection against diarrhoea of 21% (95% CI

−3 to 38).[35,39] A meta-analysis of case-control studies provided evidence of decreased odds of cholera infection when using safe storage (OR 0.55, 95% CI 0.39 to 0.8).[37]

Hygiene promotion of handwashing and safe food handling is considered a crucial step alongside water treatment to break transmission from soiled hands regardless of vaccination status.[42] Soap distribution and hygiene promotion permitted increased self-efficacy, risk perception, and an enabling social context to increase hygienic behaviours among populations affected by cholera in Chad (through self-report) and Bangladesh (observed).[36,41,58] There is currently no evidence for the effectiveness of household spraying on the reduction of household contamination.[36,38] Preliminary results from an exploratory study found that spraying chlorine solution on household surfaces (e.g., dirt walls) until visibly wet led to a rapid reduction of *V cholerae* 30 min after spraying, which was sometimes followed by re-contamination.[43] Alternatively, hygiene kits provide cleaning materials for ongoing disinfection.[38,44] For the disinfection of corpses, an increased attack rate following a funeral was observed among villages in Guinea-Bissau that did not practice disinfection, compared with those that did (RR 2.6, 95% CI 1.9–3.8).[45]

Although WASH interventions for cholera are under-researched, there is substantial knowledge about how to improve its rapid uptake by use of simple interventions, emphasising preparedness measures and facilitating delivery through channels familiar to the community, like CHWs.[38,40] CATI is well positioned to improve uptake by providing local support to households.

DETERMINING THE SPATIOTEMPORAL SCALE OF ELEVATED INFECTION RISK

We summarised the studies that evaluated the risk of infection among people exposed to suspected cholera cases within spatiotemporal (or spatial only) windows (e.g., within 25m of the primary case household, 3 days after onset), compared with any other person in the population outside this window (appendix A.7).[46-55] Spatial-only studies showed increased risk extending up to 150 m in Kolkata, India, and 500 m in Matlab, Bangladesh.[48] In urban Kalemie, Democratic Republic of the Congo, and N'Djamena, Chad, within a 5-day period after the primary case visited a health facility, a gradient of elevated risk (RR>1) extended from 20m (RR>20, commensurate with the household and its immediately surrounding area) to a threshold of 220m (in Kalemie) and 330m (in N'Djamena).[49] A reanalysis of data from a cluster RCT of OCV effectiveness in Kolkata, India, limited to a maximum 55m radii around index cases, found a gradient of elevated risk during 7 days up to a threshold of 50m (RR 2.5, 95% CI 1.7–3.8) and

the highest risk within 10m (11.4, 6.9–19.0) of the primary case.[46] The elevated risk decreased after 7 days and 100m in N'djamena and Kalemie, and 14 days in Kolkata.[46,49] In rural Matlab, Bangladesh, an analysis of cohorts of primary cases and uninfected controls, using increments of 50m, found a gradient of elevated risk up to 400m, 6 days after a primary case visited a health facility (RR 1.5, 95% CI 1.03–2.1).[51] The highest risk existed up to 50m from 3 days (RR 35.7, 95% CI 22.9–55.7) to 6 days (28.2, 16.6–48) and extended to 23 days (1.9, 1.4–2.8).[51] This result suggests a spatiotemporal window extending to 7 days and 50m around the primary case.[51]

Shared risk factors and behaviours among neighbouring households might underpin the risk presented by the spatiotemporal windows. In Dhaka, Bangladesh, the type of water source, distance to water source, intermittent water supply, sharing a latrine, and soap availability were clustered among case households and neighbouring households, with clustering of water sources extending to 400 m.[50] Prospective studies in Dhaka estimated a high risk of household transmission, via cross-contaminated water or food.[52-54] Infection through household transmission has been measured as two to four times higher than through community sources.[52] In another study, 49% of household contacts developed diarrhoea and 21% were culture-positive during a 21-day study period.[54] A meta-analysis also showed a three times increase in the odds of infection among household contacts of a suspected case (OR 2.9, 95% CI 1.6–5.3).[55]

CATI IMPLEMENTATION AND EVALUATION

We identified CATI use during epidemics in Cameroon (Douala), Haiti (2010–11 and 2013–17), Bangladesh (Dhaka), South Sudan (Juba), Nepal (Kathmandu Valley), Yemen, and Democratic Republic of the Congo (Kinshasa; table 2.3).[56-70] CATI was implemented to address incident case-clusters within 1–2 weeks of cholera detection in Douala, Haiti (2010), and Kathmandu, and 1–4 weeks in Kinshasa.[61,63,67,69,70] In Haiti, within 2 weeks of detection, CATI provided early detection of cholera-related events to inform rapid response.[69] In 2015 in Haiti, this programme was followed by an intensive programme where case households and their 50–100 m radius were targeted.[65,66] In Kinshasa, CATI was used to target case households in a 500 m radius.[70] After the 2015 earthquake in Nepal, CATI was integrated into cholera preparedness planning using existing rapid response teams.[67] In Yemen, to direct resources 10 months into a large national epidemic, WASH and health interventions were organised by rapid response teams using a CATI approach.[65] In Juba, CATI was used at the end of a mass vaccination campaign to reduce transmission around sporadic cases.[64]

Table 2.3 *Implementation of case-area targeted intervention during acute epidemics and endemic transmission scenarios, by year*

	Douala, Cameroon (2004)[61,63]	Haiti (national; 2010–11)[69]	Dhaka, Bangladesh (2013)[60]	Juba, South Sudan (2015)[64]	Kathmandu Valley, Nepal (2016)[67]	Haiti (national; 2013–2017)[62,65,66]	Yemen (national; 2017–18)[65]	Kinshasa, Democratic Republic of the Congo (2017–18)[70]
Transmission	Epidemic in endemic area	Epidemic (first wave)	Endemic	Epidemic in endemic area	Epidemic in endemic area	Endemic (second wave)	Epidemic (second wave)	Epidemic in endemic area
Duration	Jan–Aug, 2004 (8 months)	Nov, 2010–11 (12 months)	June, 2013, to Nov, 2014 (17 months)	Aug, 2015 (1 month)	June–Nov, 2016 (6 months)	July, 2013–17 (48 months)	Aug, 2017–present	Nov, 2017–18 (12 months)
Size (cases)	8005	519 690	Not reported	1818	169	177 709	>1 million	1712
Epidemic phase	Early (within 2 weeks of onset)	Early (within 2 weeks of onset)	Not applicable (RCT)	Tail of epidemic	Early (within 2 weeks of onset)	Midway	Midway	Early (within 2 weeks of onset)
Delay	Within 1 week	Approximately 2 weeks	Not applicable (RCT)	Approximately 1 week (post-OCV campaign)	None	Not applicable	Not applicable	Within 1–4 weeks
Intended timing	Same or following day	Within 24 h of alert	Within 36 h of alert	Not reported	Within 48 h of case presentation	Within 48 h of case presentation	Within 24 h of alert	Within 1 week
Cases targeted	Suspected cases from CTUs	Alerts of increased caseloads or deaths	Culture-positive cases only	RDT-positive (enriched) cases only	Culture-positive cases only	Alerts of increased caseloads or deaths	Alerts of increased caseloads or deaths	Suspected cases from CTUs in most affected health zones with culture-confirmed outbreaks
Ring size targeted	Directly adjacent households	Neighbourhood related to alert	Case household only	Neighbourhood around a case household	100 m radius around case household	50–100 m radius around case household	50–100 m radius around case household	500 m radius around case household
Interventions used	ACP and HHS (case household only); ACP, HP, and WCT (wells; adjacent households); ACP (guardians in hospital)	Event-based surveillance	HP (household visits daily for 1 week and handwashing station); POUWT and safe storage (3 m; case household only)	Single-dose OCV, hygiene kit including POUWT, soap, and HP (community)	POUWT and safe storage, HP (case household only); WCT and HP delivered by CHW (community)	POUWT and safe storage, HHS, HP, and ACP (case household only); case finding, WCT, HP, and hygiene kit (community)	POUWT and safe storage, HHS, and HP (case household only); case finding, WCT, HP, and hygiene kit (community)	POUWT and safe storage, HHS, HP, and ACP (case household only); case finding, HP, hygiene kit, and bladders (community)
Team composition	Health promoter for household visit	Health and WASH staff, and logistician	Health promotor for household visit	Health, WASH, and vaccination staff	Epidemiologist or clinician, GIS staff, and CHWs	Team lead, WASH staff, health promoter, and nurse (for ACP)	Personnel from Water Ministry	Supervisor, health promoters, and sprayers
Cost	Not reported	Not reported	US$45·50 (per household for 7 days); US$227·50 (per case averted)	Not reported	Not reported	US$583 338 (monthly programme cost); US$10 234 (monthly team cost)	US$1·5–1·8 million (monthly programme cost) US$2400–3000 (monthly team cost)	Not reported

ACP=antibiotic chemoprophylaxis. CHW=community health worker. CTU=cholera treatment unit. GIS=geographic information system. HHS=household spraying. HP=hygiene promotion using trained personnel. OCV=oral cholera vaccination. POUWT=point-of-use water treatment. RCT=randomised controlled trial. RDT=rapid diagnostic test. WASH=water, sanitation, and hygiene. WCT=water collection treatment.

Table 3: **Implementation of case-area targeted intervention during acute epidemics and endemic transmission scenarios, by year**

Events triggering CATIs

Triggering occurred after cases sought care for diarrhoea at health facilities. Suspected cases in Douala and suspected case clusters in Kinshasa were exhaustively responded to.[61,63,70] CATIs were launched for cases testing positive by enriched rapid diagnostic test (RDT; Juba) or culture (Dhaka and Nepal).[60,64,67] In Haiti and Yemen, case clusters with above-threshold levels of suspected cases and deaths during the previous 7 days were responded to.[65,66]

Interventions

The most widely used strategy was comprehensive WASH including POUWT and safe storage (at the household level), and water treatment and hygiene promotion (at the community level).[61-63,65,67,70] In Haiti and Yemen, CATI focused on WASH interventions to improve hygiene and access to safe water in remote and rural areas.[65,66] In Kinshasa, emphasis was also placed on increasing community-level water supply and handwashing stations.[70] ACP using doxycycline was used in Douala, Haiti, and Kinshasa.[61,63,70] In Douala and Kinshasa, adjacent households were considered at high risk given population density, and therefore ACP with WASH was prioritised to act immediately to curtail interpersonal transmission.[61,63,70] OCV was used in Juba, through leftover stock from a vaccination campaign.[64] In Kathmandu, OCV was intended to provide extended protection, but could not be procured from the global stockpile.[67]

Spatiotemporal windows

In Haiti, Kathmandu, and Yemen, radii of 50–100m were aimed for (estimated as ten to 20 households in Haiti).[65-67] Directly adjacent households in Douala and the neighbourhoods of cases in Juba defined ring sizes.[61,63,64] The intended timing of the initial household visit after case presentation ranged from 24h (Douala, Haiti [2010–11], and Yemen) to 48h (Haiti [2013–17] and Kathmandu).[61-65,67] Most reports did not describe the duration of CATI activities. In Kinshasa, a large 500m ring was targeted over 14 days by dividing the ring into grid squares of 20–30 households.[70]

Coverage of alerts and intervention delays

Among city-wide epidemics, the proportion of cholera alerts addressed by CATI ranged from 54% of culture-confirmed cases in Kathmandu, 82% of RDT-positive cases in Juba, health zones covering 78% of the caseload in Kinshasa, to 84% of suspected cases in Douala (table 2.4).[61,63,64,67,70] Among large epidemics, coverage of alerts varied (53% of small-scale outbreaks in Haiti and 83% of confirmed and 32% of suspected cases in Yemen).[65,66] In Kathmandu, a

survey 6–8 months after implementation estimated that 30% of catchment households received messaging through CATI.[67] In Juba, 51% (95% CI 42–60) of surveyed respondents reported vaccination through CATI.[64] OCV was not restricted to people living in the neighbourhood and surveys might have biased toward lower coverage.

Mean delays from case presentation to implementation of 3.9 days (range 1–9) occurred in Kathmandu, with 3 days attributed to culture confirmation.[67] In Juba, a mean delay of 3.4 days (range 1–6) reflected the time for RDT enrichment and organisation of OCV.[64,91] Delays also reflected challenges in reaching communities. In Haiti, 75% of home visits were completed within the first 24 h of case presentation and 85% within 48 h in 2018.[65] Given extremely restricted humanitarian access in Yemen, a high proportion of home visits were made within 48 h (46%) and 72 h (69%).[65]

COSTING

Costing for CATI was rarely reported. Yemen and Haiti documented average costs of US$3000 and $10 234 per team per month, respectively.[65] In Dhaka, the cost per household was $45.50 and the cost per case averted was $227.50.[60]

Table 2.4 *Evaluations of CATI categorised by measurement of effects*

	Interventions	Cases (or households) reached	Proportion of cholera alerts responded to	Mean delay (detection to household visit)	Coverage (of ring)	Study design and limitations	Estimated effects
With effect estimates							
Centre Department, Haiti (2015–17)[62]	POUWT and safe storage, HHS, HP, and ACP (case household only); case finding, WCT, HP, and hygiene kit (community)	10 428 suspected cases; 452 outbreaks	53% of outbreaks responded to	>7 days (48 [20%] of 238); 3–7 days (40 [17%] of 238); 2 days (43 [18%] of 238); ≤1 day (107 [45%] of 238)	NR	Quasi-experimental study with groups stratified by response promptness; 47% of the outbreaks were not responded to with CATI; ACP not used consistently or use not recorded consistently	A first complete prompt CATI (≤1 day after outbreak onset) reduced accumulated cases by 76% (95% CI 59–86), and outbreak duration by 61% (41–75), as compared with a first complete delayed CATI (>7 days after outbreak onset); the temporal response was consistent for smaller delays
Dhaka, Bangladesh (2013)[55,60]	HP (household visits daily for 1 week and handwashing station); POUWT and safe storage (3 m; case household only)	Enrolled 84 culture-confirmed cases and 84 culture-confirmed controls (RCT)	All enrolled culture-positive cases (RCT)	None (as per study protocol)	NR	Individual RCT; intensive 7-day home visit protocol; large proportion of household contacts were not enrolled (27%), although they did not differ by group	Among household contacts in intervention group: reduction in symptomatic infections (OR 0·00, 95% CI 0–0·62; no symptomatic infections were found among intervention contacts); reduction in culture-confirmed cases (0·5, 0·21–1·18); no *Vibrio Cholerae* in drinking water (0, 0–1·08); 6–12 months post-intervention: increase in handwashing with soap at a key time during structured observation (4·71, 2·61–8·49); reduction in households in the very high-risk category for stored drinking water (0·38, 0·15–0·96)
Douala, Cameroon (2004)[61,63]	ACP and HHS (case household only); ACP, HP, and WCT (wells; adjacent households); ACP (guardians in hospital)	5020 suspected cases; 161725 contacts	84% of suspected cases	NR	NR	Post-hoc analysis; observational study; no comparison group	Proportion of contacts among all suspected cases decreased from 30% in first month to <1% in the last month; all stool samples remained susceptible to antimicrobials
Kinshasa, Democratic Republic of the Congo (2017–18)[70]	POUWT and safe storage, HHS, HP, and ACP (case household only); case finding, HP, hygiene kit, and bladders (community)	NR	Health zones where 78% of cases originated	NR	NR	Post-hoc analysis; observational study; no comparison group; use of ACP was unmeasured	Weekly case count decreased by 71% (4 weeks after the peak of the outbreak) and 83% (8 weeks after the peak)
Effects not measured							
Juba, South Sudan (2015)[64]	Single-dose OCV, hygiene kit including POUWT, soap, and HP (community)	14 RDT-positive suspected cases (of 17 identified)	82% of RDT-positive suspected cases	3·4 days (range 1–6)	51% (95% CI 41·7–60·3) vaccination coverage for sites	Post-hoc analysis; denominator for coverage indicator unclear given that CATI was positioned in the neighbourhood around a case household and not a door-to-door campaign	No effects measured
Kathmandu Valley, Nepal (2016)[67]	POUWT, safe storage, HP (case household only); WCT and HP delivered by CHW (community)	169 culture-confirmed cases	54% of culture-positive suspected cases	3·9 days (range 1–9); 1·7 days after culture result	30·2% (no 95% CIs reported) increased knowledge of cholera among CATI-targeted communities	Post-hoc analysis of delay between detection and implementation; coverage surveys done 1 year after CATI, increasing recall bias	No effects measured
Yemen (2017)[65]	POUWT and safe storage, HHS, and HP (case household only); case finding, WCT, HP, and hygiene kit (community)	NR	83% of culture-positive cases; 32% of suspected cases	In 2018, 3% of suspected cases responded to within 24 h; 43% within 24–48 h; 23% within 48–72 h	NR	Post-hoc analysis only; no impact measured; surveillance data used are difficult to interpret as they includes a high proportion of non-cholera diarrhoea	No effects measured

ACP=antibiotic chemoprophylaxis. CATI=case-area targeted intervention. HHS=household spraying. HP=hygiene promotion using trained personnel. NR=not reported. OCV=oral cholera vaccination. POUWT=point-of-use water treatment. RCT=randomised controlled trial. RDT=rapid diagnostic test. WCT=water collection treatment.

Table 4: **Evaluations of CATI, categorised by measurement of effects**

EFFECT ON THE REDUCTION OF TRANSMISSION

The potential effect of CATI on the reduction of transmission was investigated using a computational model of an epidemic in N'Djamena that compared CATI in a spatiotemporal radius of 100 m with uncontrolled transmission.[57] OCV, POUWT, and ACP delivered individually through CATI were projected to shorten the epidemic duration by 68% (IQR 62 to 72%), 21% (7 to 35%), and 2% (−11 to 8%), respectively.[57]

Four evaluations with effect estimates were done in Douala, Kinshasa, Dhaka, and Haiti (2015–17);[60-63,70] two studies[60,62] were controlled (table 2.4). In Douala, where ACP and well chlorination were used, a post-hoc analysis of surveillance data without a comparison group showed a decrease in secondary attack rates among contacts of suspected cases from 30% during the first month to less than 1% in the last month of the epidemic.[61,63] This decrease suggested that ACP was effective in reducing the bacterial load among household contacts. The epidemic continued with a similar dissemination pattern to a previous outbreak, suggesting that the intervention package could not interrupt environmentally mediated transmission (noting that well chlorination is ineffective).[36,63] In Kinshasa, using intensive WASH in the household and the community and ACP for household contacts, caseloads decreased by 71% in 4 weeks and 83% in 8 weeks after the outbreak peak.[70] Although an uncontrolled study, the staggered implementation across sites over 4 weeks showed similar reductions across outbreaks.

An RCT in Dhaka in which households of RDT-positive and culture-confirmed cases were randomly assigned to an intensive hygiene intervention showed a reduction in incidence of symptomatic infection (OR 0, 95% CI 0–0.62; no events in the intervention group) and a non-significant reduction in asymptomatic and symptomatic cases (0.5, 0.21–1.18) among household contacts.[60] Participants' handwashing self-efficacy was enabled by instruction, equipment, POUWT, and soap.[58] At 6–12 months, handwashing was sustained and stored water had a below-threshold coliform count.[59,68] Contaminated household water was a risk factor for infection.[56] It is unlikely that this intensive programme would be realistic for outbreak response.

In the Centre Department (Haiti), CATI's effect on epidemic duration and caseload was evaluated using a quasi-experimental design with groups stratified by the promptness of response.[62,66] 238 (53%) of 452 outbreaks (defined as at least two suspected cases and at least one positive culture or a severely dehydrated case) that were prioritised for the evaluation were responded to with CATI (i.e., POUWT, hygiene promotion, hygiene kits, ACP [non-systematically], and

community water treatment). Compared with CATI implemented more than 7 days after outbreak onset, CATI implemented within 7 days after outbreak onset reduced attack rates by 76% (95% CI 59 to 86) and outbreak duration by 61% (41 to 75). A relationship with the timeliness of response suggested that CATI was effective. The reductions in attack rates (63%, 95% CI 24 to 82 vs 39%, −38 to 73) and duration (74%, 43 to 88 vs 58%, 11 to 80) increased significantly if ACP was used, suggesting an intervention-specific effect of ACP. However, inconsistency in the use of ACP and other interventions potentially reduced overall impact. The programme might not have been operationally efficient. Most of the 3887 CATI responses were triggered by syndromically diagnosed cases, of which 16% were done in a setting meeting the outbreak criteria above.

CONCEPTUAL FRAMEWORK

To apply the evidence to a conceptual framework, each intervention was placed along a timeline that started with the identification of the primary case(s) and followed the spatiotemporal radius of 100 m over 7 days (figure 2.1). The highest risk of transmission occurred among household members, followed by adjacent households, and households in the ring. Fast-acting interventions within the case household reduce transmission (e.g., ACP and POUWT facilitated with safe storage, soap, and hygiene promotion). ACP for adjacent households promptly reduces risk, considering that case households are small units wherein few people are exposed to the primary case, and risk of exposure might be high in the community.[92] POUWT, storage, and soap (or hygiene kits) rapidly facilitate reduced transmission in adjacent households. Single-dose OCV implemented in the ring over several days focally reduces spatial transmission, whereas mass vaccination campaigns can be prepared should the outbreak expand. Hygiene promotion facilitated by CHWs is undertaken to promote uptake and extend CATI activities.

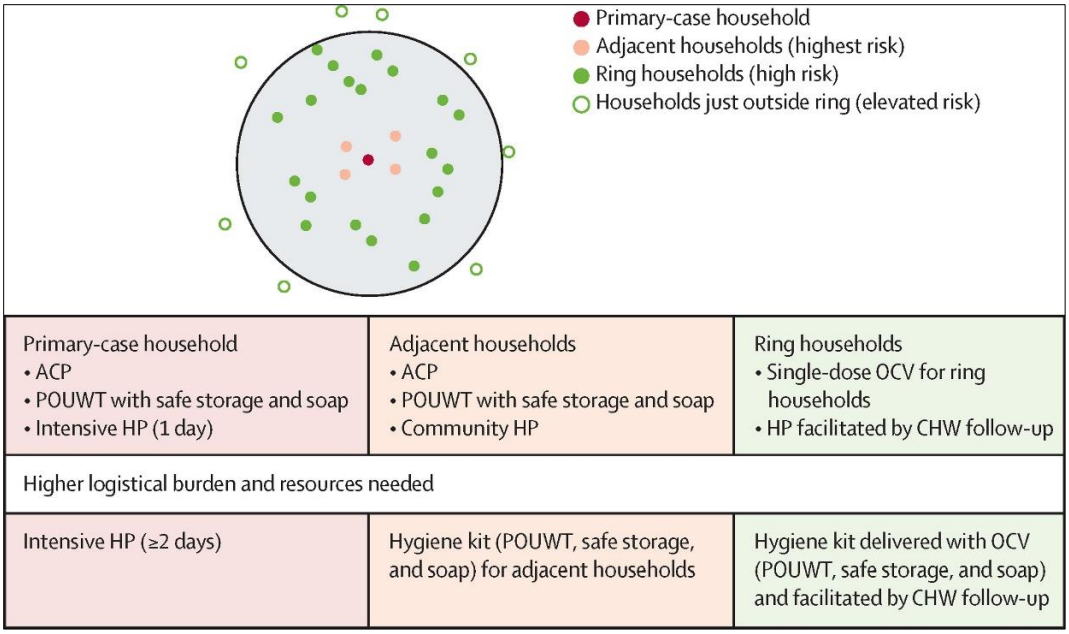

Figure 2.1: *Conceptual framework for CATI delivered within a 100 m radius and 7 days*

ACP=antibiotic chemoprophylaxis. POUWT=point-of-use water treatment. HP=hygiene promotion. CHW=community health workers. OCV=oral cholera vaccination (single dose).

DISCUSSION

Our analysis integrates multiple lines of evidence on the effective implementation of CATI during cholera epidemics. We found moderate evidence that ACP, intensive hygiene promotion, POUWT, and single-dose OCV can rapidly limit transmission. Four studies indicated a high-risk spatiotemporal ring of 50–100 m over 7 days in urban and rural contexts, probably related to intense household transmission and shared risk factors among households. This result specifies an implementation radius that has been used in Haiti, Nepal, and Yemen. CATI's ability to address more than 80% of epidemic alerts suggests feasibility across settings.[61,63-65] Although additional rigorous evaluation is needed, two controlled studies showed a reduction in household transmission when targeting case households (Bangladesh), and in duration and size of case-clusters when targeting radii (Haiti).[60,62] These studies reflect the findings of mathematical models where CATI[57] using OCV, or similar OCV-targeting strategies,[93] showed reduced outbreak size and duration.

CATI's effectiveness in reducing local transmission depends on the ability of combined interventions to affect both transmission routes with a rapid onset of protection and an adequate radius of implementation. Rapidly acting interventions such as ACP and household WASH are a priority. ACP can protect uninfected and infected hosts, and was shown to increase the effect of a WASH-focused CATI.[62] Handwashing and hygienic behaviours underlie household transmission.[38,40] Single-dose OCV should be strongly considered for CATI, as it is the only intervention to provide extended protection within a week, and is as effective as two doses over a 2 month to 1 year period.[24,27] For further application, a live-attenuated OCV has shown a 24 h onset to protection in an infant rabbit model.[94] Although the current evidence supports ring sizes of approximately 100m, practical evaluation of the feasibility of implementation should be undertaken, particularly in urban contexts. The potential benefits of doing CATI in a densely packed population, in terms of potential impact and resource savings, must be considered alongside the feasibility of achieving coverage within a 1-week period.

Two elements, the sensitive surveillance of case clusters and diagnostic specificity, provide the essential foundation for implementing CATI rapidly and accurately so as to not waste resources. Diagnostic specificity can be enhanced at the local level by using enriched RDTs to identify cholera alerts.[91,95] With mean delays of 4 days involving confirmation (Kathmandu) and RDT enrichment and OCV implementation (Juba), CATI would not be fast enough to interrupt the first generation of transmission, even if the onset of protection was immediate.[64,66] National preparedness and control plans should proactively integrate epidemiological scenarios for the use of CATI to organise support for surveillance and its interventions. Global preparedness policy requires consideration of CATI's particular use of interventions. The global OCV stockpile does not address provision for CATI, although vaccine supply is increasing and disbursing small batches to countries before the cholera season should be attainable.[29,72] The Global Task Force on Cholera Control supports ACP for closed settings (e.g., prisons) but requires more evidence to inform guidance for community contacts.[71]

Two related areas for development are to establish costs and models for scaling up interventions. Monthly costs for national coverage of CATI in Haiti and Yemen (without OCV) were within range of a one-dose OCV campaign in Lusaka (USD$1 million).[32,65] However, these costs reflect national, UNICEF-supported responses, which might exceed costs of smaller outbreaks and for national or non-governmental organisations. Maintaining implementation during a growing epidemic is challenging and resource intensive. Few CATI experiences used

CHW networks or oral rehydration points despite them providing an infrastructure to engage communities and continue the delivery of CATI interventions, particularly where humanitarian access is poor.[67,96]

To date, most CATI strategies have focused on household WASH, with minimal integration of ACP and OCV. Prospective studies should evaluate the effect of packages of interventions that combine immediate effects of interventions with longer-term protection by OCV. Given the logistical and ethical difficulties in doing RCTs during epidemics, quasi-experimental designs with mathematical modelling and costing should be considered.[57,97] CATI could contain, in theory, low-level transmission during the dry season to prevent *V cholerae* from seeding and proliferating during the rainy season.[98,99] Such opportunistic timing could be evaluated, given the difficulties in maintaining CATI during a large epidemic. Finally, the effectiveness of ACP for cholera requires evidence that considers different drug classes and the emergence of antibiotic resistance, similar to current investigations of ciprofloxacin use for ACP during meningococcal meningitis epidemics.[92,100] Although increases in macrolide resistance occurred during a large trial of azithromycin to reduce child mortality in Niger, the comparatively small volumes distributed for CATI might carry less risk of resistance.[101,102]

Conclusion

To both contain an outbreak and protect against ongoing risk of infection, we consider the core components of effective CATI to be: sensitive surveillance and local RDT capacity; integration of rapidly protecting interventions in adjacent households (ACP, POUWT, and hygiene promotion) and extended-protection interventions in the ring (OCV); and resources to mount implementation in 50–100 m rings. Delays in cholera detection and response due to weak surveillance, slow reactivity of actors, insufficient preparedness, and conflict will continue to undermine cholera response.[34,80,84] CATI as a new model for cholera response can purposively address these barriers and provide a model for future integrated epidemic response.

CONTRIBUTORS

RR, FC, and WJE developed the concept for the Scoping Review. RR searched the literature, extracted the data, synthesised the data, wrote the original draft of the manuscript, and prepared the tables and figures. All authors contributed to the interpretation of the data and the revision of the manuscript.

DECLARATION OF INTERESTS

The authors declare that they have no competing interests.

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SUPPLEMENTARY INFORMATION (APPENDIX A)

- Search strings
- Websites searched and organizations contacted
- Data abstraction variables for CATI descriptions and evaluations
- Retrieved articles (April 24, 2020)
- Risk of bias assessment
- Table S1. Estimates of the effectiveness of individual interventions against infection and/or development of symptoms
- Table S2. Spatiotemporal studies of cholera infection risk

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Chapter 3: Early detection of cholera epidemics to support control in fragile states: estimation of delays and potential epidemic sizes

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Student ID Number	071663	**Title**	Mr.
First Name(s)	Ruwan		
Surname/Family Name	Ratnayake		
Thesis Title	Case-area targeted intervention for the control of cholera epidemics in crises: from spatial mathematical modelling to field evaluation		
Primary Supervisor	Prof. Francesco Checchi		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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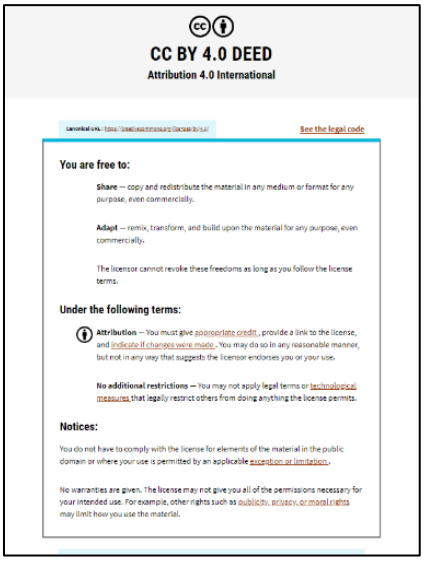

BRIDGING PASSAGE

Rationale for study: Cholera tends to occur and propagate explosively in fragile and conflict affected states (FCAS). Building on the scoping review of CATI, I needed to understand how feasible it would be to implement an early, rapid response to contain small outbreaks in resource-poor, crisis-affected settings. This involved measuring response times and other milestones for past outbreaks.

Overview of methods: I constructed a list of cholera outbreaks in FCAS from 2008 to 2019. This involved a formal systematic review of scientific articles and retrieval of grey literature reports (i.e. epidemiologic reports, after-action reviews, etc.). I evaluated the delays from symptom onset of the first known case to earliest dates of outbreak detection, investigation, response, and confirmation (wherever these dates were available). To gauge the impact of delays, I used a branching process model to estimate the potential epidemic size and interquartile range. To understand if any known factors were associated with delays to response (signal type, context, crisis, WHO region, and year of onset), I conducted regression analysis. I identified potential predictors of reduced delay from the case studies of the outbreaks.

Main conclusion: From the review of 76 outbreaks in 34 countries, median delays to case presentation at a health facility and response were 5 and 10 days, respectively. The 10-day delay resulted in large clusters that would be difficult to contain, but the delay to presentation of 5-days reveals an opportunity for earlier intervention (i.e., via CATI), if cholera is suspected and tested. Qualitative findings include that event-based detection, rapid diagnostic testing for cluster validation, and integrated alert, investigation, and response are core to rapid response.

Role: I developed the concept and study design, searched the literature, compiled the data, led the regression and modelling analyses, and wrote the original draft.

Use of findings in Ph.D. and beyond: I used the findings to inform the design of CATI for MSF, specifically to understand what a timeline would look like in a FCAS. I used the timeliness findings to inform modelling. It has been cited in a practice guideline for timely outbreak response in *The Lancet* and in the WHO's Early Warning Alert and Response Operational Guidelines.

Early detection of cholera epidemics to support control in fragile states: estimation of delays and potential epidemic sizes

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ABSTRACT

Background: Cholera epidemics continue to challenge disease control, particularly in fragile and conflict-affected states. Rapid detection and response to small cholera clusters is key for efficient control before an epidemic propagates. To understand the capacity for early response in fragile states, we investigated delays in outbreak detection, investigation, response, and laboratory confirmation, and we estimated epidemic sizes. We assessed predictors of delays, and annual changes in response time.

Methods: We compiled a list of cholera outbreaks in fragile and conflict-affected states from 2008 to 2019. We searched for peer-reviewed articles and epidemiological reports. We evaluated delays from the dates of symptom onset of the primary case, and the earliest dates of outbreak detection, investigation, response, and confirmation. Information on how the outbreak was alerted was summarized. A branching process model was used to estimate epidemic size at each delay. Regression models were used to investigate the association between predictors and delays to response.

Results: Seventy-six outbreaks from 34 countries were included. Median delays spanned 1-2 weeks: from symptom onset of the primary case to presentation at the health facility (5 days, IQR 5—5), detection (5 days, IQR 5—6), investigation (7 days, IQR 5.8—13.3), response (10 days, IQR 7—18), and confirmation (11 days, IQR 7-16). In the model simulation, the median delay to the earliest day of response (10 days) with 3 seed cases led to a median epidemic size of 12 cases (upper range, 47) at 10 days and 8% of outbreaks ≥20 cases (increasing to 32% at 30 days, with a 30-day delay to the earliest day of response). Increased outbreak size at detection (10 seed cases) and a 10-day median delay to the earliest day of response resulted in an epidemic size of 34 cases (upper range 67 cases) at 10 days and <1% of outbreaks <20 cases. We estimated an annual global decrease in delay to response of 5.2% (95% CI 0.5—9.6, p=0.03). Outbreaks signalled by immediate alerts were associated with a reduction in delay to response of 39.3% (95% CI 5.7—61.0, p=0.03).

Conclusions: From 2008-2019, median delays from symptom onset of the primary case to case presentation and to the earliest day of response were 5 days and 10 days, respectively. Our model simulations suggest that depending on the outbreak size (3 versus 10 seed cases), in 8% to 99% of scenarios, a 10-day delay to response would result in large clusters that would be difficult to contain. Improving the delay to response involves rethinking the integration at local

levels of event-based detection, rapid diagnostic testing for cluster validation, and integrated alert, investigation, and response.

Keywords: armed conflict, cholera, communicable disease control, epidemics, outbreaks, refugees, surveillance

BACKGROUND

Cholera transmission was reported in 34 countries in 2018 and 55 countries in 2019.[1,2] The disease is estimated to be substantially under-recorded.[3] Large cholera epidemics frequently coincide with armed conflict and humanitarian crises, including those in Democratic Republic of the Congo, Iraq, Somalia, South Sudan, and Yemen.[4-8] At the start of a cholera outbreak, transmission is driven by the low capacity to detect and isolate the first identified cases. Inadequate preparedness and poor access to case management drives increased mortality. The rapid detection and control of small outbreaks is therefore key for efficient control before an epidemic propagates.[9]

In 2017, the Global Task Force on Cholera Control (GTFCC) recommended that countries increase their capacity to contain small outbreaks, using rapid response teams, to aid efforts to substantially reduce global transmission by 2030.[10] However, little is known about the global capacity for rapid detection of, and response to, cholera outbreaks. In a review of the detection of all-pathogen outbreaks in Africa reported in the World Health Organization's (WHO) Disease Outbreak News from 1996 to 2014, the median time from onset of symptoms of the first identified case (or health facility visit, if unavailable) to discovery of the outbreak (defined, for example, as the declaration of the outbreak or appearance in an official report) was 27 days [95% CI 20—31.5].[11] A review of all-pathogen outbreaks in fragile and conflict-affected states from 2000 to 2010 found a similar median delay of 29 days [range 7—80] from symptom onset of the first identified case to detection of the outbreak and a median delay of 7 days [range, 0-30] from detection to investigation.[12] For cholera, a month-long delay in detection represents approximately 6 median serial intervals and thus, a high potential for uncontrolled transmission.[13]

To understand the potential for early detection and rapid response for cholera outbreaks in fragile and conflict-affected states, we examined temporal trends in cholera epidemics to evaluate with what delays the first case or cluster presented, was detected, investigated, responded to, and was confirmed by laboratory culture. We modelled epidemic sizes corresponding to these delays. To explain these delays, we investigated the mechanisms for early warning of these outbreaks, predictors of delays, and global improvements in reducing delays.

METHODS

COMPILATION OF CHOLERA OUTBREAKS

The period of 2008 to 2019 was chosen to reflect recent experience with cholera response. A list of countries that appeared ≥2 times during this period on the World Bank's Harmonized List of Fragile Situations, and had a documented cholera burden as per the GTFCC's 2017 list of cholera-affected countries, was compiled (appendix B.1). [10,14] Small-island states affected mainly by climate change rather than conflict were excluded. A list of countries meeting the fragility criteria but not included in the GTFCC list were included if they were documented using other sources as having had cholera outbreaks from 2008 to 2019 (i.e., Iraq, Myanmar, and Syria). Cholera-affected countries that did not meet the fragility criteria but either (a) hosted refugees (i.e., Kenya, Tanzania, and Uganda) and/or (b) border fragile and conflict-affected states with cholera outbreaks (i.e., Benin, Ethiopia, Niger, Nigeria, Tanzania, and Zambia) were included. Given that no annual list of annual cholera outbreaks exists, a list of outbreaks was compiled using a two-step process. We first reviewed WHO's annual cholera reports to identify which countries reported transmission during the study period. [15] Countries that do not routinely report cholera to WHO but are known from other sources to have had cholera outbreaks were included (e.g., Ethiopia and Myanmar). We then sought details on the occurrence of sub-national outbreaks from WHO's Disease Outbreak News and UNICEF's Cholera Outbreaks in Central and West Africa Bulletin (2015-9). [16,17] The GTFCC definition of a cholera outbreak was applied (cholera-free region: ≥1 culture-confirmed case and evidence of local transmission or, year-round transmission: unexpected increase in magnitude or timing of suspect cases over 2 weeks with laboratory confirmation). [18] As stool sampling and transport is often unfeasible in insecure settings, we included instances where cholera alerts were identified (e.g., one case of acute watery diarrhoea (AWD) testing positive for cholera by rapid diagnostic test (RDT)). [19] Finally, we included cholera alerts that triggered the cholera investigation mechanism, but where testing detected another pathogen, in order to explore detection and investigation mechanisms.

COMPILATION OF REPORTS ON CHOLERA OUTBREAKS

We searched the peer-reviewed literature for further identification and reporting on cholera outbreaks. Peer-reviewed articles were sourced from PubMed/MEDLINE using a date-specific keyword search ("country AND cholera"). Given that only a small number of outbreaks are reported in the scientific literature, we searched the grey literature, including epidemiological summaries, national cholera preparedness and response plans, and non-peer reviewed studies.

The sources included: (1) Reliefweb (a repository of documents and data from humanitarian crises) using a date-specific keyword search ("country AND cholera"; "UNHCR AND cholera"); and (2) regional outbreak bulletins and journals including WHO EMRO Weekly Epidemiological Monitor (2008 to 2019), WHO AFRO Outbreaks and Emergencies Bulletin (2017-9), WHO SEARO Journal of Public Health, WHO WPRO Western Pacific Surveillance and Response Journal, and UNICEF Cholera Outbreaks in Central and West Africa Bulletin (2015 to 2019).[16,20-24] The Program for Monitoring Emerging Diseases (ProMED) database of disease observations from media sources was used to fill in missing information on dates, but was not used as the primary source of information.[25] When little information was available from the sources above, websites of ministries of health and crisis-specific surveillance systems (e.g., early warning alert and response systems or networks (EWARS/EWARN) or disease early warning systems (DEWS)) were searched. An example includes the EWARN of the Syrian Assistance Coordination Unit for Northern Syria.[26]

INCLUSION CRITERIA AND DATA EXTRACTION

Outbreaks were included if at least two of the following dates were available: (1) dates of symptom onset of the primary case, and/or case presentation, and/or outbreak detection, and (2) dates of investigation and/or response. If the date of symptom onset for the primary case was missing, it was estimated as 5 days before the date of case presentation (equal to the median delay for outbreaks with available date of symptom onset), or date of outbreak detection if date of case presentation was unavailable. If the date of case presentation was unavailable, it was replaced by the date of outbreak detection. The earliest dates of (1) symptom onset for the first identified primary case, (2) case presentation to a health facility, (3) detection of outbreak/alert raised, (4) investigation by local health authorities, (5) response, and (6) laboratory confirmation by culture were extracted (Table 3.1). We defined the date of response as the earliest date by which a cholera-specific control measure was applied to the outbreak-affected area (e.g., water, hygiene, and sanitation (WASH) activities, setup of case management, active case-finding, community-based activities, and delivery of cholera kits). The starting month and year of the outbreak, geographical context (i.e., urban, rural, or displacement camp), type of crisis or fragility (i.e., armed conflict, fragile state, natural disaster, refugee setting, non-fragile state bordering a fragile state), and WHO region were extracted. Any additional information on factors that may have contributed to the observed delay, including presence of an early warning function, were extracted. Details on the signal type for outbreak detection were recorded, if

available, as a (1) *formal alert* detected by health workers reported immediately within the surveillance system, (2) *informal alert* from community members or a non-governmental organization (NGO) reported immediately, or (3) *weekly data analysis* of surveillance trends.

Table 3.1: *Dates used to estimate delays in detection, investigation, and response for cholera outbreaks*

Table 1 Dates used to estimate delays in detection, investigation, and response for cholera outbreaks

Date	Defined as earliest date (by priority)
Date of start of outbreak	1. Symptom onset for first identified case 2. Case presentation to health facility (less 1 day)
Date of alert/outbreak detection	Alert issued from health facility, community health worker, community member, local public health office, or laboratory
Date of investigation	Investigation by local authorities
Date of earliest response	Any cholera-specific response activity (case-finding, control measures by health facility or public health office, household/community WASH, case management)
Date of laboratory confirmation	First documented culture confirmation

ANALYSIS OF DELAYS AND THEIR PREDICTORS

For each outbreak, median delays and their interquartile ranges (IQR) were calculated by subtracting the date of symptom onset of the primary case from the dates of: (1) case presentation, (2) outbreak detection, (3) investigation, (4) earliest response, and (5) laboratory confirmation. For each outbreak, the dates were graphed on a timeline. We also calculated the delays based only on the 25 outbreaks for which the date of symptom onset was available.

To investigate the association between the observed delay from symptom onset of the primary case to response and potential predictor variables, a multivariate ordinary least-squares regression model was used. Delay to response was log-transformed to produce a normalized distribution. Extreme values in delay to response were judged to represent meaningful delays rather than data errors and were retained in the dataset. Predictor variables included signal type, context, crisis, WHO region, and year of outbreak onset (to detect any secular trend). Akaike Information Criterion (AIC) and a step-wise selection process was used to assess model fit and complexity. In separate regressions, year of outbreak onset was used as a predictor variable to investigate secular trends for delays to case presentation, outbreak detection, investigation, and confirmation. Loess curves were used to visualize the temporal trends using a smoothed trend line that down-weighted extreme values. 27 Percent change and 95% confidence intervals were presented for each regression.

BRANCHING PROCESS MODEL

A preliminary review of retrieved reports demonstrated that the early epidemic sizes at the dates that the outbreak was detected and responded to were rarely documented. Instead, to estimate the potential early epidemic sizes at each delay, a branching process model was used to estimate the median and range of epidemic sizes at the time points indicated by the median delays to case presentation, investigation, response, and confirmation. [28-30] We simulated multiple outbreaks using 10,000 runs and calculated the proportion of these outbreaks with early epidemic sizes in a 5 to 30 day period after detection below the threshold of 20 cases, which we selected arbitrarily as having the potential to be contained. Transmission started with a seed case(s) which generated secondary cases from a negative binomial distribution $\boldsymbol{Z \sim \text{NegB}(R_E, k)}$ with a mean equivalent to the reproduction number (R_E, 2.5[13,31], reflecting early and high transmission potential among an unvaccinated population) and heterogeneity introduced by a dispersion parameter (k, 4.5, reflecting low overdispersion in R_E). [32] Each new infection drew a time of infection from a serial interval distribution $\boldsymbol{S \sim \text{gamma}(\text{shape}=0.5, \text{rate}=0.1)}$ with a mean of 5 days. [4,13,33] We assumed that at the time of outbreak detection, there were 3 seed cases, and that all resulting infectious persons were symptomatic. Simulations would end by chance when either the cases did not produce additional secondary cases, or they reached 1,000 cases (representing a large outbreak). In a sensitivity analysis, we considered outbreaks of larger size at detection (i.e., 10 and 20 seed cases).

All analyses were carried out in R statistical software version 4.0.3. [34]

RESULTS

DESCRIPTION OF OUTBREAKS

Seventy-six outbreaks from 34 countries met the inclusion criteria. Overall, 1,970 documents were reviewed, and 138 documents were retained (1-4 documents per outbreak including 28 peer-reviewed articles and 110 grey literature sources as listed in appendix B.2). [35-172] Where countries reported only acute watery or severe diarrhoea as a proxy for cholera (e.g., Ethiopia, Myanmar) [173,174] or where surveillance was poor due to conflict in remote areas (Myanmar, Northern Nigeria, Syria as documented by Sparrow and colleagues) [19], few or no reports were located. Few reports from endemic countries with ongoing transmission (e.g., Cameroon, Democratic Republic of the Congo, Somalia) were found, likely due to the difficulty in

ascertaining start dates. Three false alerts resulting in the exclusion of cholera were identified in Cameroon (2) and Syria (1); we described these outbreaks qualitatively and left them out of the quantitative analysis. [101,102,109] One alert of an RDT-positive case where culture could not be obtained due to ongoing conflict was identified in Syria, and kept in the quantitative analysis (noting that confirmation was not possible). [84,85] Fifty-one (67%) of the 76 outbreaks were missing the date of onset of symptoms for the primary case.

Narrative descriptions and sources of information for outbreaks are compiled in appendix B.2. Most reports were from Africa (80.3%, mainly Chad, South Sudan, Burundi, and Uganda) and the Eastern Mediterranean region (13.2%, mainly Yemen, Iraq, and Syria) (Table 3.2). Outbreaks occurred during armed conflicts (e.g. Afghanistan, South Sudan, Yemen), after natural disasters (e.g. cyclones in Mozambique, post-earthquake in Nepal), in fragile situations (e.g. Angola, Chad), in refugee settlements (e.g. camps in Kenya and Tanzania), and in countries bordering cholera-affected fragile states (e.g., Benin, Tanzania). Most reports (56.6%) were from urban sites. Where the information was available (55/76 outbreaks), most (83.6%) were detected through formal and informal alerts compared with weekly data analysis (16.4%).

DELAYS AND POTENTIAL EPIDEMIC SIZES

Median delays are listed in Table 3 and histograms of the delays are listed in appendix B.3. Timelines of the individual outbreaks are visualized in Figure 3.1. Including only outbreaks with an available date of symptom onset produced congruent estimates, indicating some bias by the small number of outbreaks with available values for the date of symptom onset (appendix B.6). The median delay from date of the first identified case's symptom onset to case presentation at the health facility was 5 days (IQR 5—5). The median delays between symptom onset of the primary case and detection (5 days, IQR 5—6), investigation (7 days, IQR 5.8—13.3), and earliest response (10 days, IQR 7—18) spanned 1 to 2 weeks. Across countries, these delays varied; investigations and responses were routinely launched on the same or next day in Cameroon and Nepal, while long delays of 70 days in Uganda in 2015, 79 days in Chad in 2010, and 84 days in Yemen in 2011 were reported. The median delay to laboratory confirmation, for the 41/76 outbreaks for which the information was available, was 11 days (IQR 7—16), similar to the delay to response. Countries affected by conflict frequently had delays from symptom onset of the primary case to response greater or equal to 2 weeks (Figure 3.1).

Table 3.2 Characteristics of outbreaks, 2008-2019

Table 2 Characteristics of outbreaks, 2008–2019

Characteristic	*N* (%)
WHO region	
Africa (AFRO)	61 (80.3)
Eastern Mediterranean (EMRO)	10 (13.2)
South-East Asia (SEARO)	3 (4.0)
Americas (PAHO)	1 (1.3)
Western Pacific (WPRO)	1 (1.3)
Context	
Urban	43 (56.6)
Rural	27 (35.5)
Refugee or displacement camp	6 (7.9)
Crisis	
Fragile situation	31 (40.8)
Armed conflict	25 (32.9)
Country bordering FCAS	10 (13.2)
Natural disaster	5 (6.6)
Refugee setting	5 (6.6)
Surveillance system *N = 47 (not reported for 29 outbreaks)*	
Early warning function	36/47 (76.6)
Through routine surveillance	22/36 (61.1)
EWARS/DEWS	14/36 (38.9)
Routine surveillance	11/47 (23.4)
Signal *N = 55 (not reported for 21 outbreaks)*	
Alert	46/55 (83.6)
Formal alert	37/46 (80.4)
Informal alert	9/46 (19.6)
Weekly data analysis	9/55 (16.4)

Several outbreaks were detected when already large, challenging containment (e.g., Afghanistan, 2011, 255 cases, ID 2; Chad, 2017, 50 cases and 13 deaths, ID 19; Ethiopia, 2015, 268 cases, ID 28; Haiti, 2010, >1000 cases, ID 32). Table 3.4 summarises the model-simulated early epidemic sizes that the outbreaks could have reached by the date of different delays and different initial outbreak sizes. With 3 seed cases at detection, a median delay to case

presentation of 5 days resulted in a median epidemic size of 9 cases (upper range, 29 cases) at 5 days, with nearly all outbreaks <20 cases (98.6%). A median delay to response of 10 days resulted in a median epidemic size of 12 cases (upper range, 47 cases) at 10 days, with a comparable proportion of outbreaks <20 cases (92.6%). Lengthening the delay to response to 30 days resulted in an upper range of 72 cases at 30 days, with 67.7% of outbreaks remaining <20 cases. Using 10 seed cases to simulate outbreaks of larger size at detection, a median delay to case presentation of 5 days resulted in a median epidemic size of 28 cases (upper range, 55 cases) at 5 days, with a minority of outbreaks <20 cases (5.7%). With a median delay to response of 10 days delay, there was a median epidemic size of 34 cases (upper range, 67 cases) at 10 days, with <1% of outbreaks <20 cases. At 30 days, the upper range was 100 cases at 30 days, with <1% of outbreaks remaining <20 cases. With 20 seed cases at detection, outbreaks enlarged quickly, reaching a median of 55 cases (range 30—89) at 5 days, with a median delay to response of 5 days and median of 65 cases (range 40—110) at 10 days, with a median delay to response of 10 days.

Table 3.3 *Median delays (with interquartile range (IQR) and range)*

Table 3 Median delays (with interquartile range (IQR) and range)

Delay	Median delay (days) (IQR)	Range (days)
Delay to case presentation ($n = 76$)		
Symptom onset to case presentation	5 (5–5)	0–22
Delay to detection ($n = 76$)		
Symptom onset to outbreak detection	5 (5–6)	0–29
Case presentation to outbreak detection	0 (0–0.3)	0–24
Delay to investigation ($n = 48$)		
Symptom onset to investigation	7 (5.8–13.3)	0–84
Case presentation to investigation	2 (1–8)	0–62
Delay to response ($n = 67$)		
Symptom onset to response	10 (7–18)	0–84
Case presentation to response	6 (2.5–13.5)	0–74
Delay to confirmation ($n = 41$)		
Symptom onset to confirmation	11 (7–16)	0–74

Table 3.4 *Simulated epidemic sizes (with SD and range), and proportion of outbreaks <20 cases for outbreaks of 3, 10, and 20 seed cases at detection*

Table 4 Simulated epidemic sizes (with standard deviation (SD) and range), and proportion of outbreaks < 20 cases for outbreaks of 3, 10, and 20 seed cases at detection

		3 seed cases		10 seed cases		20 seed cases
Delay from onset of symptoms (primary case)	**Median delay (days)**	**Median epidemic size (SD, range)**	**% outbreaks < 20 cases**	**Median epidemic size (SD, range)**	**% outbreaks < 20 cases**	**Median epidemic size (SD, range)**
Case presentation or outbreak detection	5	9 (3.7, 3–29)	98.6	28 (5.7, 12–55)	5.7	55 (7.4, 30–89)
Investigation	7	10 (4.4, 3–40)	96.9	31 (6.1, 11–61)	1.6	60 (8.2, 34–99)
Response	10	12 (5.1, 3–47)	92.6	34 (7.0, 16–67)	< 1	65 (8.8, 40–110)
Confirmation	11	12 (5.4, 3–50)	91.9	35 (7.1, 13–69)		67 (9.1, 41–105)
Delay from onset of symptoms (primary case)	**Counterfactual delay (days)**	**Median epidemic size (SD, range)**	**% outbreaks < 20 cases**	**Median epidemic size (SD, range)**	**% outbreaks < 20 cases**	**Median epidemic size (SD, range)**
14-day delay	14	14 (6.0, 3–51)	85.8	37 (7.8, 17–79)	< 1	70 (9.7, 41–113)
21-day delay	21	16 (7.4, 3–63)	76.6	40 (9.0, 16–87)		74 (10.8, 43–124)
30-day delay	30	18 (8.9, 3–72)	67.7	43 (10.3, 18–100)		78 (12.2, 43–131)

Legend: *DRC* Democratic Republic of the Congo, *CAR* Central African Republic, *PNG* Papua New Guinea

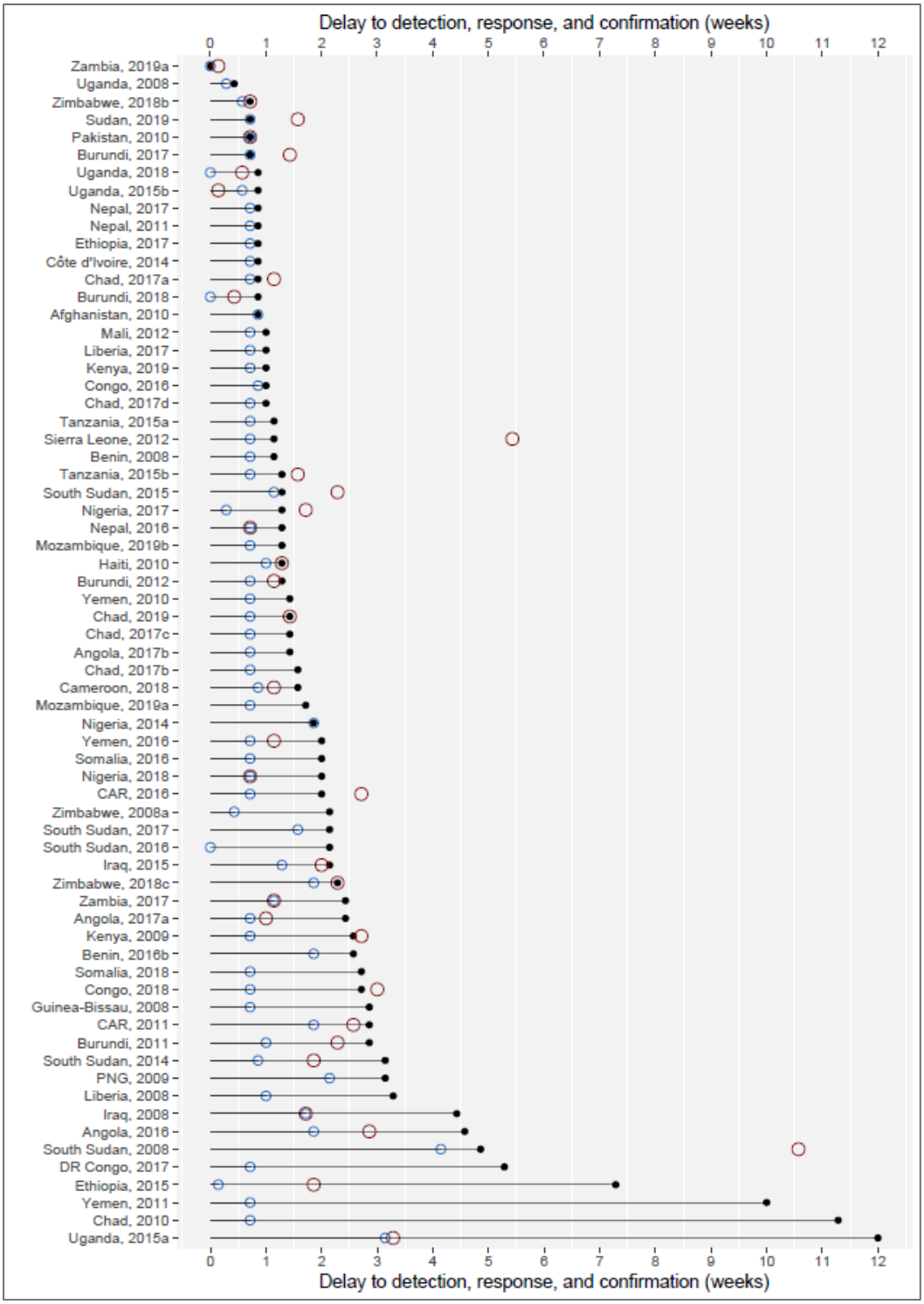

Figure 3.1 *Delay in weeks from date of onset of symptoms to outbreak detection (blue circle), response (black circle), and confirmation (red circle), by outbreak, 2008-2019 (excluding outbreaks missing response date).* ***Legend:*** *DRC, Democratic Republic of the Congo; CAR, Central African Republic; PNG, Papua New Guinea.*

FACTORS ASSOCIATED WITH DELAYS

Given that the signal type was complete for 55/76 observations, two models were implemented: a multivariable adjusted model (including year of outbreak onset, WHO region, context, and crisis type), and a bivariate model for signal type only (informal/formal alert versus weekly data analysis). Using AIC for the multivariable model, including only year of outbreak onset returned the lowest AIC score (appendix B.4). A weak crude association between year of outbreak onset and delay to response, with an annual decrease in response time of 5.2% (95% CI 0.5—9.6, p=0.03) was found (visualized in Figure 3.2). This model met the assumptions for linearity and homogeneous variance, and explained 6% of the variance. Similar decreases in delay to detection, investigation, and confirmation were found (Figure 3.2 and appendix B.5). In the second model, alerts (versus data analysis) were associated with a reduction in response time of 39.3% (95% CI 5.7—61.0, p=0.03) (boxplot displayed in Figure 3.3). The model met the assumptions for ordinary least-squares regression but one extreme value in delay affected the leverage. The model explained 8% of the variance.

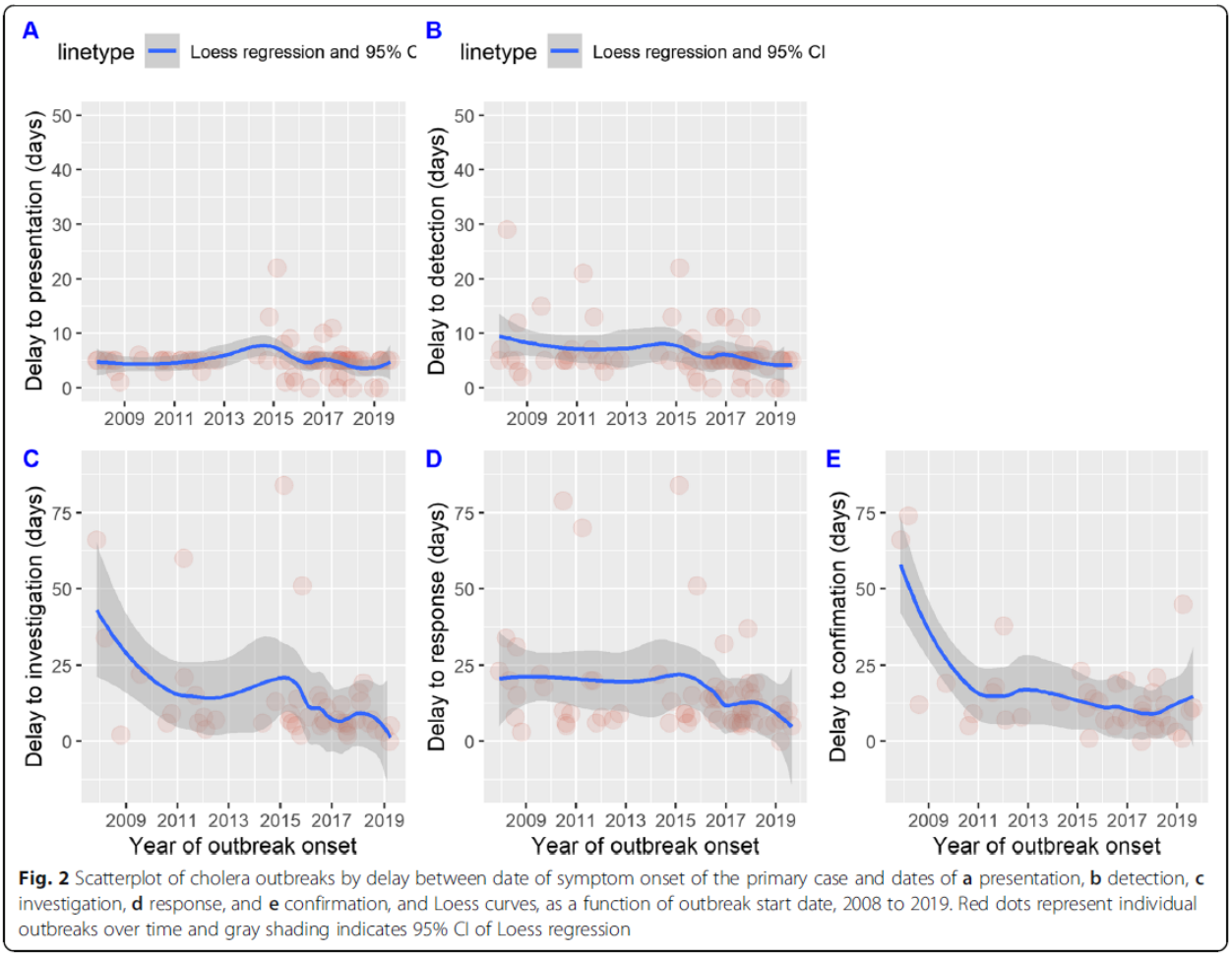

Fig. 2 Scatterplot of cholera outbreaks by delay between date of symptom onset of the primary case and dates of **a** presentation, **b** detection, **c** investigation, **d** response, and **e** confirmation, and Loess curves, as a function of outbreak start date, 2008 to 2019. Red dots represent individual outbreaks over time and gray shading indicates 95% CI of Loess regression

Figure 3.2 *Scatterplot of cholera outbreaks by delay between date of symptom onset of the primary case and dates of presentation, detection, investigation, response, and confirmation and Loess curves as a function of outbreak start date 2008 to 2009.*

More information from the examination of outbreaks is illustrative of the use of alerts. Of the 83.6% of outbreaks detected through alerts; 37/46 (80.4%) were through alerts by a health worker or community health worker and 9/46 (19.6%) through informal alerts by community members. For example, in 2015, in Aleppo, Syria, an alert was issued through the EWARN via phone after RDT testing of a suspect, and an investigation initiated based on the positive result (2-day delay to investigation, ID 63). In 2017, in a displacement camp in Northern Nigeria, an alert of a suspect case was issued by MSF by phone through the EWARS on the same day of case presentation (2-day delay to investigation, ID 48), demonstrating the rapid recognition of a suspect case by health workers. [172] Comparisons of outbreaks within countries are instructive. In

Benin, of two outbreaks in rural areas detected in 2016, one was detected through an immediate call to public health authorities (5-day delay to detection, ID 7) while issuance of the alert on the weekly set day of routine surveillance data transmission resulted in a 13-day delay to detection (ID 8). In Central African Republic in 2011, an alert from the community of multiple suspect cases was issued late (13-day delay, ID 16) compared with 2016 when an alert from Red Cross volunteers was issued in half the time (5-day delay, ID 17).

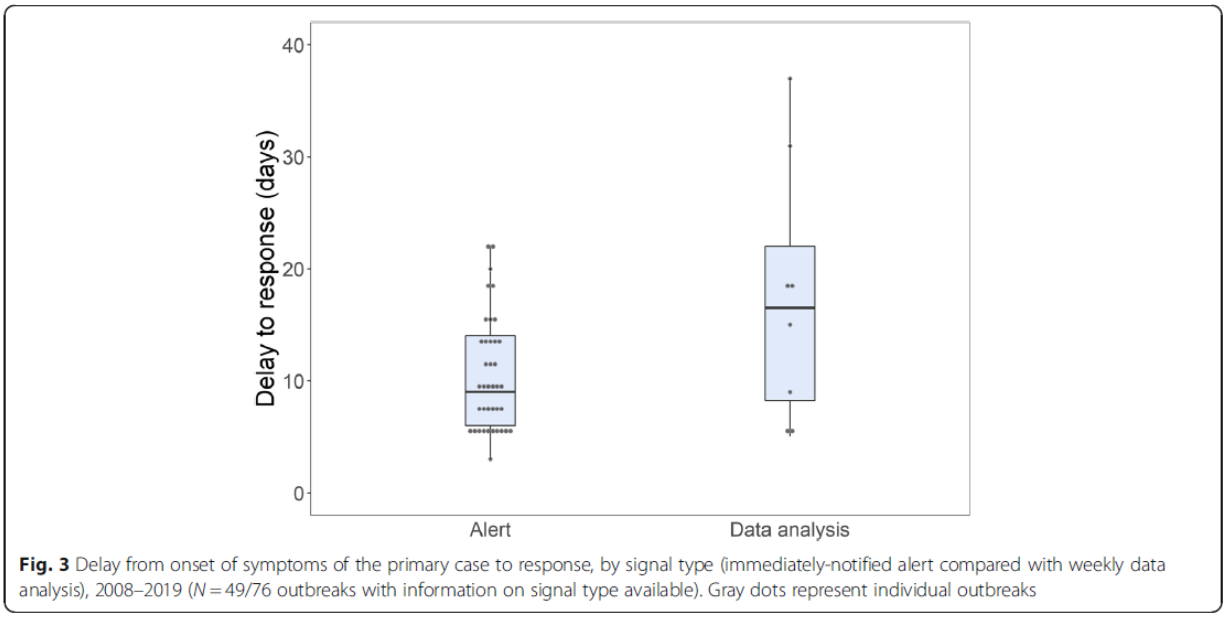

Fig. 3 Delay from onset of symptoms of the primary case to response, by signal type (immediately-notified alert compared with weekly data analysis), 2008–2019 (*N* = 49/76 outbreaks with information on signal type available). Gray dots represent individual outbreaks

Figure 3.3: *Delay from onset of symptoms of the primary case to response, by signal type (immediately-notified alert compared with weekly data analysis), 2008–2019 (N = 49/76 outbreaks with information on signal type available).*

In several instances, early warning systems further benefited from rapid investigation and response. For example, in Afghanistan, in 2010 the DEWS provided a response mechanism to link the detection of a large cluster of 60 suspect cases in a remote and insecure village by a local NGO with rapid action which reportedly led to containment within a month (6-day delay to investigation, ID 1). In 2011, the DEWS in Afghanistan detected an already-large outbreak of 255 suspect cases in multiple clusters but with a rapidly-administered response (21-day delay to investigation, ID 2). Reduced transmission within 3 months followed. In Liberia in 2017, a suspect case that died en-route to the health facility was detected based on symptoms, triggering a rapid response to isolate additional cases in the index case's village (7-day delay to investigation, ID

38). In Chad in 2017, two suspect cases among children which resulted in rapid progression to death were reported to the local health facility, who investigated the source village and found a larger cluster of 50 cases and 13 deaths (6-day delay to investigation, ID 19). Though already a large outbreak, this led to a response on the following day.

Information in reports suggested improvements in surveillance, investigation, and response over time. In Cameroon in 2016, two false alerts for cholera later attributed to food poisoning and rotavirus were made by health workers and community members respectively, and led to rapid investigation upon detection, testing by RDT and culture, and ongoing control activities during the investigation period (ID 13, 14). In Somalia, faster response in insecure urban areas using EWARS in 2016 and 2018, can be compared to a lack of a comprehensive early response during ongoing transmission over 2 months in 2008 (14 and 19-day delays versus 2-month delay, ID 54-56). Nepal's EWARS facilitated rapid detection and response to clusters from 2011 onwards (total delays 6-9 days, ID 42-44).[76,131,163] In 2016, RDT capacity was added at health facilities to enable better discrimination between alerts of cholera or diarrhoea due to other pathogens.[162]

POTENTIAL FACTORS RELATED TO LONG DELAYS TO RESPONSE

Long delays from symptom onset of the primary case to response (~2 weeks) were observed in 29/67 (43.2%) outbreaks for which a response date was available. These appeared to be related to poor sensitivity of the formal surveillance system due to the remote locations of outbreaks[64] (Papua New Guinea, ID 52); insecurity posed by armed conflict (Somalia, 2008, ID 54; South Sudan, 2008, ID 57; Yemen, 2011, ID 72); reliance on laboratory confirmation to declare an outbreak before initiating a comprehensive response (Iraq, 2008, 2015, ID 33, 34, South Sudan, 2014, ID 58); assuring government declaration and mobilization of non-governmental actors (CAR, 2011, ID 16); a less effective local response which required reinforcement by capacity from the national level or other partners (Congo, 2018, ID 25; Ethiopia, 2015, ID 28; Guinea-Bissau, 2008, ID 31; South Sudan, 2017, ID 61; Uganda, 2015, ID 68; Zimbabwe, 2018, ID 79)[114]; and missed superspreading events (e.g., a funeral in Zimbabwe, 2018, ID 79).[137]

DISCUSSION

In an era of large-scale cholera epidemics in conflict settings like Yemen and previously cholera-free settings like Haiti, improving and sustaining early detection and response to small outbreaks remains critical for averting large-scale epidemics. Reducing delays in the timelines of patients presenting to health facilities, increasing capacity of health workers to recognize suspect cases of cholera, and reinforcing local investigation and response therefore remain as important as vaccination and other emerging tools. Some of the largest outbreaks in recent years in South Sudan (2014-6), Ethiopia (2015 onwards), and Zambia (2017-8) have suffered from late detection and/or response, which has led to surges of cases that have overwhelmed health systems. [132,141,175-177]

Our findings indicate that from 2008 to 2019, median delays from symptom onset of the primary case to case presentation at the health facility and to response were approximately 5 days and 10 days, respectively. Longer delays to response were documented across the whole time period, despite consistent detection of outbreaks within 5 days. Evaluations from Nigeria, Yemen, and other settings have shown that reasons for delays to detection include poor population access to health services due to disrupted health systems and/or insecurity, difficulty in discerning diarrhoea and dehydration due to cholera from other causes without rapid diagnostics, reliance on laboratory confirmation before initiating response, and less effective local response. [172,178,179] Epidemic control more than 2 weeks post-onset carries a strong risk of epidemic propagation, particularly where the population is highly mobile. Our simple model simulations and sensitivity analyses suggest that with 3 seed cases, in 2% to 33% of scenarios such delays could result in clusters of 20 or more cases that would be difficult to contain. Comparatively, a field investigation and preliminary response to contain transmission done at the time of case presentation (~1 week) could potentially reduce the probability of reaching these epidemic sizes to 2% to 4% of scenarios. If the outbreaks are detected with 10 seed cases, even within ~1 week, 95% of outbreaks could accumulate 20 or more cases within 5 days, and thus would be difficult to contain.

Early detection and response are major aims of the *Ending Cholera* roadmap. There are two reasons to believe that policy and practice have somewhat narrowed the gap between detection and response. First we found a global improvement in time to response that corroborates a previous analysis of improvements for detection of all-pathogen outbreaks in low and middle-

income countries from 1996-2014.[11] This may be related to more attention and investment by governments and the GTFCC to the impacts of cholera epidemics in fragile states, given a decade of large and devastating cholera outbreaks in Haiti and across West and Central Africa, the Horn of Africa and the Gulf of Aden.[10] Some countries appear to have documented improved capacity for detection and response as shown in this analysis (e.g. Chad, Nepal, Somalia). This may be reflected by investments into epidemic strategies like the Joint External Evaluation process which have specified critical gaps for improvement.[180-182]

Detailed case studies of cholera outbreaks provide practical observations on the mechanisms of surveillance, diagnosis, and response which can reduce delays. Early detection with high-quality epidemiological data has been augmented with the use of: sentinel site surveillance at hospitals equipped with RDTs and trained and vigilant health workers in Kathmandu, Nepal[163]; community-based surveillance using existing community health worker or Red Cross volunteers networks to enable early warning of clusters in the community before patients appear at health facilities in Central African Republic and Haiti[72,153,183,184]; and other event-based surveillance mechanisms, including phone hotlines and mobile phone fleets, to enable immediate notification of suspect events in public, private, and NGO clinics and in the community, as seen in Northern Nigeria and Cameroon.[172,185,186] Response should not be delayed by poor laboratory capacity. A potentially stronger role for health workers in local facilities exists in their use of enriched, high-specificity RDTs[187] and aligned probable case definitions to validate clusters of suspected cholera cases that can trigger an immediate investigation and response.[163,172] This is directly applicable in certain remote districts and insecure areas where laboratory confirmation will be slow. Timely field investigation and preliminary response remains promising as most outbreak reports cited the use of an early warning alert system, with several examples of integrated investigation and response capacity. We consider that an integrated alert and at least a preliminary response to an outbreak within one week of onset should be possible in fragile settings.[188] However, despite the presence of EWARS in nearly 80% of the outbreaks examined, the median delay to response was 10 days. Where EWARS was used successfully to link early detection with a preliminary and robust response, for example in Afghanistan (2010-1), Nepal (2011-6), and Northern Nigeria (2018), a timely response was judged to be dependent on adequate and trained human resources (e.g. district-level rapid response teams and/or local health facility staff capable of multidisciplinary investigation and a generic response to stem transmission[64,163]), and the ability to mount at least a preliminary response moving forward independent of laboratory confirmation.

[53,76,101,102,140,162,172] To that end, investigation and response were integrated in Afghanistan (2010) where a local NGO was trained rapidly to carry out a comprehensive community response, as they had more access to the area than health authorities in an insecure area.[53] In Chad (2017), investigation was carried out by the staff of a local health facility, who also initiated the preliminary community response.[138]

It is important to consider the limitations inherent to a retrospective review of data from secondary sources. First, as no global registry of cholera outbreaks exists, we relied on the manual compilation of available situation reports and articles. The most comprehensive source, WHO's current compilation of annual cholera data, does not provide detailed information on outbreaks and misses non-reporting countries. The small annual numbers of outbreaks pre-2015 may reflect the few global data sources available. As well, larger outbreaks are more likely to be detected, responded to, and therefore documented and included here. Second, the delays are estimates of reality; dates from situation reports are likely inaccurate to an unquantifiable degree as the exact dates of local investigation and response may be subjective and documented infrequently. The identification of the primary case(s) depends on the depth of the field investigation, and with a multi-pathway pathogen like *V. cholerae* that causes a range of disease severity, transmission chains may be missed. Fifty-one (67%) of the 76 outbreaks were missing the date of onset of symptoms for the primary case, which then had to be estimated, limiting accuracy. Delay estimates were biased by the small number of outbreaks with available values for the date of symptom onset. The dates of response were based on the judgement of the timing of the first transmission-reducing intervention and thus may represent variable intensity of response across outbreaks. Of note, the longest delays to response noted during outbreaks in Chad, Ethiopia, Somalia, and Uganda were related to the first viable response after an inadequate local response. To address these inconsistences, we sourced multiple reports per outbreak to triangulate the information and obtain a clear timeline, and excluded a large number of outbreaks where reports lacked detailed dates. Second, we note that while outbreaks are likely to occur during conflict, they are difficult to detect amidst violence where surveillance coverage is poor.[19] These outbreaks, with potentially high mortality, may have gone undetected, unless they occurred in urban areas and/or propagated to a point of being overwhelming, as in South Sudan in 2014 and Yemen in 2016.[4,132] Third, the simple branching process model used here for a time-limited window of less than 30 days is for illustration purposes only. The model did not take into account key sources of uncertainty including initial susceptibility to infection

(influenced by prior cholera infection or vaccination), heterogeneity in contact and transmission routes, depletion of susceptible persons, and the time-varying R_t value.

The documentation of the occurrence and features of cholera outbreaks is currently very heterogeneous. A real-time global database, preferably maintained by WHO regional offices, to prospectively log data and metrics from outbreaks of cholera, as well as other epidemic-prone diseases, would yield superior accuracy for the evaluation of detection and response timeliness on an annual basis. We suggest that at the regional level, standard outbreak event reports be used track events and metrics to track progress in timely detection and response. WHO AFRO's Weekly Bulletin on Outbreaks and Emergencies provides an existing template which can feed into such a global database. [20] WHO AFRO has used this tool to provide annual metrics of timeliness in outbreak response for epidemic-prone diseases from 2017 to 2019, demonstrating reduced time from symptom onset of the primary case to outbreak detection (defined as alerting national authorities) from 14 (IQR 6–37) days in 2017 to 4 (IQR 1–11) days in 2019. [189]

CONCLUSIONS

Cholera epidemics will continue to appear unpredictably and cause serious morbidity and mortality in countries affected by armed conflict and fragility. Cholera surveillance and response is dependent on rethinking the timely detection, investigation, and response to primary cases at the local level. This includes reinforcing outbreak detection through, event-based surveillance methods, consistent weekly reporting using standard case definitions, and systematic use of enriched RDTs, and then integrating early investigation with preliminary local response. These measures should increasingly underpin the detection and containment of emerging epidemics.

List of abbreviations

AIC: Akaike information criterion, AWD: acute watery diarrhoea, CI: confidence interval, DEWS: disease early warning system, EWARN: early warning alert and response network, EWARS: early warning alert and response system, FCAS: fragile and conflict-affected situation, IQR: interquartile range, GTFCC: Global Task Force for Cholera Control, NGO: non-governmental organization, OCV: oral cholera vaccination, R_E: effective reproduction number, RDT: rapid diagnostic test, SD: standard deviation, WASH: water, sanitation, and hygiene, WHO: World Health Organization

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The dataset supporting the conclusions of this article is available in the Github repository, [https://github.com/ruwanepi/Detection-analysis].

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

SUPPLEMENTARY INFORMATION (APPENDIX B)

- **Appendix B.1.** Countries investigated.
- **Appendix B.2.** Outbreaks by country, date of onset, delays (detection, investigation, response), signal, source, and description of investigation and response.
- **Appendix B.3.** Histograms of delays from symptom onset to (A) case presentation, (B) outbreak detection, (C) investigation, (D) response, and (E) confirmation.
- **Appendix B.4.** Overview of alternative models for the main analyses.
- **Appendix B.5.** Model parameters for additional delay analyses.
- **Appendix B.6.** Delays calculated using outbreaks with date of symptom onset of primary case (N=25)

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Chapter 4: Spatiotemporal modelling of cholera and its implications for control, Uvira, Democratic Republic of the Congo

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	071663	**Title**	Mr.
First Name(s)	Ruwan		
Surname/Family Name	Ratnayake		
Thesis Title	Case-area targeted intervention for the control of cholera epidemics in crises: from spatial mathematical modelling to field evaluation		
Primary Supervisor	Prof. Francesco Checchi		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Emerging Infectious Diseases (currently a preprint, https://www.medrxiv.org/content/10.1101/2023.08.22.23294124v1)
Please list the paper's authors in the intended authorship order:	Ruwan Ratnayake, Jacqueline Knee, Oliver Cumming, Jaime Mufitini Saidi, Baron Bashige Rumedeka, Flavio Finger, Andrew S. Azman, W. John, Francesco Checchi, Karin Gallandat

Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived of the work, searched the literature, extracted the data, synthesised the data, wrote the original draft of the manuscript, prepared the tables and figures, interpreted the data and revised the manuscript.

SECTION E

Student Signature	[redacted]
Date	September 18, 2023

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Date	18 September 2023

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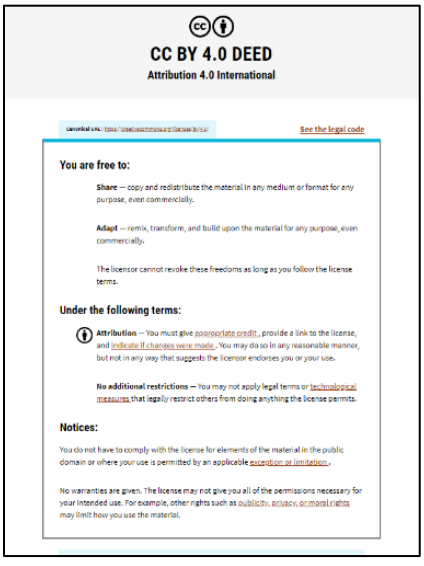

BRIDGING PASSAGE

Submitted to *Emerging Infectious Diseases, July 30, 2023*

Rationale for study: To better inform the mathematical modelling of case-area targeting interventions (CATI) in a setting in the Democratic Republic of the Congo (DRC), I carried out an analysis of the spatiotemporal clustering of cholera cases (i.e., how closely in time and space cholera cases are found) using five years of cholera surveillance data with rapid diagnostic testing. This data was sourced from Uvira, South Kivu, DRC, which is part of an international hotspot of endemic cholera in the African Great Lakes Region.

Overview of methods: I combined both global clustering statistics (i.e., the tau statistic) and local clustering statistics (i.e., the space-time scan statistic) to show, respectively, the general tendency of cases to cluster, and the expected density of cases at specific locations within a given area and when this amount is exceeded. Practically, this provided annual and total estimates of the zone of infection risk around a given case, and the timing and locations of clusters across Uvira.

Main conclusion: Elucidating cholera's specific clustering patterns in an endemic setting successfully provided key information on where intensive transmission is occurring early on, within small areas. I detected 26 clusters of mean radius 652m and mean duration 24.8 days, and these typically preceded seasonal outbreaks. In 2020, the infectious risk zone was 600m and enlarged to 1100m during the whole period.

Role: I developed the concept and study design, sourced the data from the Uvira study team, led the analyses, and wrote the original draft.

Use of findings in Ph.D. and beyond: I used the findings to inform the seeding of the outbreak and infection risk zone for the mathematical modelling of CATI described in Chapter 5. I presented the findings to the DRC Ministry of Health for the discussion of findings from the overall Uvira piped water evaluation.

Spatiotemporal modelling of cholera and implications for its control, Uvira, Democratic Republic of the Congo

Submitted to *Emerging Infectious Diseases.*

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ABSTRACT

The African Great Lakes region including Eastern Democratic Republic of the Congo is a hotspot for cholera transmission. We evaluated the local and global clustering of cholera using 5 years (2016—2020) of suspected cases positive by rapid diagnostic test in Uvira, South Kivu to detect spatiotemporal clusters and the extent of zones of increased risk around cases. We detected 26 clusters (mean radius 652m and mean duration 24.8 days) which recurred annually in three locations and typically preceded seasonal outbreaks. We found a 1100m zone of increased infection risk around cases during the 5 days following clinic attendance for the 2016—2020 period and a 600m radius risk zone for 2020 alone. These risk zone sizes correspond with the area typically used for targeted intervention in the Democratic Republic of the Congo. Our findings underscore the value of the site-specific evaluation of clustering to guide targeted control efforts.

Keywords: cholera/epidemiology; Democratic Republic of the Congo; outbreaks/ prevention & control; spatio-temporal analysis; transmission dynamics, *Vibrio cholerae*

INTRODUCTION

Cholera outbreaks continue to impact communities that lack access to safe water and adequate sanitation. (1-4) In these communities, cholera's relatively high reproduction number and short median incubation period (1.4 days, 95% credible interval 1.3—1.6) (1, 5) mean that an initial cluster can rapidly propagate across space. During outbreaks, household fecal-oral transmission through contaminated water, food, and fomites and direct contact becomes substantial and therefore, interventions to prevent infection of household contacts can reduce household transmission. (1, 6-8) Spatiotemporal clustering patterns around affected households have also demonstrated the propagation of transmission between neighbouring households. (9, 10) To attenuate and possibly contain transmission during outbreaks based on this natural clustering, case-area targeted interventions (CATI), consisting of an early, multisectoral response within a 100—500m area around case-households, have been proposed. (11-13) CATIs typically include water, sanitation, and hygiene (WASH) interventions to improve water quality and safety (i.e., point of use water treatment, safe drinking water storage containers) and promote hygiene practices like handwashing, antibiotic chemoprophylaxis, and sometimes, oral cholera vaccination (OCV). (13) CATIs with WASH have been a major component of response strategies in Haiti and Yemen (13, 14) while CATIs with WASH and OCV have been used to suppress small outbreaks after mass vaccination campaigns in Juba, South Sudan and Kribi, Cameroon. (15, 16) In the Democratic Republic of the Congo (DRC), similar area-targeted interventions have included the distribution of hygiene kits to case-households and the targeting of WASH interventions to a 500m radius around the most recent cases. (8, 17)

Studies in urban Kalemie, DRC and N'Djamena, Chad have estimated the zone of increased risk of infection around incident cases of at least 200m within the first 5 days after case presentation and in rural Matlab, Bangladesh, up to 450m within the first 3 days after case presentation. (9, 10) As CATIs and other targeted interventions become part of routine public health practice (14), more insight is required into the size and duration of the spatiotemporal zones of increased infection risk required to achieve a substantive impact on transmission, particularly in endemic areas. The size of the zone is likely influenced by factors that determine the strength of community transmission including population density, immunity, vaccination coverage, access to safe water and sanitation, and timeliness of the response. (3, 13)

Cholera has been endemic in the African Great Lakes Region including Eastern DRC since at least 1978 and now contributes substantially to the global cholera burden. (2, 18-22) The *V. cholerae* O1 sublineage AFR10 was introduced from South Asia to East Africa in the late 1990s, and has been driving transmission across the region during the last two decades. (23, 24) In Uvira, South Kivu, DRC, cholera is endemic with stable transmission punctuated by seasonal outbreaks. (18) Using an enhanced clinical surveillance system with rapid diagnostic testing that was setup in Uvira's cholera treatment units to support an impact evaluation of water supply infrastructure improvements (25), we investigate the location, timing, and annual prediction of spatiotemporal clustering and to estimate the extent of spatiotemporal zones of increased cholera risk around incident cases in an endemic setting.

METHODS

SETTING

Uvira is a town of approximately 280,000 located on the shore of Lake Tanganyika, an internationally-designated transmission hotspot where suspected cholera cases are reported year-round. (18-20) Seasonal emergence of cholera in Uvira is driven by seasonal exposure to aquatic reservoirs of *V. cholerae* in lakeside waters and person-to-person transmission, excess rainfall linked to fecal contamination of water sources, interruption of water supply and conflict and forced displacement. (18, 20, 26-28) Several city-wide interventions have been implemented including a water supply infrastructure program to improve the production and supply of piped drinking water for which construction started in 2018 and mass vaccination that took place from July to October 2020. (25)

DATA SOURCES

We used a line list of suspected cases (i.e., passing ≥3 loose or watery stools in 24 hours) who received care between 2016 and 2020 at either the Uvira General Hospital's cholera treatment centre (CTC) or the Kalundu cholera treatment unit (CTU, which opened in July 2019). Since April 2016, as part of an evaluation of a water supply infrastructure improvement program, rectal swabs collected from suspected cases have been systematically tested using an RDT (Crystal® VC O1/O139, Arkray Healthcare Pvt. Ltd, Gujarat, India) after a 6 hour enrichment period in alkaline peptone water at ambient temperature. (25, 29) The pooled sensitivity and specificity

estimates for enriched Crystal® VC RDTs are 83% (95% CI 67—92) and 98% (95% CI 94—99). (30) We extracted data for 2016—2020, including date of admission, completion of RDT and result, and avenue of residence (i.e., a small census enumeration area of mean size of 1177 (range 180—5711) persons based on population sizes estimated from 2017 official records. (31) The mean avenue area is 0.08 km^2 and minimum, maximum, and mean distances between avenue centroids are 0.0437m, 12.4km, and 3.1km, respectively. We based the main analyses on enriched RDT-positive cases given the presence of systematic testing in the CTC/CTU and assessments done at the CTC between 2017—2018 where only 40% of suspected cases were confirmed by polymerase chain reaction. (32)

DESCRIPTIVE ANALYSIS AND SEASONAL DECOMPOSITION

We described suspected cases using incidence per 10,000 population, proportion tested with RDT and proportion tested that were RDT-positive. To identify the timing of the cholera season, we analysed the seasonal decomposition of the weekly incident series of RDT-positive cases with seasonal and trend decomposition using LOESS STL (locally estimated scatterplot smoothing). This method decomposes the time series into trend, seasonal, and random error components based on a two-week trend window and fixed seasonal pattern, and uses the additive model as the seasonal trends appeared relatively constant over time. (33) Missing data were integrated over the case-series with multivariate imputation using chain equations (MICE). This was done as the case series had some missing values (i.e., zero cases reported on some days), whilst LOESS STL requires that the time series contains no missing values. MICE assumes that data are missing at random; this assumption is met as case data is missing completely at random whereby the probability of missingness did not depend on a specific day, week, or month or any other plausible unobserved data. (34)

METHODS FOR SPATIOTEMPORAL CLUSTERING

We used two different methods to measure spatiotemporal clustering for different phenomena. The *space-time scan statistic* describes local clustering, or the expected density of cases at specific locations within a given area. (35) This gives the timing and locations where cases cluster, exceeding their expected density. The *tau statistic* (τ) describes global clustering, or the overall tendency for cases to occur near other cases in space and time. (36) This suggests the geographic and temporal extents of the zones of increased infection risk. See Appendix C.1 for the mathematical formulation of these statistics.

LOCAL CLUSTERING TO IDENTIFY RECURRENT LOCATIONS AND TIMING OF SEASONAL OUTBREAKS

We used the space-time scan statistic to retrospectively detect the presence and location of spatiotemporal clusters. We conducted the analysis for the entire period (2016—2020) and by year. A relative risk (RR) compares the observed versus expected number of cases inside and outside of a cluster. Poisson distribution of the cases per avenue was assumed. To find the most likely cluster, candidate clusters were ordered by a log-likelihood ratio (LLR) where the cluster with the largest LLR is the least likely to be due to chance and therefore, the most likely cluster. The significance of each cluster was evaluated using Monte Carlo simulation to compare the original dataset with 999 random replicates produced under the null hypothesis.

We examined the entire dataset (i.e., a retrospective scan). We restricted the temporal and spatial windows to capture brief time periods (7—60 days) and a radius that included ≤10% of the population at-risk. To capture clustering that persisted across years, we also used a longer temporal window (7—365 days) for 2016—2020.

To explore whether the space time scan statistic produced signals that preceded outbreaks, we conducted prospective scans of each of the clusters that were detected retrospectively. This was done to detect the earliest warning signal that indicates when that cluster would have first been detected. We simulated repeated prospective scans on the date of the retrospective cluster start day and each successive day (up to 4 weeks later) and calculated the median and IQR of the delay where a prospective scan would have first detected the cluster from the date produced by the retrospective scan that used more case data, and the cluster size at first detection. We visualized on the epidemic curve the timing of the first day of each retrospective cluster. To explore where transmission predominated, we calculated the proportion of the years that the avenue was included in any cluster from 2016—2020, ranging from 0 (not included in any cluster) to 5 (included in a cluster every year). (37)

GLOBAL CLUSTERING TO INFORM THE BOUNDARIES OF RISK

We estimated the tau statistic (τ) for the entire period (2016—2020) and annually to quantify the spatial extent of the risk zone around an index case. (36) As the dataset only contained the date of the visit to the CTC/CTU as opposed to the date of symptom onset, this represented the risk of developing medically-attended disease, which we assumed indicates severe dehydration/diarrhea (compared with mild dehydration/diarrhea). This approach defines clustering in terms of how likely it is that any pair of cases are potentially transmission-related,

within a given distance between the cases. Accordingly, we first classified each pair of cases as potentially transmission-related if their dates of presentation were within 0-4 days of each other (approximately one serial interval). (5) τ is the RR that an individual in the population within a given distance band (d_1, d_2, e.g., 100m, 150m) from an incident case also becomes a case that is potentially transmission-related, compared to the risk of any individual in the population becoming a potentially transmission-related case. τ >1 indicates evidence of clustering within the given distance band.

As we lacked individual household locations of cases, τ reflects the spatial scale of the avenues. We estimated τ with a moving window of 50m computed every 10m at distances from 420m (as 5% of inter-avenue centroids fell below this value) to 2500m (approximate width of Uvira). We calculated the 95% CIs using the 2.5th and 97.5th quantiles from 1000 bootstrap replicates. We evaluated τ over a 5-day window which included the date of case presentation, and a 4-day window which excluded the date of case presentation to account for a more realistic response started the day after. (9) To smooth the artefactual fluctuations resulting from the resolution of the data and smaller sample size of annual datasets, we calculated a moving average over the previous 10m. We defined the high-risk zone around incident cases as the radius up to which the moving average's lower 95% CIs crossed 1.0 for ≥30 consecutive meters. We defined another elevated-risk zone around incident cases as the radius up to which the moving average point estimate crossed 1.0 for ≥30 consecutive meters. To explore the potential biases from using centroids compared to household locations, we conducted a simulation study where we randomly assigned household locations within each case's avenue and then estimated τ using a lower distance range (75—2500m) (Appendix C.2, Figures 1—4).

For both the scan statistics and τ, we carried out sensitivity analyses using all suspected cases (i.e., RDT-positive and negative cases, and untested cases that met the suspected case definition).

All analyses were carried out in R software (v. 4.1.2) using the rsatscan (v. 1.0.5) and IDSpatialStats (v. 0.3.12) R packages to calculate the scan statistic (with SaTScan™ v. 10.0.2 software) and τ. (38-41) Ethical approval was provided by the London School of Hygiene and Tropical Medicine (#10603-5) and the University of Kinshasa School of Public Health (#ESP/CE/173B/2022).

RESULTS

5,447 suspected cases were recorded from 2016 to 2020. 3,456 (63.4%) of the 5,447 suspected cases were tested, of which 1,493 (43.2%) of the 3,456 tested cases were RDT-positive (Figure 1). Testing was not done when RDTs were stocked out, patients were admitted at nighttime and discharged by morning, patients refused, or the technician was ill. Percent positivity among those tested ranged from 36.6% to 46.9% (Table 4.1). Stable, seasonal transmission was observed with seasonal outbreaks typically beginning in the dry season (at the end of June/July to early October), followed by lower transmission in the rainy season (October—March/April) (Appendix C.3, C.4). In some years, multiple peaks were seen in February and in the second half of the year between August and October (Figure 4.1). Peaks typically reached 80—100 weekly suspected cases. Earlier transmission starting in March was seen in 2019 and 2020.

Table 4.1: *Description of testing among suspected cholera cases, Uvira, 2016 to 2020*

	2016	**2017**	**2018**	**2019**	**2020**
No. suspected cases	1341	1134	1000	922	1050
No. suspected cases per 10,000 population	47.9	40.5	35.7	32.9	37.5
No. (%) suspected cases that were RDT-tested	617 (46.0)	857 (75.6)	533 (53.3)	597 (64.8)	852 (81.2)
No (%) RDT-positive cases among RDT-tested	226 (36.6)	374 (43.6)	233 (43.7)	260 (43.6)	400 (46.9)

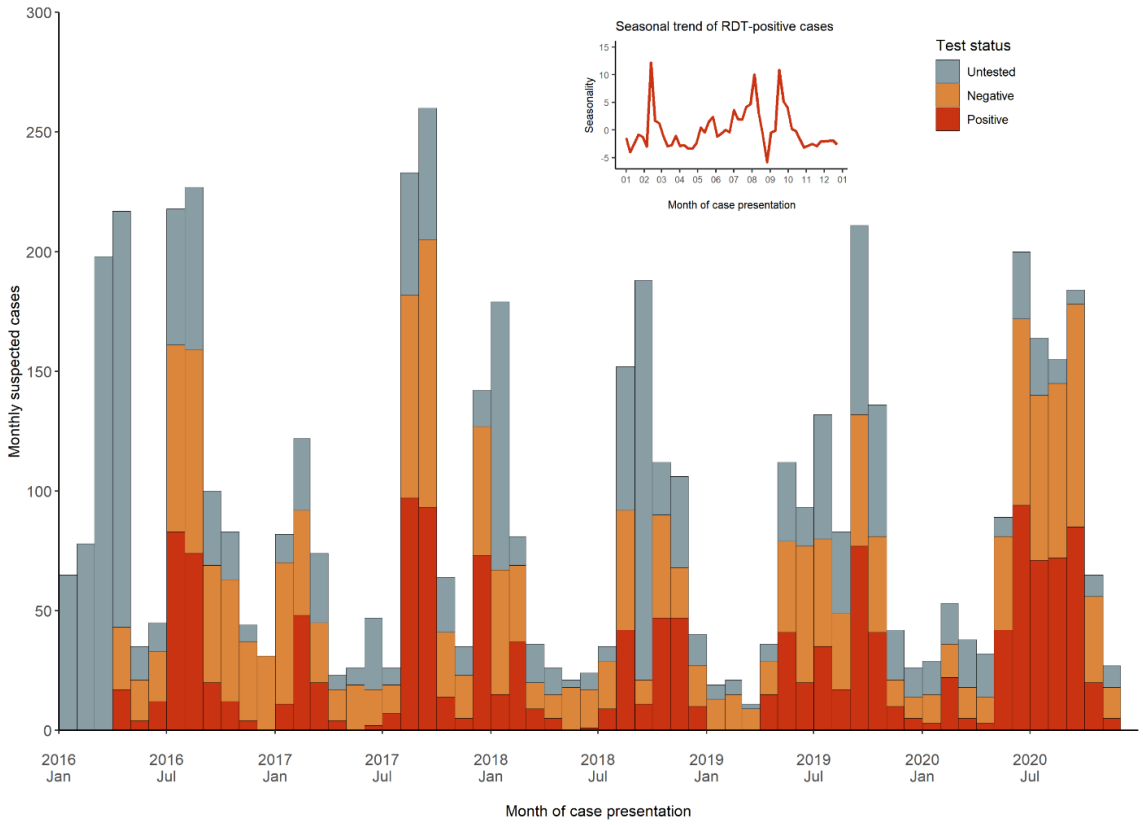

Figure 4.1 *Cholera, Uvira, 2016—2020: Epidemic curve of monthly suspected cases by test status with seasonal trend of monthly RDT-positive cases (inset)*

Twenty-six spatiotemporal clusters were detected (Table 4.2). The mean cluster radius was 652m (range, 308—1582), mean size was 20 cases (range, 4—48), and mean duration was 24.8 days (range 1—58). The annual comparison of clustering demonstrated clustering in similar locations each year (Figure 2). The date of the first day of a retrospectively detected cluster usually (though not always) anticipated a surge in transmission over the next weeks, for all seasonal outbreaks except for early 2016 and 2017 when there were few cases tested (Figure 4.3, top). The median delay to the early warning signal (i.e., the number of days between retrospective detection date with all available data and the earliest prospective detection date) was 1 day (IQR 0—3) with a maximum delay of 23 days (Table 4.2). The median cluster size at signal detection was 3 cases (IQR 2—7) with a maximum size of 21 cases. Persistent clustering was seen in the north-central and southern areas, some distance away from the CTC (Figure 4.3, bottom). The 2016—2020 scan did not show clusters persisting between years but found larger clusters of 175—226 cases in the same locations. Sensitivity analyses of suspected cases found more clusters (N=32) of a similar mean radius and range (590m, range 270—1557) and larger mean size and range (37 cases, range 2—130) and longer duration (27.8 days, range 5—59), in similar locations (appendix table C.5, appendix figure C.6).

Table 4.2 Spatiotemporal clusters of RDT-positive cholera cases detected through annual scanning at the avenue level, Uvira, 2016—2020

Year	No.	Cases observed: expected	Population at-risk	RR[†]	Cluster radius (m)	Cluster start date (mm/dd)	Cluster duration (days)	Signal delay (days)[‡]	Size at signal (cases)
2016	1	20:1	30553	20.9	1140	08/05	18	8	11
	2	28:3	34232	10.5	497	06/25	48	0	2
	3	17:1	30758	13.8	717	07/22	23	5	12
	4	15:1	31240	11.9	758	06/29	23	1	4
	5	4:0	6579	344.4	376	04/09	1	0	3
	6	14:2	30082	8.8	668	07/21	30	0	3
	7	9:1	27452	12.6**	368	07/26	14	3	4
2017	1	48:4	51012	13.0	811	08/07	40	2	2
	2	32:2	43992	16.4	657	08/20	23	1	13
	3	32:4	49794	7.7	880	08/23	44	0	2
	4	13:1	51016	16.4	378	12/24	7	0	2
	5	12:2	50635	7.6**	368	08/23	15	12	2
2018	1	20:1	28884	26.6	1116	10/26	13	6	9
	2	11:1	31204	22.7	475	02/13	7	0	3
	3	8:0	25148	40.6	662	08/28	3	0	4
	4	7:0	17345	18.6**	308	11/10	10	1	3
2019	1	23:1	33751	18.6	743	09/10	18	1	7
	2	21:3	33162	9.0	755	09/07	35	0	12
	3	12:1	16210	12.3	309	04/27	29	1	2
	4	11:1	16495	13.2	527	09/07	24	0	2
	5	6:0	15001	27.8**	368	06/30	6	0	2
2020	1	42:6	60378	7.8	1048	07/29	58	2	3
	2	27:3	42423	8.7	599	07/15	46	23	21
	3	17:1	56029	19.1	1582	02/20	9	0	2
	4	30:5	63207	6.5	343	05/30	46	2	6
	5	32:6	63593	5.8	501	06/01	55	4	6

* p-value < 0.001 ≥ p-value <0.01; ** p-value < 0.001. [†] RR, relative risk. [‡] Signal delay indicates the number of days between retrospective detection date with all available data and the earliest prospective detection date.

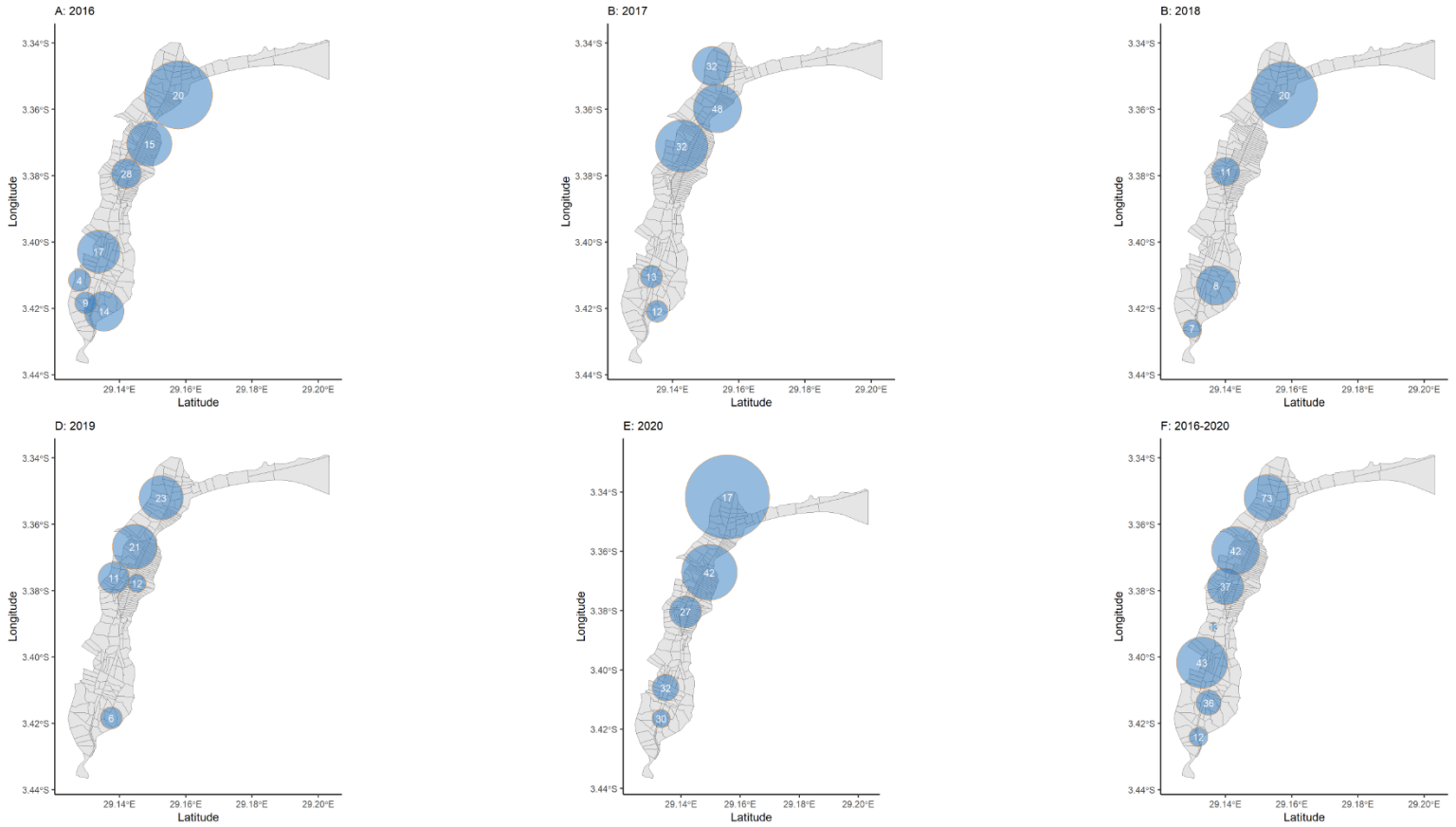

Figure 4.2 *Spatial distribution of spatiotemporal clusters of RDT-positive cholera cases at the avenue level, Uvira, 2016—2020. Clusters have a relative risk >1, p<0.05. The size of the orange circle depicts the spatial radius and the number of cases, in white.*

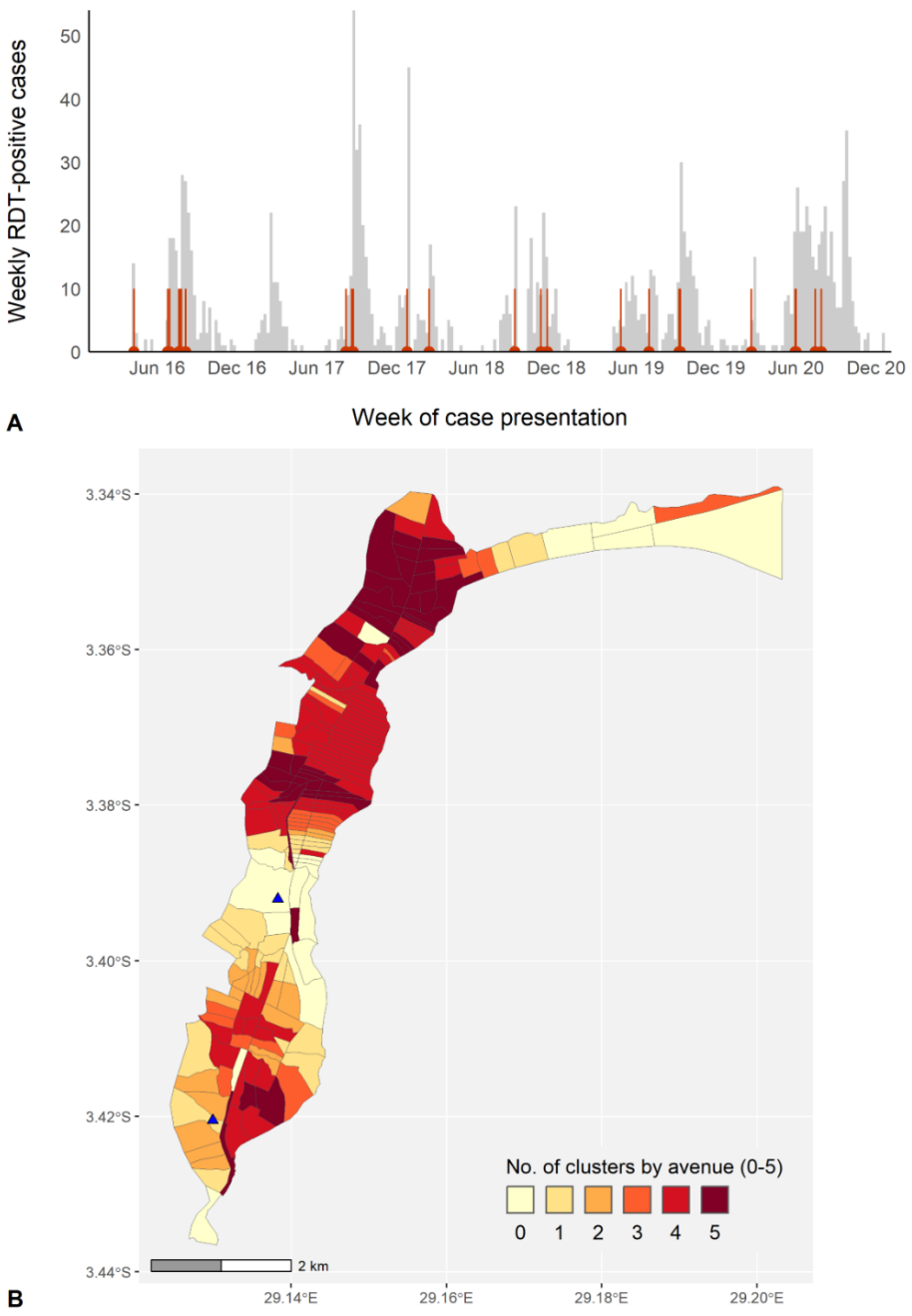

Figure 4.3 *Cholera, Uvira, 2016—2020: (A) Epidemic curve showing weekly number of RDT-positive cholera cases based on week of presentation and start dates of 26 clusters (red vertical lines), (B) Cluster persistence within avenues for RDT-positive cases* showing the number of years affected by clustering within avenues. The cholera treatment centre (top) and unit (bottom) are marked with blue triangles.

Among RDT-positive cases from 2016—2020, within the first 5 days after a case presented for care, the high-risk zone extended from the case residence to 1105m and the risk remained elevated up to 1665m (maximum moving average $\tau = 1.8$, 95% CI 1.4—2.3, Figure 4.4A). During days 1—4, when a response can be more realistically mobilized, the risk zones remained similar (Figure 4.4B). Examining RDT-positive cases in 2020 alone, the high-risk zone extended to a smaller radius of 585m, and the risk remained elevated up to 1915m (maximum moving average $\tau = 1.8$, 95% CI 1.0—2.9, noting the wider confidence intervals for the smaller 2020 dataset, Figure 4.4C). During days 1—4, the risk zones were 425m and 1915m, respectively (maximum moving average $\tau = 1.7$, 95% CI 1.1—2.6, Figure 4.4D). In the sensitivity analysis of suspected cases from 2020, the trends remained like RDT-positive cases in 2020 (Figure 4.4C, 4.4D versus 4.4E, 4.4F). For suspected cases, during days 1—4, these risk zones were 1155m and 2075m, respectively (maximum moving average $\tau = 1.6$, 95% CI 1.3—2.0, though a drop in the lower CI was observed at 635m, as marked by first vertical dashed line in Figure 4.4F). Results by year for RDT-positive cases showed lower ranges in the radii of the high-risk zone (425m across all years except 2017 where it is 875m) and the elevated zone (1125—1485m) (appendix figure C.7). Using simulated individual household locations (from 75—2500m for days 0—4), the results were similar to the main analysis of centroid locations with a moving average $\tau \geq 2.0$ measured from 75m to 275m (maximum moving average $\tau = 2.4$, 95% CI 1.7—3.3), a similar high-risk zone radius of 1415m, and a similar descending trend in risk over distance, central tendencies and correlation coefficients (appendix C.2).

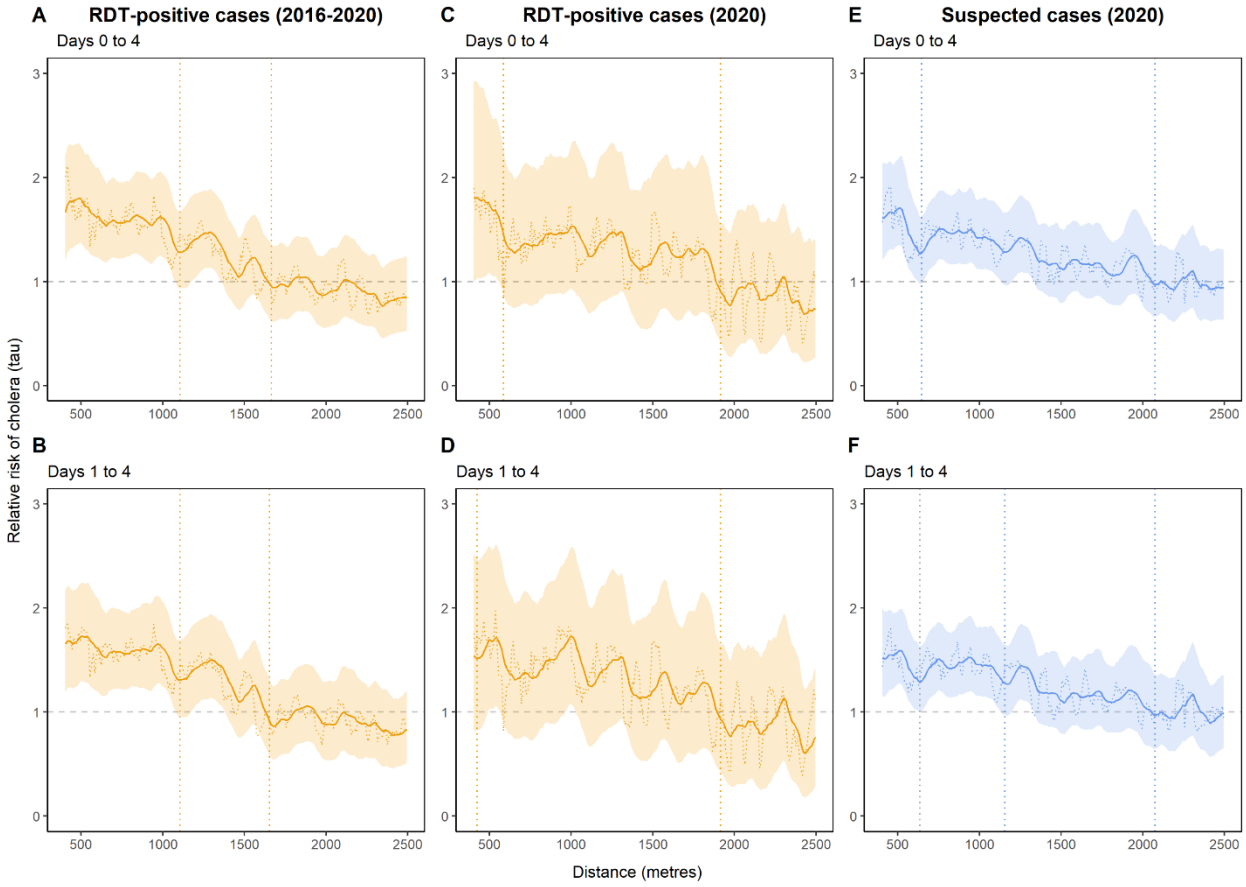

Figure 4.4 *Cholera, Uvira, 2016—2020: Moving average estimates of τ (relative risk) and 95% CIs (solid line and shading) with point estimates (dashed horizontal line) for days 0—4 (panels A, C, E) and days 1—4 (panels, B, D, F), for RDT-positive cases (in orange) and suspected cases (in blue) for cholera in 2016—2020 (panels A, B) and (panels C, D, E, F), using 1000 bootstrap samples. The vertical dashed lines indicate the spatial extent of the zone of high-risk where the lower 95% CI crossed 1.0 for ≥30m consecutively (first line) and zone of elevated risk where the point estimate crossed 1.0 for ≥30m consecutively (second line).*

DISCUSSION

We provide insight into clustering dynamics from one of the world's most burdensome cholera hotspots. Elucidating clustering patterns in an endemic setting can specify where intensive transmission is occurring early on, within small areas. Our results suggest that targeted interventions can take advantage of this natural clustering to mitigate seasonal outbreaks before they enlarge. Cities like Uvira, Goma and Bukavu are thought to regularly seed regional outbreaks; investigating transmission routes and coordinating prevention and control strategies there can have substantial public health benefits. (18)

The two clustering methods produced aligned results. When evaluating the 2016—2020 period, a 1105m high-risk radius around RDT-positive cases within the 5 days after case presentation was estimated with a $\tau \leq 1.8$. The risk zone for 2020 showed a 600m high-risk radius with a $\tau \leq 1.8$. These radii are consistent with those estimated for Matlab, Bangladesh (500m, within 4—6 days post-presentation, RR = 1.9). (10) In Uvira, an elevated-risk radius up to 2000m around cases demonstrates the persistence of risk in a densely-populated city. The risk zones remained intact after a 1-day delay wherein it is realistic to launch a response. The τ estimates are higher than estimates from N'Djamena (220m) and Kalemie (330m), likely reflecting propagation among neighbouring households, but it should be noted that we do not include distances <420m. (9) To explore this omission further, the simulation of household locations produced similar risk zones and an initial increase in risk from 75—275m equivalent to $\tau < 2.5$. There may be additional epidemiological differences including increased environmentally-mediated transmission, immunity, population density, and mobility related to seasonal fishing and trading.

The space-time scan statistic demonstrated a mean radius (650m) among the 26 spatiotemporal clusters which emerged in the south and central-north areas. This is similar to the τ high-risk zone for 2020 (600m). The start date of the retrospectively-detected cluster acted as an alarm that usually preceded the onset of seasonal outbreaks. The early warning signal for these clusters was delayed by a median of 1 day (whereas delays of >1 week for 3 clusters are not feasible for rapid response).

Our study's main strength is the use of high-specificity RDT-positive cases as compared to suspected cases alone. Previous analyses have relied on suspected cases which may overestimate risk due to inclusion of other diarrheal pathogens. (9-11) Our sensitivity analyses based on suspected cases showed similar results but with likely false positive clusters detected

and a larger radius. In Uvira, the CTC/CTU may not be the main source of care for diarrhea, particularly when mild. In a 2021 community survey of health-seeking practices among Uvira residents, most persons with any diarrhea in the past week (70%) reported that they first visited pharmacies for care, rather than CTCs (4%). (42) Use of medically-attended cases introduces a potential bias of including only moderate to severely-ill cases, and therefore missing the transmission from milder cases. This is mitigated if medically attended cases represent a random proportion of all cholera cases. A major limitation is that the spatial resolution is based on avenue centroids, not household locations. This misses household transmission and case-pair distances <420m, where 5% of distances fell. Our simulations of household locations showed qualitatively similar trends, with higher τ at a smaller radius. Other limitations of the τ statistic include limited power to detect true risk areas using narrow distance bands where the sample size of related pairs is small. (43) The τ trendline and its sampling error are not smooth, as the clustering algorithm is recalculated every 50m and the moving average recalculated every 10m. Given that annual estimates are based on <500 RDT-positive cases, evaluation of the minimum number of cases needed for reliable τ estimation is needed. (43) For both τ and the space-time scan statistic, a circular radius has reduced sensitivity to detect the true geographical extent of noncircular clustering or an outbreak (i.e., an outbreak along the coastline, as might be the case in Uvira given its lakeside position), though detection appears unaffected. (35)

The results can inform control measures for seasonal outbreaks. The mapping of persistent clustering can be used to prioritize persistent high-recurrence hotspots for preventative measures, where transmission occurs early and predictably. Aiming for high coverage and uptake of preventative interventions in these areas can reduce exposure, reinfection, and transmission. Daily prospective scanning for local clustering could aid in early cluster detection across Uvira. (39) The radii of 100—500m used for a CATI strategies in DRC (17, 44) are justified by these findings and could perhaps be enlarged further. A 600—1105m radius of infection risk would include several thousand persons and would be logistically prohibitive to cover rapidly (i.e., within the 3 to 5 day risk window). However, CATIs may be considered for early containment of (a) potential zones of infection around new cases in less affected areas that fall outside of the known high-recurrence areas, (b) small outbreaks among lakeside communities in hotspots which may seed larger outbreaks (18), and (c) sporadic cases after mass vaccination (15). Building on previous and current studies (9, 10) and operational

experience (17, 44), a 200—600m radius can be used to narrow down areas for CATIs where transmission is likely.

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DATA AVAILABILITY: All data and code produced are available online at https://github.com/ruwanepi/Uvira_spatiotemporal

SUPPLEMENTARY INFORMATION (APPENDIX C)

- **Appendix C.1** Statistical framework for local and global clustering statistics
- **Appendix C.2** Simulations to compare centroid-geotagged cases with cases with simulated individual household locations
- **Appendix C.3** Trend, season and remainder decomposition using a trend window for smoothing of 14 days and seasonal window for smoothing including the entire period
- **Appendix C.4** Normal Q-Q plot of residuals (remainder) and verification of a heavy-tailed skew approaching a normal distribution of residuals (indicating a mix of structure and noise)
- **Appendix C.5** Sensitivity analysis: spatiotemporal clusters of suspected cholera cases, Uvira, 2016—2020
- **Appendix C.6** Sensitivity analyses of prospectively detected spatiotemporal clusters of suspected cholera cases, 2016—2020.
- **Appendix C.7** Cholera, Uvira, 2016—2020: Annual and aggregated moving average estimates of τ (relative risk) and 95% CIs (solid line and shading) for days 0—4. 2016—2020 in black, 2016 in purple, 2017 in orange, 2018 in green, 2019 in blue, 202 in red

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Chapter 5: Case-area targeted intervention with vaccination to rapidly control cholera outbreaks: a spatial modelling study

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Thesis Title	Case-area targeted intervention for the control of cholera epidemics in crises: from spatial mathematical modelling to field evaluation		
Primary Supervisor	Prof. Francesco Checchi		

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Supervisor Signature	[redacted]
Date	18 September 2023

BRIDGING PASSAGE

Rationale for study: Using findings from the three previous studies on intervention effectiveness, timeliness of outbreak response, and spatiotemporal clustering of cholera in Uvira, I attempted to quantify CATI's potential impact in limiting the size of an outbreak in its early phase (specifically, the first 60 days of the outbreak).

Overview of methods: This was achieved using a spatially explicit metapopulation (patch) model of cholera transmission. The model used case data sourced from Uvira, South Kivu, DRC, which is part of an international hotspot of endemic cholera in the African Great Lakes Region. We used the model to assess the impact of variation in transmission rate, delays, and vaccine availability on outbreak containment (i.e., local elimination of cases).

Main conclusion: Our model demonstrates the potential for early containment of outbreaks using CATI with vaccination with fewer resources than mass campaigns. CATI without vaccination reduced transmission but not spatial propagation and had a low probability of containment.

Role: I developed the concept and study design, sourced the data from the Uvira study team, led the analyses, and wrote the original draft.

Use of findings in Ph.D. and beyond: I plan to use the findings to inform the planning of CATI strategies with MSF and Epicentre. The results help to advocate for use of small stocks of vaccines in-country for preparedness and early response to cholera outbreaks. I plan to submit this manuscript to PLOS Global Public Health.

Case-area targeted intervention with vaccination to rapidly control cholera outbreaks: a spatial modelling study

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ABSTRACT

Background: Since 2022, cholera transmission has been rising global and vaccine supplies have become constrained. Therefore, control strategies for small outbreaks in communities most at-risk are critical. Case-area targeted intervention (CATI) with single-dose vaccination, water treatment, and antibiotic chemoprophylaxis may be able to rapidly control small outbreaks at the town or district level.

Methods and Findings: To quantify CATI's potential impact in limiting the size of an outbreak in its early phase, we developed a spatially explicit metapopulation (patch) model of cholera transmission. We parameterised the model using data from Uvira, South Kivu, Democratic Republic of the Congo (located in the African Great Lakes Region cholera hotspot). A force of infection was used that declined with increasing distance from patches with infections. CATI was implemented in an approximate 150m radius around new cases. We used the model to assess the impact of variation in transmission rate, delays, and vaccine availability on outbreak containment (i.e., local elimination of cases). We compared these strategies to mass campaigns with vaccination and water treatment. Under a base scenario (effective reproduction number, 1.5 and delay to implementation, 2 days), CATI with single-dose vaccination, antibiotics, and water treatment could contain outbreaks and prevent spatial propagation. The proportion of simulations resulting in containment (94.8%) and median time to containment (34 days, IQR 27—42) improved upon mass campaigns (45.8% of simulations contained in 53 median days (IQR 47—56)) and targeted less than 6% of the population receiving mass campaigns. CATI with antibiotics and water treatment without vaccination reduced transmission but not spatial propagation and had a low probability of containment (27.4% of simulations).

Conclusions: Our model demonstrates the potential for early control using CATI with vaccination with fewer resources than mass campaigns. This suggests a viable, localised strategy to contend with limited vaccine supply and other resource constraints.

INTRODUCTION

Since 2022, several large cholera epidemics have occurred in countries that have been cholera-free for many years (i.e. Afghanistan, Haiti, Lebanon, Pakistan, South Sudan, and Syria) or through transmission exacerbated by flooding and/or population displacement in cholera-endemic countries (i.e., Cameroon, Democratic Republic of the Congo (DRC), Malawi, and Mozambique).[1] The largest cholera burden still arises from hotspots in Sub-Saharan Africa and South Asia (i.e., African Great Lakes region, Lake Chad Basin, and Ganges Delta).[2,3] Cholera outbreaks are difficult to control, given cholera's relatively high reproduction number and short incubation period, which compounds the risk of small outbreaks propagating and expanding rapidly.[4] This is a particular concern for countries affected by humanitarian crises, where public health systems are severely weakened and risk factors for transmission, including poor water and sanitation, displacement, and compromised immunity from malnutrition, are continually present.[5]

In an evaluation of mass vaccination campaigns from 2013 to 2018 which used the Global Oral Cholera Vaccine (OCV) Stockpile, the mean delay from the first laboratory confirmation of cholera or occurrence of a humanitarian emergency to a week after the start of the campaign (when immune responses would be expected to occur) was 66 days.[6] Containment strategies during the early stage of outbreaks, which target people at the highest risk of infection, may be more rapid, nimble, and may use less resources compared to mass campaigns over large geographical areas.[7] Such containment strategies could also help to suppress transmission while mass campaigns are being prepared. Cholera vaccine stocks are severely limited, an ongoing issue which is projected to last into 2026 and has necessitated single-dose vaccination, despite a recommended two-dose schedule.[8] Case area-targeted intervention (CATI) may be a useful tool to address these and other resource (e.g. funding) constraints.[7] CATI aims to control outbreaks while they are still small by interrupting transmission with multiple interventions (antibiotic chemoprophylaxis, water, sanitation and hygiene (WaSH) interventions, and vaccination) addressing multiple routes of transmission in geographic 'rings' of 100–250m around the household of the index case.[7,9,10] Since the mid-2000s, CATI using WaSH interventions alone has been a major pillar of cholera control strategies supported by UNICEF in Haiti, Yemen, Zimbabwe, and Mozambique.[11]

A scoping review of CATI suggested that the combination of point-of-use water treatment (POUWT), hygiene promotion including hand-washing with soap, antibiotic chemoprophylaxis, and single-dose vaccination shows promise for the rapid reduction of localized transmission.[7] A single vaccine dose may substantially extend the strength and duration of CATI effectiveness. When used reactively against outbreaks, high short-term effectiveness at 2 months was estimated in a population with prior exposure to cholera in Juba, South Sudan (87.3%, 95% CI: 70.2—100) and in a cholera-naïve population in Lusaka, Zambia (88.9%, 95% CI: 42.7—97.8).[12,13] Protection is less effective among children under 5 years of age (i.e., in Dhaka, Bangladesh, where 58% of study cases were under 5 years of age, single-dose effectiveness at one year was 40%, 95% CI: 11—60).[14-16]

Analyses suggest a spatiotemporal zone of high infection risk of within 100m—250m and 7 days around case-households that is suitable for the logistics of CATI, as well as a larger radius of elevated risk up to 1000m.[17-19] A review of time to detection and response to cholera outbreaks in fragile states found that the median delay between symptom onset of the first-detected case to outbreak detection is 5 days (IQR 5—6), indicating that rapid response is plausible within the first 7 days.[20] An observational study of WaSH-driven CATI in Centre Department, Haiti from 2015 to 2017 demonstrated a relationship between the speed of implementation and reductions in incidence of suspected cholera and outbreak duration.[10]

If CATI with vaccination can be implemented rapidly at first detection of a case and use less resources to contain (and eliminate) cholera locally, it could become a valuable tool for global cholera control. This strategy does entail challenging requirements, including (i) rapid and near-exhaustive detection of new cases, (ii) efficient coverage of households in the 100-200m ring within the 7-day high-risk period, and (iii) efficient use of vaccine doses, given scarcity. To explore CATI's impact under a range of implementation delays and intervention strategies, we developed a spatially explicit metapopulation model and used it to simulate cholera transmission in Uvira, a cholera-endemic city in the DRC. We aimed to quantify the potential value of CATI for the containment of cholera within Uvira during the first 60 days of an outbreak.

METHODS

STUDY POPULATION

Uvira is a town in South Kivu that is located on the shore of Lake Tanganyika, a hotspot with an apparent environmental reservoir of *V. cholerae* around which suspected cases are reported year-round.[21] Flooding during the rainy season, combined with limited sanitation infrastructure, results in frequent faecal contamination of water sources and seasonal outbreaks. Several city-wide interventions have been implemented including piped water infrastructure to improve the production and supply of drinking water for which construction started in 2018, and a two-dose OCV campaign from July to October 2020.[22]

We sourced the population size from the 2017 census, which is projected based on earlier data.[23] The total population (N = 280,000) was distributed spatially according to the remotely-sensed built-up population density estimated from the WorldPop raster map of the DRC (2020) which contains the total number of individuals per 100m^2 grid cell as estimated by Random Forest-based redistribution.[24] The population is randomly assigned locations with a probability proportional to the estimated average built-up density. We subdivided Uvira's municipality into a grid of 100 m^2 'patches' with non-zero population resulting in 2003 patches of mean size 140 persons (range, 28—442) using a shapefile of South Kivu sourced from Geographic Services Inc.'s Human Geography Database (Figure 5.1).[25] This spatial setup approach was adapted from Brady et al.[26]

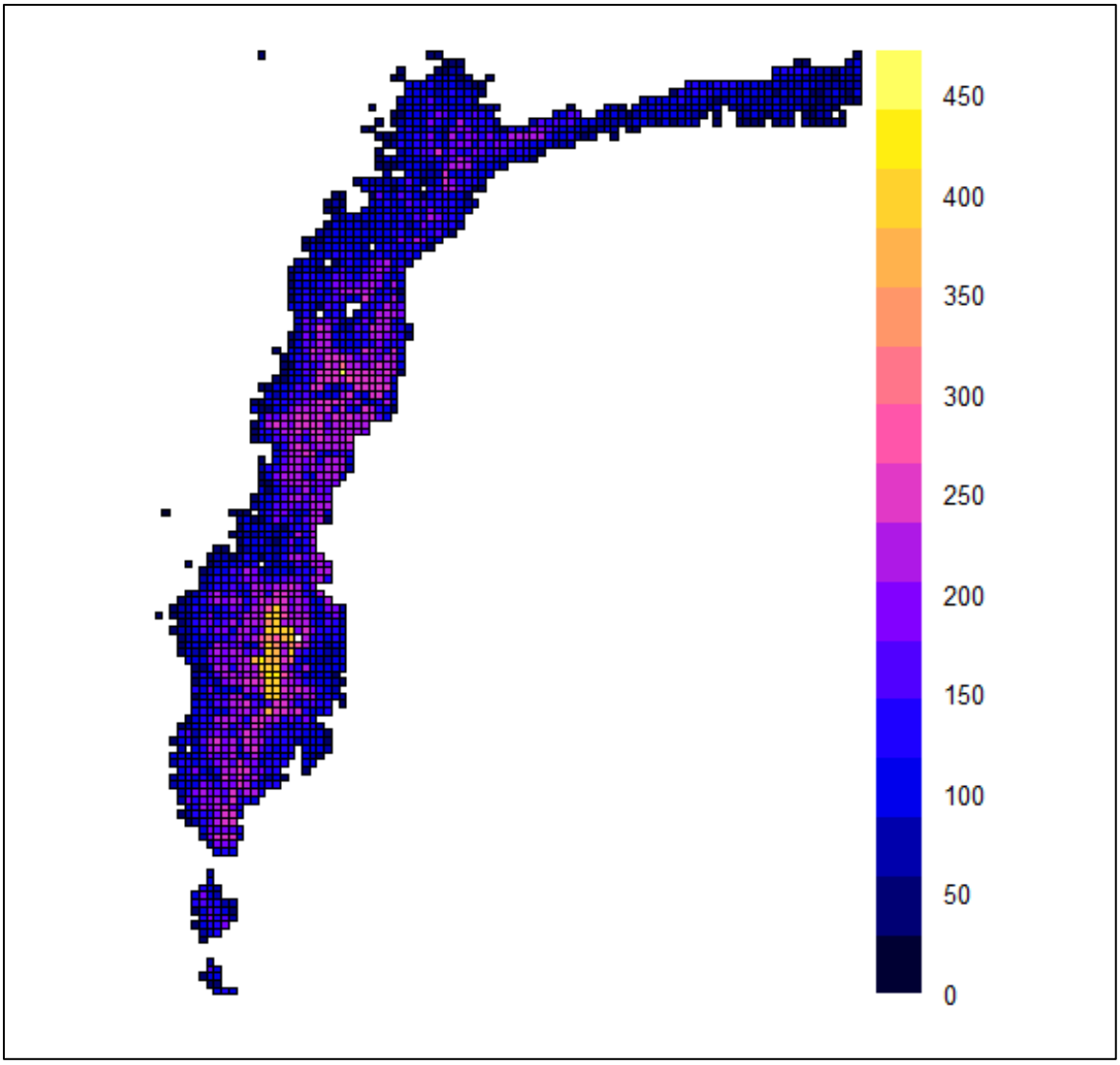


Figure 5.1 Patch structure by population density (legend: number of persons per 100m^2 grid cell), Uvira, South Kivu, Democratic Republic of the Congo. Source: GSI, 2022. [25]

MODEL STRUCTURE

We implemented a spatially explicit, stochastic, metapopulation model[26,27], accounting for the well-documented spatial heterogeneity of cholera transmission[9,18,28] and the role of stochastically driven extinctions of transmission when small numbers of infectious individuals are introduced into the population. Individuals are tracked within each patch i as susceptible, exposed, infectious, or recovered (S_i, E_i, I_i, R_i). Transmission between patches is simulated by a distance-based force of infection function. Instead of explicitly modelling the travel of individuals between

patches, we assume distance to be an adequate proxy of mobility and relative contact between patches.

We ran the model from the date of infection of the first symptomatic case to 60 days to investigate CATI's potential for early control. Given the short duration, demographic processes (i.e., births, deaths, migration) are considered negligible. We do not account for deaths due to cholera infection, as we assume that timely access to care from the existing cholera treatment centre in the city, and therefore prompt rehydration therapy, should reduce the case-fatality ratio.

MODEL STATES

Hereafter, we consider *patch i* the patch receiving the force of infection, and *patch j* as all other patches that apply the force of infection on *patch i*. Within a patch i, individuals are assumed to mix homogeneously. Exposed but not yet infectious individuals ($E_{i,t}$) pass through an average incubation period of 2 days (similar to the median incubation period of 1.4 days, credible interval 1.3—1.6[4]), before becoming either symptomatic (and thus infectious) or asymptomatic (and non-infectious). Harris et al. documented that among a cohort of contacts of confirmed cases in Dhaka, Bangladesh, 43% of those infected (as confirmed by rectal swab culture or vibriocidal antibody response) were asymptomatically infected.[9] Thus, we assume that 50% of exposed persons become asymptomatic. Asymptomatic individuals shed approximately 10^3 vibrios per gram of stool for a single day, and therefore we consider they do not contribute to the force of infection.[29] Asymptomatic individuals become immune (move to the recovered state) for the remainder of the simulation.[29,30] Weil and colleagues found that among a cohort of contacts of cholera cases in Dhaka, symptomatically infected individuals shed for an average of 5 days.[31] Therefore, we assume that symptomatic infectious individuals move to the recovered state after an average of 5 days ($1/\gamma$). Cholera infection and vaccination confer immunity which lasts longer than 60 days. Therefore, re-infection is not factored into this model.

We used a stochastic Poisson process to determine the expected number of events (i.e., individuals entering the state) for each state at each time step (Box 5.1). We assumed that individuals transition from exposed to infectious states and from infectious to recovered states according to an exponential distribution of mean δ and γ, respectively.

Box 5.1. Stochastic simulation within *patch i*

We calculate the expected number of events (i.e., individuals entering the state) to be approximately Poisson distributed for exposed (infected), symptomatically infected, and recovered individuals for the time interval, t. 1/ δ is the mean incubation period, and 1/γ is the mean infectious period. Note that the spatial force of infection ($\lambda_{i,t}$) determines the force of infection on patch i, by summing infections over all other patches j ($\beta \sum_{j=1}^{N} I_{j,t} K_{ij}$, where β is the probability of infection per contact between infectious and susceptible individuals, $I_{j,t}$ are the number of infectious individuals in patch j and K_{ij} are the kernels between patch i and other patches j).

$$P\left(\frac{\Delta E_{i,t}}{\Delta t} \middle| S_{i,t}, I_{j,t}\right) \sim \text{Poisson}(S_{i,t}\lambda_{i,t}/N_i)$$

$$P\left(\frac{\Delta I_{i,t}}{\Delta t} \middle| E_{i,t}\right) \sim \text{Poisson}(\alpha E_{i,t})$$

$$P\left(\frac{\Delta R_{i,t}}{\Delta t} \middle| I_{i,t}\right) \sim \text{Poisson}(\gamma I_{i,t})$$

The compartments are updated with the number of individuals entering and exiting the states. φ denotes the proportion of asymptomatic infections (these are considered non-infectious and moved to the recovered state, to denote protective immunity for the study period). For simplicity, we do not include effects of the interventions here. These calculations are however, integrated in the model.

$$S_{i,t} = S_{i,t} - \frac{\Delta E_{i,t}}{\Delta t}$$

$$E_{i,t} = E_{i,t} + (1 - \varphi)\frac{\Delta E_{i,t}}{\Delta t} - \frac{\Delta I_{i,t}}{\Delta t}$$

$$I_{i,t} = I_{i,t} + \frac{\Delta I_{i,t}}{\Delta t} - \frac{\Delta R_{i,t}}{\Delta t}$$

$$R_{i,t} = R_{i,t} + \frac{\Delta R_{i,t}}{\Delta t} + (1 - \varphi)\frac{\Delta E_{i,t}}{\Delta t}$$

TRANSMISSION DYNAMICS

We model cholera as direct transmission through exposure to freshly shed bacteria in a hyper-infectious state into the local environment (i.e., through shared contaminated food and water in the household) leading to a process of rapid infection, and place less emphasis on environmentally-mediated transmission through contamination of water distribution systems with vibrio persistence leading to delayed infections.[32-34] During an outbreak, we consider that the direct route is the vehicle for epidemic propagation and accounts for the entire force of infection.[17-19,34] This also simplifies the issue of uncertain parameterization of the concentration and role of *V. cholerae* in water sources.[35,36] To inform the exposure parameter (β, defined as the probability of infection per contact between infectious and susceptible individuals), we chose an expected effective reproduction number (R_E) at the start of a new outbreak (1.5 or 2.0), based on recent epidemics in endemic settings where populations possessed some prior immunity in South Sudan and Yemen.[37-39]

Each *patch j* that has ≥1 infectious individual at time *t* exerts a spatial force of infection $(\lambda_{i,t})$ on a given *patch i*. This spatial force of infection is based on a power-law-distribution-based kernel that has been used to describe short-term human travel behaviour.[40-42] The spatial force of infection is then interpreted as the proportion of the total force of infection across all patches that is due to transmission from *patch j* to *patch i*, and which depends on the distance between *patch i* and *patch j* (Equation 1, adapted from Finger et al).[9] A distance matrix was constructed to measure distances between the centroids of each patch. The kernel K_{ij} originates from the centroid of each symptomatically infected individual's patch and decreases with distance. The maximum distance that marks the end of the zone of infection risk (1000m from a new case within a 5-day period after case presentation) was derived from our previous analysis of Uvira case data using the tau statistic, a relative risk-based estimator of the geographic and temporal extents of the zones of increased infection risk.[17,43]

Equation 1: $$\underbrace{K_{ij} = \frac{a-2}{2\pi\left(d_0^{-a+2} - d_{max}^{-a+2}\right)} d_{ij}^{-a}}_{if\ j=i,\ K_{ij}=1.0}$$

where d_0 is half the grid cell size used (50m), d_{max} is 1000m from an incident cholera case[17], d_{ij} is the distance between a given *patch i* and *patch j*, and a is a normalization constant greater than 2 chosen to ensure the integral of the kernel over space is equal to 1.[40] Note that *patch i* has a kernel of 1.0 as it has a distance of zero to itself, and no reduction in its force of infection would be required. During each timestep, the kernels are summed to calculate the force of infection $(\lambda_{i,t})$ on a given *patch i* as the sum of risk contributed from all *patch j* that have at least one infectious individual (Equation 2).[28]

Equation 2: $$\lambda_{i,t} = \beta \sum_{j=1}^{N} I_{j,t} K_{ij}$$

where, β is the probability of infection per contact between infectious and susceptible individuals, $I_{i,t}$ are the number of infectious individuals in *patch i*, $I_{j,t}$ are the infected persons across other *patches j*, and K_{ij} are the kernels between *patch i* and other *patches j*.

STARTING CONDITIONS

We use a line list of suspected cases from the 2019—2020 cholera outbreak in Uvira to seed a simulated epidemic with the first case-clusters of 9 cases detected in 3 patches in epidemiological week 49, 2019, in northern and central Uvira (previously detected using the space-time scan statistic[44] for cluster detection, see[17]). We assume that 20% of the first detected suspected cholera cases are undetected and increase the case count proportionally for the initial seed. We assume a proportion of the population is already immune due to recent infection during the previous cholera seasons or the 2020 two-dose vaccination campaign. This is determined by a random number from a uniform distribution of 25—50%. This proportion is moved from S_i to R_i before the simulation begins.

CATI TRIGGERING AND SPATIAL EXTENT OF IMPLEMENTATION

In the model, the occurrence of a new symptomatic case in a patch with no previous cases triggers CATI. An average delay of 2 days from the onset of symptoms of a case(s) to full coverage of CATI implementation is applied to represent delays (i.e., for the case to present to the clinic, verification with an enriched RDT (i.e., up to 6 hour enrichment process) [22], and to full coverage of the ring.

Previous analyses suggest that a 100 to 200m radius around cases carries the highest risk of infection in the first 5 days after case presentation. [18] Limiting CATI to this high-risk zone also seems logistically feasible (and is currently used in practice). [11,45] We thus simulate CATI as occurring within an approximate 150m intervention radius originating from the affected patch with the first case cluster (this equates to the patch itself and up to 9 contiguous neighbouring patches: see Figure 5.2). The approximate 150m radius was calculated according to the distance between the index patch centroid and other patch centroids. However, antibiotics are only administered to households in the affected patch (as neighbouring households are more likely than other households in the ring to be close contacts who may already be exposed).

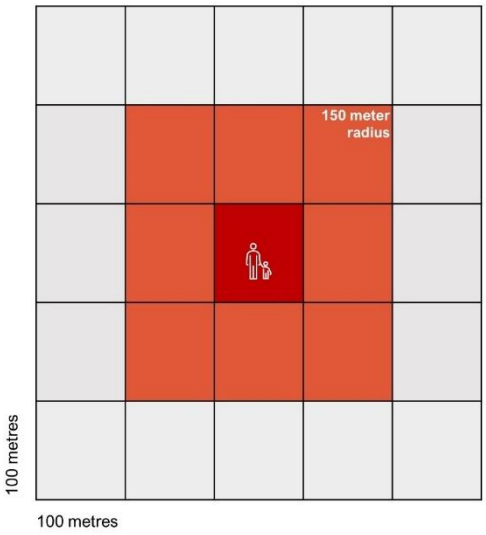


Figure 5.2 Spatial schematic of the approximate radius of CATI interventions around a new case-cluster, namely an approximate 150m radius which receives vaccination and water treatment (in orange and red) and in the affected patch which receives antibiotics, vaccination, and water treatment (in red).

CATI INTERVENTIONS

CATI is simulated with 3 interventions that have different mechanisms of protection and durations of effect (Table 5.1).[7]

Table 5.1. Effect sizes of CATI interventions and related parameters

Intervention	Effect size (95% CI) and other parameters	Reference
Antibiotic chemoprophylaxis *against symptomatic infection and duration of pathogen excretion*	95.5% (70.4—99.9) *at 2 days	Lewnard et al[46], Finger et al[9], based on Reveiz et al[47] and Echevarria et al[48]
	2-day duration of adequate drug concentration to eliminate *V. cholerae*	Khan et al[49]
	2.74 (2.40—3.07) day reduction in duration of pathogen excretion among symptomatic cases	Finger et al[9], based on Leibovici-Kalter et al [49,50]
Point of use water treatment *against exposure to V. cholerae*	66% (56—77) *all-cause diarrhea	Wolfe et al[51]
Single-dose vaccination *against symptomatic infection and all-or-none protection against infection*	87.3% (70.2–100.0)*at 2 months protection against symptomatic infection	Azman et al[12] (corroborated by Ferras et al[13] and Franke et al[14])
	80% protection against infection	Assumed based on above.
	7 to 11 days to vibriocidal activity	Azman et al[12], Akhtar et al[52]

Single-dose antibiotics (i.e., doxycycline or azithromycin) reduce the probability of infection among exposed contacts by 95.5% if given promptly, and reduce the probability of symptoms once infected by reducing bacterial shedding and thus the length of the infectious period (simulated by multiplying the recovery rate by 2.74).[9,46-48,50] Antibiotic effects last 2 days, after which the concentration of the antibiotic is too low to inhibit *V. cholerae*.[49,53,54] POUWT including Aquatabs, a narrow-necked drinking water container, and soap are given to households within patches that are contiguous to the index patch (an approximate 150m radius) and prevent exposure of susceptible individuals to *V. cholerae* in contaminated water by 66%.[7,51] We assume that sufficient WASH materials are given to households and their uptake is sustained until the end of the 60 days. We modelled single-dose vaccination by assuming two effects: (1) a reduction in the risk of infection modelled by moving 80% of susceptible individuals to the recovered state; and (2) a reduction in the probability of developing symptomatic cholera once

infected by 87%.[9,12,55] Vaccine protection sets in only after a week, consistent with an observed antibody response of 7 to 11 days. [12,52] Patches that were treated once cannot be retreated (i.e., effects cannot be multiplied) as vaccination and POUWT are modelled as having a continuous effect until the end of the study period. The one exception is for a previously treated patch that had not already received antibiotics and contains a new case. Here, only antibiotics are given to the affected patch to further reduce transmission among close contacts. The model is summarized in Figure 5.3. Parameter values are listed in Table 5.2.

Table 5.2. Parameter values for the model

	Value	Reference
Fixed or varied		
Kernel parameters		
Proportion of cases undetected for the seeding event	20%	Assumed
Minimum distance for kernel, $\mathbf{d_0}$	50m	Half of grid pixel size
Maximum distance for kernel, $\mathbf{d_{max}}$	1000m	Ratnayake et al[17]
Disease parameters		
Effective reproduction number, $\boldsymbol{R_E}$	1.5, 2.0, 3.0**	Jones et al[39], Camacho et al[37], Azman et al[38]
Proportion infected who remain asymptomatic, $\boldsymbol{\varphi}$	50%, 25%**	Harris et al[30], Nelson et al[29]
Incubation period, 1/$\boldsymbol{\delta}$	1.4 days	Azman et al[4]
Infectious period, 1/$\boldsymbol{\gamma}$	5 days	Weil et al[31]
Intervention parameters		
Average delay to implementation	2 days, 3 days	Ratnayake et al[20]
CATI radius for POUWT and vaccination	150 m	Azman et al[45]
Mean household size	5	Sourced from household surveys in prospective study[45]

**Indicates parameter for sensitivity analysis

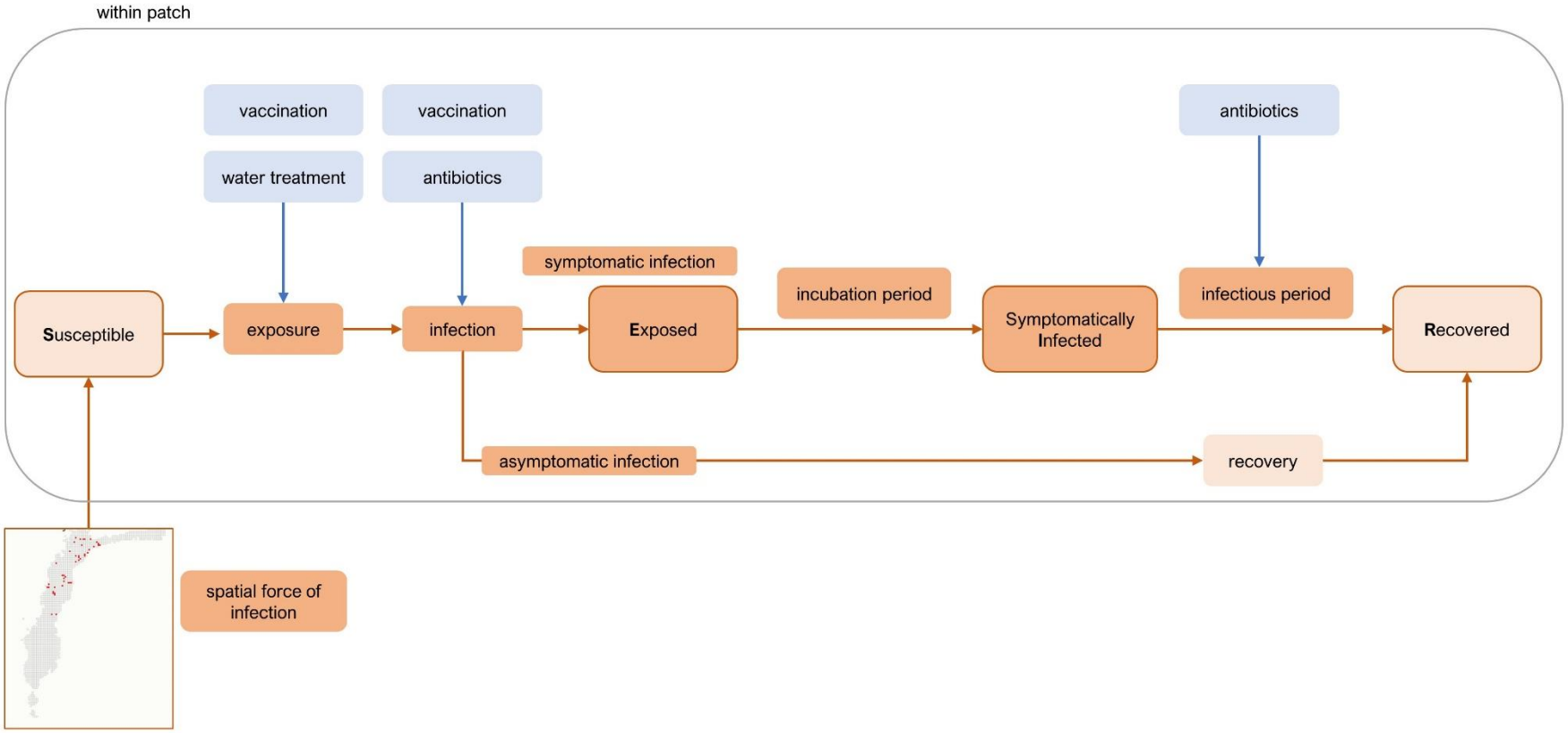


Figure 5.3 Schematic of state transitions and the mechanisms of CATI interventions

INTERVENTION STRATEGIES

The scenarios were based on considerations of the availability of vaccine, comparison of speed of implementation, and the effect of a high transmission rate (to stress-test CATI). Thus, 11 epidemic scenarios including CATI with and without vaccination, mass intervention, and uncontrolled transmission were modelled to explore variation in strategy, addition of vaccination, average delay to implementation, and strength of transmission (Table 5.3). We simulated each scenario 500 times to evaluate the median and the interquartile range (IQR) of the primary outcomes. Mass campaigns included POUWT with a 14-day delay, and single-dose vaccination with a 30-day delay targeting all patches in an approximate 1000m radius around patches with seed cases. The approximate 1000m radius was calculated according to the distance between the index patch centroid and other patch centroids.

Table 5.3 Main scenarios and sensitivity analyses (marked *)

	Intervention scenario										
	CATI + OCV	CATI + OCV	CATI + OCV	CATI + OCV	CATI + OCV	CATI no	CATI no	Mass + OCV	Mass + OCV	None	None
Scenario	1	2	3	4	5	6	7	8	9	10	11
CATI	■	■	■	■	■	■	■				
Mass campaign								■	■		
Uncontrolled										■	■
Interventions included											
Vaccination	■	■	■	■	■			■	■		
Water treatment	■	■	■	■	■	*	*	■	■		
Antibiotics	■	■	■	■	■	*	*				
Spatial targeting											
By radius, 150m	■	■	■	■	■	■	■				
By radius, 1000m								■	■		
Delay to implementation											
Delay, 2 days	■	■	■			■	■				
Delay, 3 days				■	■						
Delay, 14 and 30 days								■	■		
Effective reproduction number											
R_E , 1.5	■			■		■		■		■	
R_E , 2.0		■			■		■		■		■
R_E , 3.0			*								

STUDY OUTCOMES

The primary outcomes are the (a) proportion of model simulations resulting in containment (i.e., elimination requiring localised and ongoing intervention to be sustained[56]) or spontaneous extinction, both of which result in zero cases by day 60[56], (b) the median number of days to elimination/extinction; and (c) the mean cumulative incidence of symptomatic cases per 1,000 population by day 60. We also tracked secondary operational outcomes including the number and proportion of people and households targeted by the intervention, the number of CATIs implemented, and the number of vaccine doses, POUWT kits and antibiotics delivered. To calculate the number of households targeted, a mean household size of 5 individuals was used. [45] For each scenario, we mapped transmission in Uvira by the probability of each patch having at least one infection, among all simulations.

SENSITIVITY ANALYSES

Sensitivity to an increased 3-day delay in implementation (strategies 4, 5 in Table 2) and implementation without vaccination (strategies 6,7) were evaluated. Use of an R_E of 3.0 for the main CATI scenario (with vaccination and average 2-day delay) was undertaken to stress-test the capacity for containment given higher transmission (scenario 3). A lower asymptomatic proportion of 25% (resulting in more infectious cases), a lower vaccine effectiveness of 63%[57], and a weaker surveillance system capable of detecting 75% of symptomatic infections were assessed.

ETHICS

Ethical approval was provided by the London School of Hygiene and Tropical Medicine (Ref. no. 10603-5) and the University of Kinshasa School of Public Health (Ref. no. ESP/CE/173B/2022).

RESULTS

PROBABILITY OF CONTAINMENT OR EXTINCTION BY 60 DAYS

The outbreaks without intervention are shown in Figure 5.4. Without interventions applied, some simulations reached more than 100 cases, showing the potential for explosive outbreaks even with a relatively low R_E of 1.5. With R_E of 1.5 and when no interventions were applied, the median daily number of symptomatic infections was 19 (IQR 14—21) and 2.2% of outbreaks led to extinction. In the base scenario (where CATI including vaccination was applied with a 2-day mean delay) and R_E of 1.5, containment was the most probable outcome in 94.8% of simulations and took 34 median days to containment (IQR 27—42) (Figure 5.5.A-1). Using a delay of 3 days for CATI with vaccination, containment was probable in 93.2% of simulations and within 35 median days (IQR 28—43) (Figure 5.5.A-2). With a R_E of 2.0 and using base scenario of CATI including vaccination and 2-day mean delay, there was a slightly lower probability of containment of 87.6% among simulations and slightly higher median days to containment of 39 days (IQR 31—48) (Figure 5.5.B-1, 5.5.B-2). With an R_E of 3.0 and a 2-day delay, CATI with vaccination still usually resulted in containment but with a lower probability (in 62.4% of simulations) and a longer median time to containment of 46 days (IQR 37—52).

CATI without vaccination and with a 2-day delay could not outpace transmission and produced a low probability of containment even with R_E of 1.5 (in 27.4% of simulations). With R_E of 2.0 and CATI without vaccination, containment was very unlikely, occurring in just 5.8% of simulations (Figures 5.5.A-3, 5.5.B-3). In the mass campaigns, less than 50% of simulations resulted in containment for R_E of 1.5 (45.8%) and for R_E of 2.0, the proportion contained was 17.8% (Figures 5.5.A-4, 5.5.B-4). In sensitivity analyses using the base scenario, when vaccine effectiveness against infection and symptomatic infection was reduced from 87.3% to 63%, the probability of containment was reduced to 83%. When the proportion infected who were asymptomatically infected (and non-infectious) was reduced from 50% to 25%, the probability of containment was reduced slightly to 87%.

Table 5.4 Probability of containment and time to containment, by intervention scenario.

Intervention scenario	Weekly symptomatic infections (median, IQR)	Number (%) simulations where outbreak is contained	Days to containment (median, IQR)
R_E = 1.5			
CATI with vaccination			
1. Delay = 2d	1 (0—4)	474 (94.8)	34 (27—42)
2. Delay = 3d	1 (0—5)	466 (93.2)	35 (28—43)
CATI without vaccination			
3. Delay = 2d	6 (5—8)	137 (27.4)	**
Mass campaign			
4. Delay = 14d/30d	11 (4—12)	229 (45.8)	53 (47—56)
Uncontrolled epidemic			
5. *No intervention*	18 (14—21)	11 (2.2)	**
R_E = 2.0			
CATI with vaccination			
1. Delay = 2d	2 (0—5)	438 (87.6)	39 (31—48)
2. Delay = 3d	2 (0—6)	438 (87.6)	41 (33—48)
CATI without vaccination			
3. Delay = 2d	13 (11—13)	29 (5.8)	**
Mass campaign			
4. Delay = 14d/30d	15 (8—19)	89 (17.8)	**
Uncontrolled epidemic			
5. *No intervention*	28 (19—40)	0 (0)	**
RE = 3.0, Delay = 2.0			
CATI with vaccination			
Delay = 2d	4 (2—8)	312 (62.4)	46 (37—52)

** Where <50% of simulated epidemics were controlled, this value is not calculated.

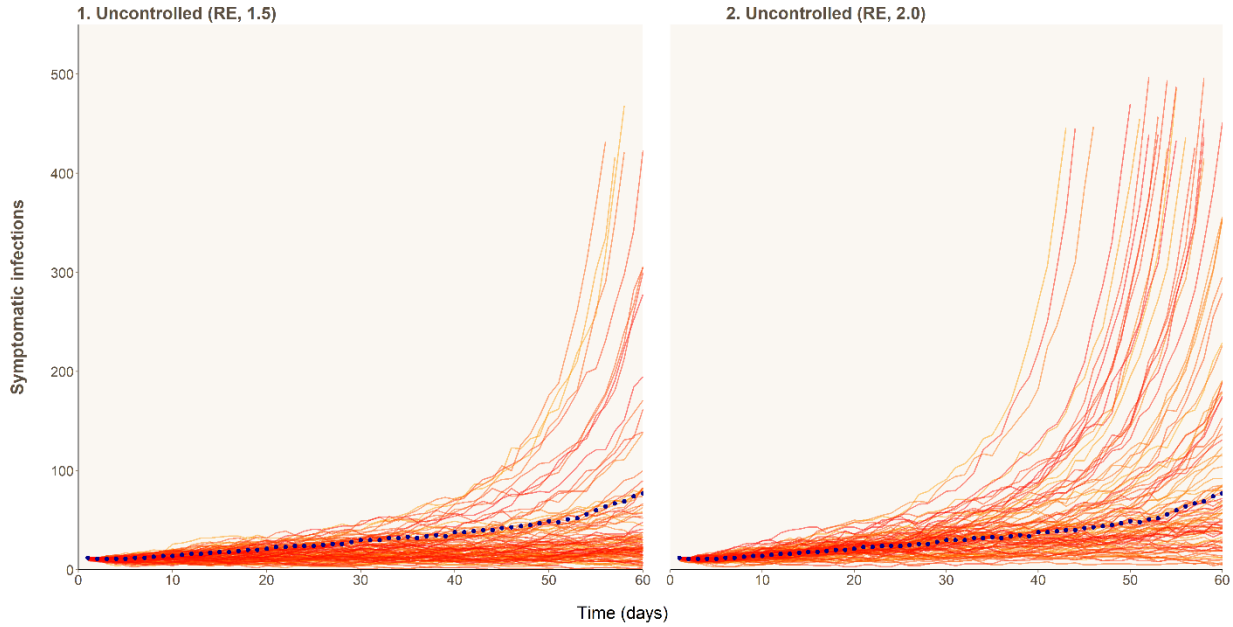


Figure 5.4. **Outbreak with uncontrolled transmission, by R_E.** Orange lines represent individual simulations, and the blue points represent the median of all simulations. (1) R_E, 1.5, (2) R_E, 2.0. Note the x-axis scale (0 to 500 symptomatic infections) which is approximately eight times larger than the simulations where interventions are implemented.

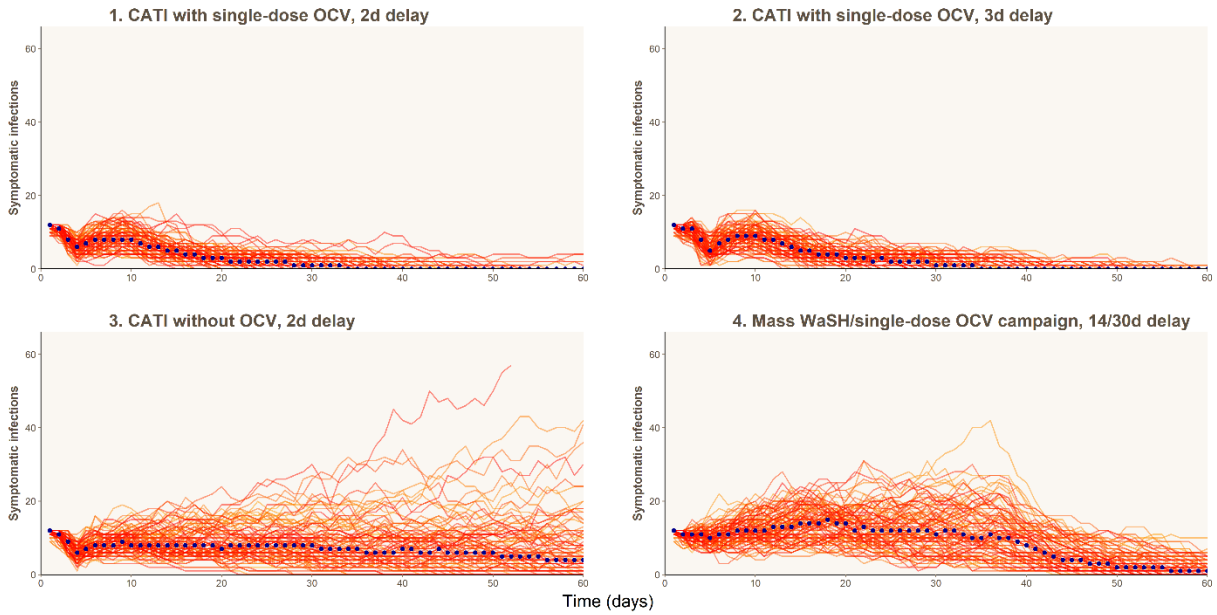


Figure 5.5.A. 'Low transmission' epidemics (R_E, 1.5) by intervention scenario. Orange lines represent individual simulations, and the blue points represent the median of all simulations. 100 individual realisations are shown for clarity. OCV, oral cholera vaccine; WaSH, water, sanitation, and hygiene.

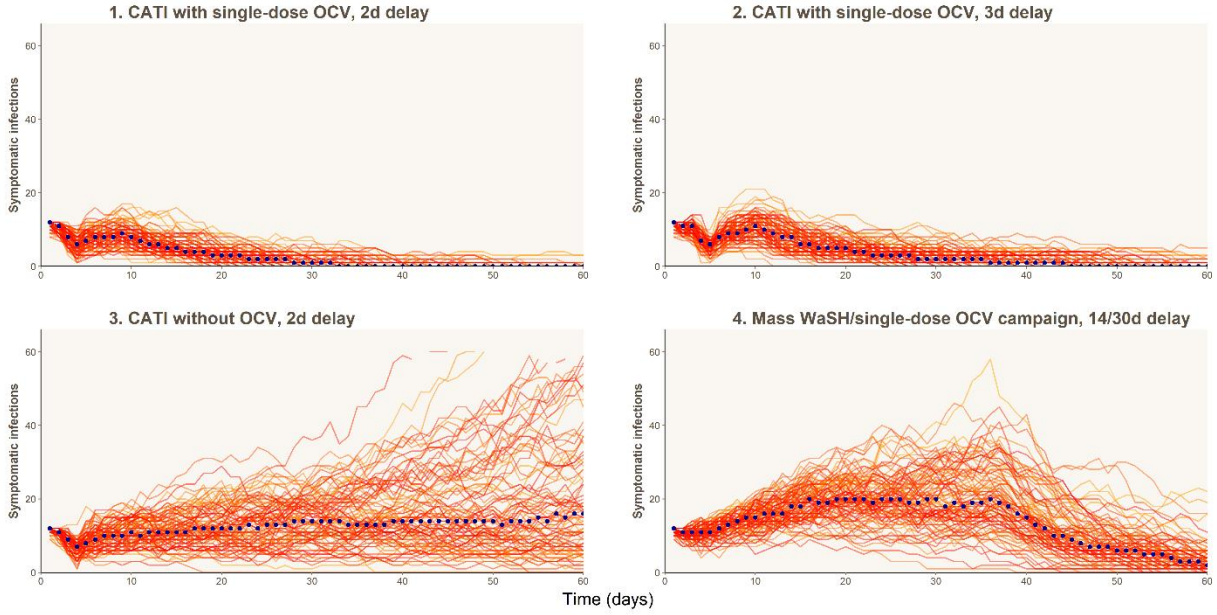


Figure 5.5.B. 'High-transmission' epidemics (R_E, 2.0) by intervention scenario. Orange lines represent individual simulations, and the blue points represent the median of all simulations. 100 individual realisations are shown for clarity. OCV, oral cholera vaccine; WaSH, water, sanitation, and hygiene.

Median number of symptomatic cases during the first 60 days

The distribution of the median daily number of symptomatic infections during the first 60 days across simulations and by scenario is shown in Figure 5.6 and Table 5.5. All scenarios with CATI including vaccination had a low median weekly number of symptomatic infections between 1 (IQR 0—4) for R_E of 1.5 and a 2-day delay, and 2 (IQR 0—6) for R_E of 2 and a 3-day delay. When CATI did not include vaccination, the median weekly number of symptomatic infections increased to 6 (IQR 5—8) for R_E, 1.5 and 13 (IQR 11—13) for R_E, 2.0. The mass campaign had the highest number of median weekly symptomatic infections of 11 (IQR 4—12) for R_E,1.5 and 15 (IQR 8—19) for R_E, 2.0. A reduction in caseload was visually apparent by day 40, following vaccination at day 30 (which takes 7 days for immunity to develop) (Figures 5A-4 and 5B-4). As seen in the boxplot, by the time the mass campaign was launched after day 14, the median case count was larger than any CATI scenario.

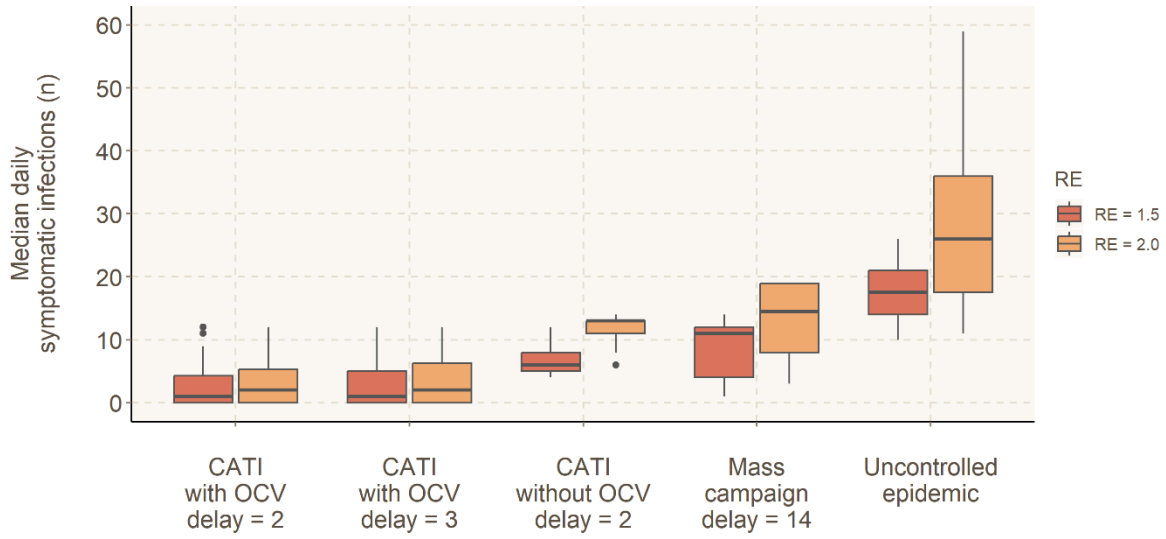
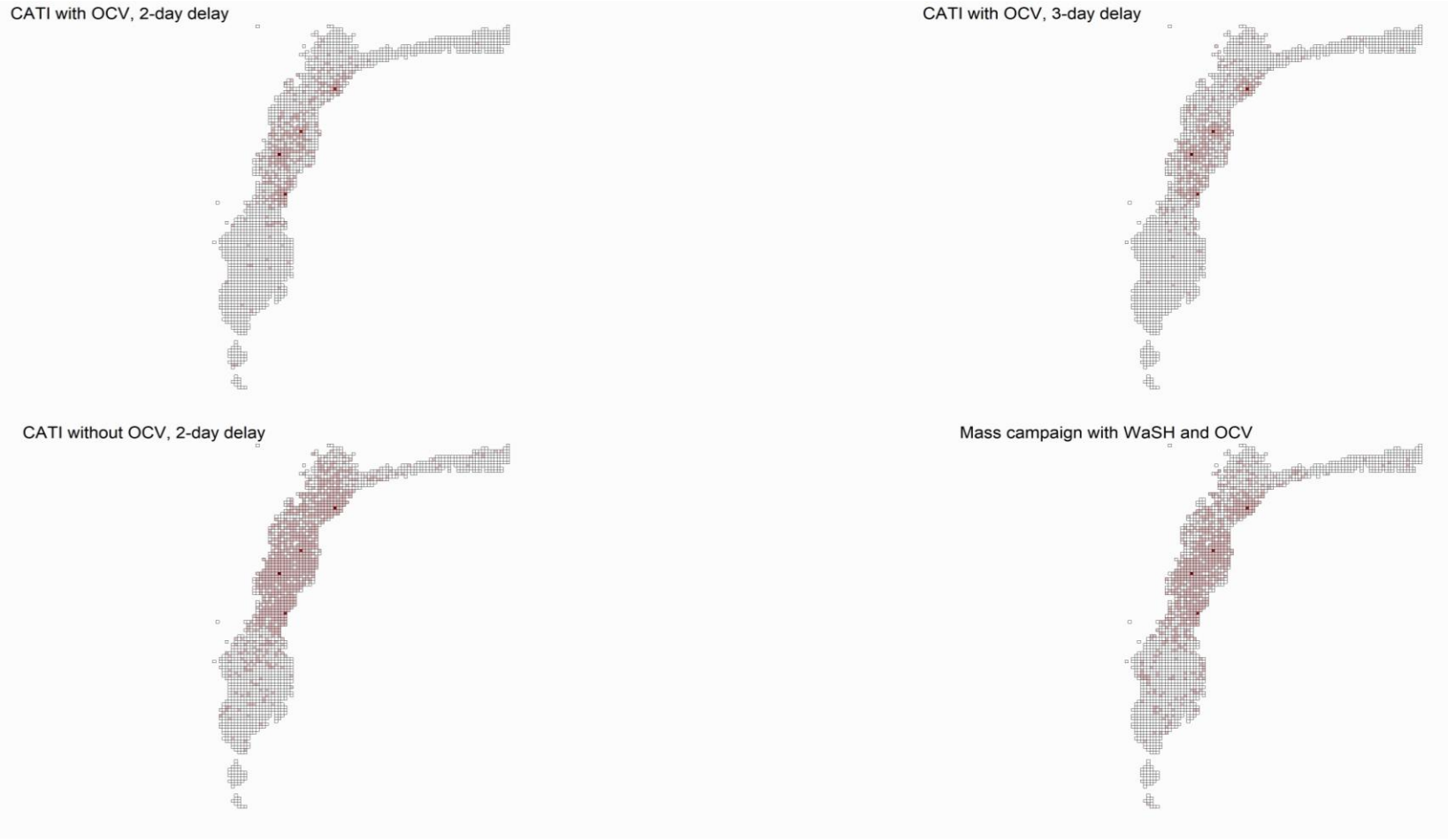


Figure 5.6. Distribution of the median daily number of symptomatic infections by intervention scenario (and uncontrolled transmission) for R_E of 1.5 or R_E of 2.0, based on 500 individual realisations. OCV, oral cholera vaccine.

Spatial propagation of the epidemic by 60 days

Figure 5.7 displays maps of the proportion of patches with ≥1 symptomatic infection among all simulations during the 60-day study period with R_E of 1.5. The darker patches have a higher probability of being included in most or all simulations. Using the base scenario of CATI with vaccination, 15.7% and 16.2% of patches are ever-affected across simulations when the delays of 2 and 3 days were applied, respectively. Spatial propagation is more pronounced when CATI is conducted without vaccination (i.e., 40.6% of patches were ever-affected across simulations) and with the mass campaign (33.6% of patches were ever-affected across simulations) and is seen to expand across the central and northern areas of Uvira.

Figure 5.7. Spatial propagation of the outbreak when R_E is 1.5



Darker shading of patches represents a higher probability of a patch having ≥1 infection over the study period, among all 500 simulations. The darkest patches represent patches where the outbreak was seeded in each scenario.

OPERATIONAL OUTCOMES

Considering an R_E of 1.5, and the base scenario of CATI with vaccination with a delay of 2 days, a median of 6,207 persons (IQR 5,555—7,432) in a median of 1,241 households were targeted (Table 5.5). This was able to contain transmission by addressing a median 5.3% of the population otherwise targeted by the mass campaign (median 116,872 persons). On average, this saved 110,665 vaccine doses and 22,335 POUWT kits (noting that median 794 antibiotic doses were used for CATI). With R_E of 1.5, CATI without vaccination targeted 12.9% more population (i.e., an additional 921 persons in 184 households), than CATI with vaccination. This resulted in an additional 184 POUWT kits used and 89% more antibiotic doses used (median 7,128, IQR 5,555—9,743). The results for R_E of 2.0 and 3.0 (CATI-only) were similar to R_E of 1.5.

Table 5.5. Operational outcomes based on 500 simulations per scenario

Scenario	CATIs (IQR) (N)	Population (IQR) (N, 1000s)	Vaccine doses (median, IQR) (N, in 1000s)	POUWT kits to households (median, IQR) (N, in 1000s)	Antibiotic doses (IQR) (N)
R_E = 1.5					
1. OCV, 2d	0—4	6.2 (5.6—7.5)	6.2 (5.6—7.4)	1.2 (1.1—1.5)	794 (682—921)
2. OCV, 3d	0—4	6.0 (5.6—7.3)	6.0 (5.6—7.3)	1.2 (1.1—1.5)	791 (682—919)
3. No OCV	5—6	7.1 (5.6—9.7)	--	1.4 (1.1—1.9)	7128 (5555—9743)
4. Mass	**	117.1 (116.4—121.8)	117.1 (116.4—121.8)	23.6 (23.3—25.0)	--
R_E = 2.0					
1. OCV, 2d	4—6	6.3 (5.6—7.5)	6.3 (5.6—7.5)	1.3 (1.1—1.5)	798 (682—950)
2. OCV, 3d	5—6	6.5 (5.6—7.5)	6.5 (5.6—7.5)	1.3 (1.1—1.5)	816 (682—1002)
3. No OCV	4—7	10 (7.2—14.9)	--	2.0 (1.4—3.0)	9953 (7166—14934)
4. Mass	**	121.0 (116.5—136.6)	121.0 (116.5—136.6)	24.3 (23.4—27.4)	--
R_E = 3.0					
1. OCV, 2d	5—5	7.1 (5.8—8.7)	7.1 (5.8—8.7)	1.4 (1.2—1.7)	906 (732—1112)

Populations are measured in 1000s (except for antibiotic doses). ** Equivalent to area covered by 86 CATIs; -- indicates the intervention was not included in scenario.

DISCUSSION

We used a spatially explicit metapopulation model to simulate the early phase of a cholera outbreak in an endemic city in the DRC. We found that using the base case scenario (R_E, 1.5, CATI implementation with a mean delay of 2 days in an approximate 150m radius using antibiotics, water treatment, and single-dose vaccination), the probability of containment at day 60 increased from 2.2% to 94.8%. While the zone of infection risk around new cases had previously been identified as 1000m in the 5 days following case presentation, it is notable that these results were possible with a CATI radius of 150m targeted around initial cases. [17] CATI with vaccination also maintained a low median case count, as compared to mass campaigns due to CATI's rapid deployment compared with the mass campaigns (2 days versus 14 and 30 days for WaSH and vaccination respectively). This characteristic could be important to ensure that treatment services are not overwhelmed by cholera cases, thereby maintaining a low case fatality ratio. CATI with vaccination targets less than 6% of the population on average than mass campaigns are assumed to reach (assuming R_E of 1.5). These results were robust to a range of different assumptions. That is, even if higher transmission (R_E , 2.0—3.0, characteristic of once cholera-naïve settings like Haiti and Zimbabwe[33,58]), or a longer mean delay of 3 days, or lower vaccine effectiveness representative of younger populations (63%), or a lower proportion of asymptomatic persons (25%) are assumed, then CATI with vaccination results in lower use of resources and a greater probability of containment than mass campaigns.

A previous model of CATI with vaccination applied to the large 2011 outbreak in N'Djamena, Chad found similar results comparing uncontrolled transmission with CATI with vaccination applied by day 50 producing a reduction in the final outbreak size by 68% (IQR 62—72) and duration by 81% (IQR 69—87). [9] This is also supported by the observation of rapid control (i.e., no new secondary cases) following CATI with vaccination following a large outbreak, mass vaccination campaign, and implementation of CATI for sporadic cases in Kribi, Cameroon in 2020. [59]

Of particular importance to current practice[11] was our finding that CATI without vaccination relying primarily on WaSH interventions was much less likely to lead to control of an outbreak and is likely to result in a higher overall use of resources (more households are targeted). CATI without vaccination tended to use more antibiotics to reduce transmission within patches with new symptomatic infections, but without vaccination, could not act synergistically to reduce

spread to other locations (40% of patches were affected compared to 16% of patches for CATI with vaccination). However, within the early phase, CATI without vaccination may be able to delay or avert a large outbreak and reduce the level of transmission to it can be controlled by an eventual mass campaign. CATI without vaccination has been carried out in Yemen and natural disasters where there is substantial geographic spread, poor access to health care, and therefore, an imperative to suppress small outbreaks and reduce transmission as quickly as possible.[37] Given that mass vaccination is not a surety, and the mean time to launch a mass campaigns is approximately 60 days following case confirmation (and given that we define the early phase of the cholera outbreak in this study as 60 days), our findings give additional rationale to the consideration of CATI driven by WaSH and antibiotics to slow epidemic growth during the preparation of mass campaigns.[6,9,10]

LIMITATIONS

The model choices made here incur important limitations. We did not model environmentally-mediated transmission from local water sources for the sake of parsimony, whereas this may be of importance in an endemic setting where communities have seasonal exposure to potential *V. cholerae* reservoirs in Lake Tanganyika.[60] Including water sources would likely reduce the impact of CATI and mass campaigns, as outbreaks may be re-seeded continuously from local water sources. However, if drinking water was sufficiently protected at the household level, CATI should still reduce transmission. We did not examine increased infectiousness of cases during the first 2 days of infection, which would likely increase exposure in households.[31,34] Prompt CATI would likely have an advantage over other strategies in reducing these exposures. Transmission in an urban environment is challenging to model as human movement is complex and can be longer distance.[61] We did not account for population migration or introductions of infected individuals from outside of Uvira as over the 60-day period, we did not expect substantial migration. For longer periods, we expect likely increases in the number of susceptible persons and infected persons entering Uvira (i.e., resulting from fishing, trade, and forced displacement). This would likely result in higher population density in focal areas, and less efficient implementation of CATI. Conversely, community protection gained through vaccination would likely be decreased with out-migration of vaccinees. We did not account for isolation of cases that seek care at the cholera treatment unit, which would reduce community transmission and increase the impact of all strategies. Given the lack of data on immunity due to prior infection and recent vaccination, and on the proportion asymptomatic, we make simplistic assumptions

about immunity levels, waning effects, and how acquired immunity influences transmission and disease severity.[29] If we had modelled asymptomatic persons as capable of shedding *V. cholerae* and infecting others (and therefore serving as an infectious reservoir), the large asymptomatic proportion (≤50% of those infected) would likely increase community transmission and challenge CATI's capacity to contain outbreaks. However, this would be observed only if there was no significant overlap between asymptomatic and symptomatic cases to signal the outbreak and the deployment of CATI. Taken together, the transmission scenario may not fully capture dynamics in Uvira. We relied on large intervention effect sizes but note that high effectiveness has been observed in trials for antibiotic clearance of *V. cholerae* (i.e., 2 days)[47,49] and in observational studies for single-dose vaccination (i.e., 2 months)[12-14] in the short-term. Given the drop in single-dose vaccine effectiveness measured by Franke et al in Haiti at month 15 (65%, 95% CI 9—87), we cannot speculate on the impact on transmission of the waning level of protection offered by CATI with vaccination later in the cholera season. This is vital for consideration if other interventions are not planned for the larger surrounding population (i.e., two-dose vaccination).

Our patch structure could not incorporate interactions at the household level, whereas an explicit focus on household contacts of cholera cases with water treatment, hygiene promotion, and hygiene kits has been shown empirically to reduce the risk of suspected cholera in the household by 66%[62] and confirmed cholera by 47%[63]. Therefore, if we incorporated well-designed household-level WaSH interventions and antibiotic chemoprophylaxis delivered through CATI, this may increase the impact of CATI. In addition, the estimate of reduction of all-cause diarrhoea with POUWT may differ from a cholera-specific estimate if the waterborne pathogens contributing to that estimate have different transmission pathways that are more amenable to chlorination.[9,51] If we had accounted for age structure, we may have been able to investigate alternative CATI strategies to target high-incidence groups (i.e., children under 15 years) who normally transmit to older household members, and when vaccinated, may confer indirect protection to older age groups.[58] We mathematically represent a complex public health intervention which is subject to many context-dependent logistical restrictions. We know the capacity for the early detection of cases in resource-poor settings via robust, community-focused surveillance systems[20,64], behavioural aspects of uptake of Aquatabs[65,66] and vaccination[59], and the logistics of the provision of sufficient and safe water[67], are all longstanding long-term challenges for disease control. We do not incorporate the effects of the large-scale, 5-

year water supply infrastructure improvement program in Uvira that reduced acute diarrhoeal diseases including cholera (see Gallandat et al[22]). This may underestimate the total impact of cholera prevention and control efforts since fewer persons would be exposed to *V. cholerae*. The duration of implementation of 3 days and implementation radius of 150m may not always be attainable, namely in dense, urban settings.[45] Finally, outbreak simulations are right-censored at 60 days, which limits our ability to determine whether outbreaks are truly eliminated and for how long.

Going forward, we outline key considerations for increasing the potential for effective CATI from these simulated results and emerging real-world experience with CATI through an ongoing observational study and case studies. [45,68]. First, the delay to implementation can be reduced substantially to 2 to 3 days on average through preparedness of local teams for deployment namely, robust coordination and trained district-level teams located close to known cholera hotspots. [20] This will aid in rapid response within the 5-day period of high infection risk[17,18]. Second, the use of RDTs to zero in on the most likely clusters could save resources, personnel, and avoid overwhelming the system to ensure lower delays to implementation where needed. Enriched RDTs are increasingly used in surveillance and at local levels, but require training and monitoring on their correct use. [64,69] Third, community understanding and commitment to implementation and uptake of CATI and their participation is core to its eventual adoption by communities, community health workers, and district health units of CATI as a strategy. This aspect cannot be explored adequately in a mathematical model, but like recent Ebola ring vaccination strategies[70] would have serious implications on effectiveness and equitable access to an effective intervention. Finally, vaccination may indeed drive CATI's effectiveness in the early containment of outbreaks using fewer resources, at the cost of attaining protection among a small population located in a few rings rather than the larger community. In outbreaks, where time is of the essence, most protection from a reactive campaign comes from the first dose. [16] Importantly, the larger impacts of mass vaccination, mass coverage and herd protection, is explicitly not the goal in such small, focused CATI rings. However, CATI potentially offers a vastly lower number of doses per case averted than a mass campaign.

CONCLUSIONS

Our model demonstrates the potential early control using CATI with vaccination with fewer resources than mass campaigns. This suggests a viable, localised strategy to contend with limited vaccine supply and other resource constraints. If borne out by ongoing observational studies of CATI with vaccination[45], our results provide additional rationale to Ministries of Health and for global policy makers for providing a policy pathway to procure small stocks of vaccine for in-country activation of CATI. This action can support systematic and early CATI implementation using far fewer resources for a reactive response, while planning carefully for preventative cholera vaccination for larger populations where needed.

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DATA AVAILABILITY: All data and code produced are available online at https://github.com/ruwanepi/Uvira_spatiotemporal

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Chapter 6: General Discussion

6 GENERAL DISCUSSION

As of mid-2023, cholera has continued its march across Africa, Asia and Haiti. As of August 15, 2023, the WHO African and Eastern Mediterranean regions continue to be the most-affected with a third of countries in each region reporting cholera since the start of 2023. [1] Depending on the continuation of these trends, the goal of reducing transmission by 90% in 20 countries by 2030 may be unrealistic. [2] Water and sanitation infrastructure remains the cornerstone of cholera prevention but progress in achieving universal piped water and sanitation infrastructure has been slow across regions and would need to increase sixfold to achieve global targets by 2030.[3] Other key risk factors for cholera transmission continue to afflict cholera-prone countries including civil conflict, forced displacement, flooding and other natural disasters, and widespread food insecurity and severe malnutrition. [4,5] Though cholera is a vaccine-preventable disease, vaccine manufacturing capacity has long been extremely limited and there is not yet a sufficient supply of vaccine to achieve the transformative goal of elimination in any given country.[6] As vaccines will continue to be in short supply up to 2026, single-dose campaigns will be the only option going forward and there will not be movement toward integration of cholera vaccines into routine immunisation within this period. [7] As outbreaks continue, there remains an imperative for improved means of reactive response for populations most at-risk, centred on WASH interventions for immediate household protection, single-dose vaccination for longer-lasting protection after 7 days, and strong coordination by the public health system.

6.1. THE THESIS

I set out to investigate CATI with vaccination in the earliest phase of outbreak containment as a reactive, multisector strategy. The aim was to produce up-to-date evidence that could feed into decision-making regarding CATI with vaccination by MSF and other non-governmental organizations and Ministries of Health, as well as contribute towards answering the research questions about CATI that have been prioritized by the GTFCC. I sought to answer the following four research questions which investigated the development of CATI, the speed by which it could be implemented, the extent of spatial risk zones targeted by CATI and occurrence of clusters to trigger CATI, and finally, the potential impact of an integrated model of an optimal CATI scenario where vaccines are available. In detail:

- What is known about the effectiveness of interventions included in the CATI package, CATI's optimal spatiotemporal scale, and its effectiveness in reducing transmission?

- What is the timeliness of response to small cholera outbreaks in fragile states, and to what extent does this support the potential utility of CATI?

- How can spatiotemporal clustering approaches be used to identify spatiotemporal zones of increased cholera risk around incident cases in an endemic setting?

- What is the potential impact of CATI for containment of outbreaks in a cholera-endemic setting?

This thesis adds to the emerging literature on WASH interventions targeted to a case's household[8,9], a retrospective study of CATI (primarily WASH-based)[10], and a modelled simulation of CATI with vaccination[11]. Moreover, I used the findings of this thesis in parallel to develop the study design for a prospective observational study of CATI with vaccination in DRC. [12]

In this final chapter, I summarize my major findings and make recommendations for CATI for cholera response. I identify limitations of the research I did and I discuss key future research questions.

6.2. SUMMARY OF FINDINGS

What is known about the effectiveness of interventions included in the CATI package, CATI's optimal spatiotemporal scale, and its effectiveness in reducing transmission?

Key findings:

- CATI could have potentially rapid and large impacts on outbreak control in the short term. There is moderate evidence that antibiotic chemoprophylaxis, single-dose OCV, hygiene promotion, and point-of-use water treatment present effective mechanisms of action for rapidly limiting transmission in the household and its high-risk radius. A high-risk spatiotemporal ring of 50–100 m across 7 days specifies the implementation radius, likely due to intense household transmission and shared risk factors among neighbouring households.

- CATI is critically dependent on early detection capacity and requires further evaluation to evaluate the effectiveness of different packages of interventions. Two controlled studies showed a reduction in the size of case-clusters and infection among household contacts and two uncontrolled evaluations suggested reductions in transmission.

I used a scoping review which integrated the scientific and grey literature to outline (a) the effectiveness and most appropriate cholera interventions that could be delivered via CATI (including, antibiotic chemoprophylaxis, vaccination, POUWT delivered to the household, water treatment of local collection sources, safe storage of treated water, household spraying, hygiene promotion, and disinfection of corpses), (b) the spatiotemporal scale of transmission around new cases, and (c) the effectiveness and feasibility of CATI in reducing transmission as measured by empirical evaluations. There was a dearth of rigorous evaluations of CATI (15 studies including only 2 controlled studies in Bangladesh and Haiti which showed a reduction in transmission in case-households and areas around case-households, respectively). This was unsurprising given the difficulties faced in conducting evaluations of response strategies during recent large epidemics in complex settings (i.e., cholera in Yemen and Ebola in West Africa and Eastern DRC).[13-16] Close examination of past studies enabled me to carefully consider gaps which should be prioritized for future evaluations of CATI, and other diseases and interventions which can potentially be controlled by targeting social and/or geographic rings around new cases.

We also highlighted a discordance in the actual strategies used by actors in terms of the trigger events, use of RDTs or culture confirmation, spatiotemporal zones, and actual coverage of alerts to new cases. These aspects make standardization of CATI, policy relevance, and coherent evaluation all difficult to achieve. There were several other gaps that are critical for building CATI strategies including costing (only two estimates have been published) [9,17], which could be used to evaluate how CATI compares to other interventions in terms of costs per case averted. Community health programs (including community-based surveillance and referral and maintenance of oral rehydration points (ORPs)) that could sustain the effects of CATI after the initial week are nearly undocumented. [18-20] Finally, a coherent global policy approach for procuring small vaccine stocks for CATI is lacking. [21,22]

Since its publication, the findings of this review were incorporated into the 2022 Cholera Seminar article in *The Lancet*. [23] Two recent papers reviewed case studies of CATI in DRC, Haiti, Northeast Nigeria, Yemen, and Zimbabwe. [24,25] The reviews noted the reliance of current CATIs on WASH and discordance in the modalities used by different actors and adherence to standards (i.e., irregular selection of the case household, specification of at-risk households, and practices depending on resource and staffing capacity). Issues with coordination among actors and integration between the several sectors involved were reported. A new evaluation has appeared, wherein D'Mello-Guyett et al found that targeting hygiene kits to case-households was effective in reducing cholera transmission among household contacts via a dose-response relationship between increased kit use and lower incidence of suspected cholera. [8]

While not a new evaluation, Rebaudet et al revisited the experience with CATI in Haiti from 2013 to 2019, and recently summarized that "Case-area targeted interventions aimed at interrupting cholera transmission were reinforced, which resulted in the extinction of the epidemic within two years". [26,27] However, when considering the multiple factors influencing cholera transmission, it is difficult to attribute extinction to a single CATI program (and one that lacked vaccination). Multiple factors influence cholera transmission dynamics, and other interventions across sectors were being conducted by other actors in Haiti. This reinforces another recommendation of the review: to develop more rigorous study designs and clear outcomes for the evaluation of novel interventions against outbreaks in crisis settings.

What is the timeliness of response to small cholera outbreaks in fragile states, and to what extent does this support the potential utility of CATI?

Key findings:

- Median delays to case presentation at a health facility and response across 76 cholera outbreaks were 5 and 10 days, providing an opportunity for earlier intervention within the first 5 days (i.e., via CATI). Median delays to detection, investigation, and response have improved since 2009.

- Locally relevant alert and verification capacity (i.e., event-based detection, rapid diagnostic testing for cluster validation, and integrated alert, investigation, and response) appears key to triggering a rapid response for cholera.

Having outlined a potentially effective strategy for CATI in the scoping review, I sought to understand the mean delays (and range) of key milestones in outbreak detection and response in fragile and conflict-affected settings, and estimated outbreak sizes given these delays. This analysis would assess whether outbreak detection and response are likely to occur within a 7-day window (and in preferably less time) while outbreaks are still small. This underscores that the surveillance system is as important an intervention as vaccination or WASH. Using an exhaustive search of cholera outbreaks and their responses from 2000—2019, I was able to determine that mean delays from symptom onset of the first detected case to detection, verification, investigation, and response have improved over time. Also, delays from symptom onset to case presentation (5 days, IQR 5—5) and investigation (7 days, IQR 6—13) were reasonable, wherein 99% and 97% of simulated outbreaks would be <20 cases. The 5-day window to case presentation is helpful for situating a reasonable timeline for implementing CATI once the index case is detected at a health facility. This also concords with the spatiotemporal scale determined through the scoping review of 50—100m within 7 days.

With this foundation, I sought to determine qualitative and quantitative evidence of determinants of early detection and response for cholera outbreaks. In particular, the application of event-based surveillance (i.e. an immediately notified alert by phone vs. weekly analysis of data) predicted a shorter delay to response.[28] This relates well to current guidance from WHO on

Early Warning Alert and Response in crises, which prioritizes an immediate alert function through dedicated phone networks and other event-based mechanisms over routine weekly analysis of surveillance data.[29] Specific features that hastened the response included local integration of RDTs to validate alerts, community-based surveillance, mobile phone integration at health facilities, and actions taken on alerts of suspect cholera cases rather than waiting for culture confirmation. This aligns well with the requirements for sensitive surveillance of suspected cholera with increased specificity where possible (i.e. using RDTs), identified as a requirement for CATI, in the scoping review.

Overall, this analysis provided some confidence that CATI could be implemented within a 5—7 day window of outbreak detection and investigation, if prepared well. Previous reviews of the timeliness of all-pathogen outbreak detection and response which found longer median delays to outbreak detection of 27 days (95% CI 20—31.5) for outbreaks reported to WHO (1996—2014) and 29 days (range 7—80) for outbreaks in fragile settings (2000—2010), respectively.[30,31] Since we published our work, a 2022 review of MSF-driven cholera outbreak responses from 2015—2018 found a longer delay to response of 23 days (IQR 14—41), which may indicate the authors' use of a more comprehensive definition of response (versus my use of any response element in the first instance) and fewer outbreaks examined.[32] WHO AFRO also published metrics on all-pathogen outbreak timeliness, finding reduced time to outbreak detection from 14 days (IQR 6—37) in 2017 to 4 days (IQR 1—11) in 2019.[33] Taken together, this may reflect better investment in global cholera detection and control since 2010, through improvements in policies, resources, training, and the effects of the scale-up of IDSR and the Joint External Evaluation exercise.[34,35] As well, in 2021, an initiative called 7-1-7 put forward simple metrics for benchmarking the delay to detection (within 7-days), investigation (within 1-day), and response (within 7-days), citing our review.[36]

How can spatiotemporal clustering approaches be used to identify spatiotemporal zones of increased cholera risk around incident cases in an endemic setting?

Key findings:

- Global and local clustering analysis can effectively specify cholera's specific clustering patterns in an endemic setting (Uvira, DRC) to provide actionable information on where intensive transmission is occurring early on and where, to inform preparedness for targeted control efforts.

- A global clustering high-risk zone for infection spanned a 600—1100m radius around new cholera cases, within the first 5 days after case presentation. Local clustering of a similar size (650m radius) typically preceded seasonal outbreaks and highlighted locations to focus prevention efforts.

Once the timing of potential CATI implementation was established in paper 2, it was important to understand in a cholera-endemic setting with regular, seasonal outbreaks where CATI-like strategies have been used (i.e., in DRC, 'quadrillage' and case-targeted hygiene kits have been implemented recently) [8,37] , whether the size of the spatiotemporal radius could be specified, and whether there were unique locations where clustering recurred. CATI could benefit from such an analysis to estimate the optimal size of the CATI radius, and the locations of recurrent, clustered transmission, to prepare and target the rapid response when seasonal outbreaks emerge. Using data from Uvira, South Kivu, DRC, I applied the tau statistic approach to outline the size of the risk zone of high and elevated infection risk around a given new case, and the space-time scan statistic to detect the timing, location, size and duration of clusters of recurrent infection. [38,39] The finding of repeated clustering in similar areas was useful in terms of specifying neighbourhoods where prevention and case management could be prepared with more precision. The size of the zone of high infection risk (i.e., RR > 1 for 1100m around a new case within the first 5 days of case presentation) was higher than previous estimates[40], and raised important questions about the extent of risk in an endemic, densely-packed and lakeside urban setting. This also highlighted an important data limitation, namely the level of analysis being the street rather than household.

It remains that rings of 100—500m in an urban setting are more logistically feasible than 1000m, so the potential impact of a smaller CATI target on a wider risk zone seemed useful to evaluate in the mathematical model in Chapter 5. Practical recommendations of the paper include emphasizing preparedness in recurring clusters, daily scanning using the space-time scan statistic for new clusters to trigger rapid response, and the use of CATI for small outbreaks in new areas and lakeside areas that may seed future outbreaks. I also relied on areal data (at the avenue/street level of the case residence) to carry out statistical analyses that were originally intended for household or health facility point locations. Using a series of simulations to scatter the household locations randomly, I showed near-equivalence of the tau results for both datasets. This provides a use case of applying the tau statistic method to small areas.

What is the potential impact of CATI for containment of outbreaks in a cholera-endemic setting?

Key findings:

- Via spatial modelling in Uvira, prompt implementation of CATI using antibiotics, water treatment, and single-dose vaccination was potentially effective in controlling cholera outbreaks within the first 60 days after onset of symptoms of the first case.

- Effectiveness was robust to higher transmission scenarios and a longer average delay to implementation, However, CATI without vaccination suppressed epidemic growth but could not control it completely.

- CATI with vaccination achieved control while targeting only <6% of the population that would otherwise be vaccinated in a mass campaign.

For Chapter 5, I integrated findings from the previous papers to develop a spatially explicit model of cholera with CATI, based on Uvira's population and layout, the optimal CATI strategies (paper 1), mean delay to intervention (paper 2), and spatiotemporal scale of risk (paper 3). This was a unique model as it used the early phase (60 days) to investigate reactive control featuring as few CATI implementations as possible. This compares to the foundational CATI model by Finger et al (2018) which evaluated whether CATI could be used to reduce transmission by day 50 in a

scenario where the epidemic was already advanced.[11] CATI was conducted repeatedly in a 150m radius around new cases, and analyses were driven by key strategic questions (i.e.: variation in transmission rates, delays to implementation, and vaccine availability). We found that prompt implementation of CATI over a 150m radius using antibiotics, POUWT and, importantly, single-dose vaccination, is potentially effective in containing cholera outbreaks in the first 60 days after the first case was notified. Effectiveness was robust to higher transmission scenarios (R_E, 1.5, 2.0, 3.0) and a longer average delay to implementation (2, 3 days). However, vaccination was required to achieve containment. Another important finding is that the radius of intervention of 150m was effective in containment despite a maximum zone of infection risk of 1000m that was derived from paper 3. CATI with vaccination on average used a small fraction (6%) of the population targeted by a more delayed single-dose mass campaign with WASH, whilst achieving containment.

In current practice CATI appears to be WaSH-driven, but this analysis found that WASH interventions, while reducing the weekly caseload, would not be likely to contain the outbreak completely. However, this does make a case for hybrid approaches with early WASH-driven CATI to suppress transmission as mass campaigns are being prepared. Overall, we found potential for early control using CATI with vaccination with far fewer resources than mass campaigns consume. However, CATI's advantage is also its limitation: a smaller protected population (discussed in Limitations below).

Far from dependency on vaccines, a case is made for the unique roles of different CATI strategies. These findings highlight the unique roles of single-dose vaccination, preparedness for early detection and response via effective surveillance systems and empowered district teams, to promote rapid containment. They also highlight the unique role of more frugal WASH-driven CATIs for suppressing transmission in remote and crisis-affected settings before mass campaigns can be prepared (if at all). The findings could serve as an advocacy point, alongside ongoing prospective studies, to permit preparedness of local level vaccination and other interventions to control outbreaks before they enlarge and to reduce pressure on cholera treatment units. This study suggests that early clusters can be acted on, if preparedness is in place.[41] Finally, in the context of scarce vaccination resources, this study highlights the potential role of small-scale vaccination with a single dose for much earlier reactive control than is the standard (i.e., given that mean time from request to the Stockpile to a vaccination campaign is around 60 days).[22]

6.3. MOVING FROM MODELLING TO AN EMPIRICAL STUDY OF CATI WITH VACCINATION

Together with Epicentre and MSF I planned to develop and conduct an observational study of CATI with vaccination during an outbreak response in Cameroon, DRC, Niger, and/or Zimbabwe in 2020. Due to the global shift in priorities to COVID-19 control, it was not possible to launch a new intervention for cholera in 2020. Instead, in parallel to the PhD research, I worked with Dr. Flavio Finger (Epicentre) to prepare a study protocol and standard operating procedures for implementation and obtained ethics approval from the IRBs of LSHTM, MSF, DRC, Cameroon, and Niger.[12] We launched the study in DRC in April 2022, led by Dr. Finger, lasting into April 2023 and producing 118 CATI rings in Nord Kivu, Haut Katanga, Kasai Orientale, and Sud Kivu where we used active surveillance through CHWs to monitor for RDT-positive cases emerging in the ring over the 30 day period following CATI, and carried out household coverage surveys in each ring to understand coverage and uptake. In Cameroon, where I was the lead investigator, I carried out two study trips to set up the study during a large and expanding epidemic in the conflict-affected Southern provinces.[42] While ultimately the conditions were not conducive to conducting the study in the middle of a large outbreak, I supported the Ministry of Health and MSF to carry out CATIs (Figure 6.1).

Figure 6.1: *Carrying out case-area targeted intervention with vaccination in Eastern Cameroon (bordering Central African Republic) with the Ministry of Health, Médecins Sans Frontières and Epicentre in September 2022.*

Number of rings by site			
Buhimba & Mugunga, Nord Kivu	42	Masisi, Nord Kivu	13
Kasika, Nord Kivu	34	Muji-Mayi, Kasai Oriental	6
Katuba, Haut Katanga	9	Minova, Sud Kivu	14
		Total	**118**

Figure 6.2. Mapping of CATI sites in the DRC including in the prospective observational study. Source: Epicentre Scientific Days presentation[43,44].

My thesis findings supported the development of this observational study. First, I used the scoping review to predicate an evidence-based design of CATI elements including the actual package of interventions, the radius of targeting, surveillance arrangements, and implementation modalities. Findings also supported the rationale for use of single-dose vaccination and antibiotics, and antimicrobial resistance surveillance. Second, using the gaps identified in the retrospective observational study from Haiti[10] (i.e., inconsistency in the use of antibiotics and other interventions, a lack of a clearly-measured ring, retrospective review of imprecise programmatic data that was collected for cholera response only, and difficulty in ascertaining whether secondary cases could be assigned to the CATI ring or not), we devised a more rigorous prospective observational study that featured a harmonized strategy for CATI, a clear exposure (delay to implementation) and a defensible outcome (RDT-positive cases in the ring during the 30 days after implementation). Given the non-randomised nature of the evaluation, I devised a method for adapting branching process modelling to simulate transmission in rings and statistical simulation to estimate the sample size of rings required to observe an impact of CATI with sufficient power (see appendix E).[45] Finally, Epicentre and MSF advocated for the use of vaccines within CATI both internally and with the DRC and Cameroon Ministries of Health based on our modelling findings of the importance of vaccination to CATI. This is notable because this necessitated MSF purchasing their own stock of vaccines dedicated for CATI for DRC from Euvichol in South Korea.

6.3.1. PRELIMINARY OPERATIONAL FINDINGS FROM CATI WITH VACCINATION IN DRC AND RELATIONSHIP TO THESIS FINDINGS

The preliminary findings from the DRC study are promising in terms of operational feasibility and coverage. These findings were discussed at the Epicentre's 2023 Scientific Days and the 2023 GTFCC Research Day (but are not for citation) [45]:

- 118 rings were targeted in a 1-year period and an entire cholera season, across 6 MSF sections who shared a local stockpile of vaccines. Implementation was slightly different by section, owing to context and capacity. The Ministry of Health required MSF to carry out a second dose of OCV 14 days after the first dose.
- MSF/MOH CATI teams demonstrated that they were well-prepared for reactive response, resulting in a lower-than-anticipated median delay to implementation of 2 days and a median delay to vaccination of 3.5 days. For the study, this made the exposure measure more homogeneous.
- Difficulties in covering a 150m ring persisted in densely populated Goma, where the decision was thus made to restrict rings to 50m over a 5-day period due to the impossibility of achieving coverage otherwise.
- Difficulties were encountered during the influx of internally displaced people into Goma city, where it became impossible to carry out CATIs for each new case, and instead expanding case management became the priority.
- Very few secondary cases were detected in the 30-day window after implementation with more than 75% of the rings having zero cases. This made the outcome measure more homogeneous.
- High survey-based single-dose vaccination coverage was assessed across rings (81.2%, 95% CI 80.6—81.9, by household survey)
- High survey-based availability of WASH materials at 30 days after CATI was noted: Aquatabs (79.0%, 95% CI 77.4—80.5), soap (88.3%, 95% CI 87.0—89.4) and drinking water container (70.8%, 95% CI 68.9—72.7) though availability of the hand-washing station was limited (46.0%, 95% CI 44.1—47.8) and the single measure of free residual chlorine in drinking water was largely considered too low for protection in 60.8% (95% CI 58.8—62.8) of households.

6.4. LIMITATIONS OF THE THESIS

I now discuss the conceptual and technical limitations of how I evaluated CATI across the four studies, which relate to four main areas (below). Ways in which to explore these limitations in future research are discussed in 6.6 Agenda for Future Research.

Lack of Global OCV Stockpile policy for CATI use limits the scope of the study findings

There is no current policy for the Global OCV Stockpile to facilitate procurement of vaccine for CATI, as theorized, modelled, and discussed in this thesis. Therefore, the limitation I face is the inability to specify a realistic intervention. In our prospective study, MSF procured vaccines from Euvichol at their own cost to create a small OCV stockpile for CATI in DRC. Elsewhere, CATI with vaccination has been done exclusively with the leftover stocks from mass campaigns (in Cameroon and South Sudan).[41,46] The latter instances prioritize suppression of sporadic transmission following campaigns. It is hoped that our research will help to advocate for small CATI stockpiles in highly prone countries. It is only then that a truly reactive CATI strategy focused on early control can be attempted and the findings modelled here, better realized.

Omission of long-term protection using CATI and mass campaigns limits the longer-term needs for cholera control

CATI remains reactive to outbreaks and small-scale, in that it will greatly benefit a very small proportion of persons who are at risk of infection, in a shortened time period. Although this has not yet been attempted, modelling and empirical evaluation of long-term protection (i.e., seroprevalence) offered by CATI plus a mass campaign would be useful. Where more resources could be made available, CATI could rapidly reduce transmission and when followed by mass campaigns, could offer longer protection to the surrounding population. In this way, it would become a more 'surgical' intervention for early response. This thesis did not explore strategies which attempted longer term protection. Combined strategies could be explored in future modelling and empirical studies.

Inadequate consideration of community engagement and uptake and effects of weakened public health systems in cholera-affected countries

As a community-targeted method, I placed less emphasis on reviewing and modelling community engagement and uptake of the interventions delivered through CATI which can facilitate its implementation and any sustained effect.[47] From observations of the prospective study, I know that communities need to be consulted about the strategy, ring and household selection, antibiotics and vaccination, and how to sustain interventions to optimize their impact. CHWs are central to simple but sustained interventions including the active surveillance of new cases, referral for care, hygiene and health promotion, and running oral rehydration points.[20,48,49] I previously reviewed factors which improved community-based surveillance programs in crisis settings which are relevant to CATI, including supervision of large CHW networks, verification of the signals of new cases that they produce, and integration of their activities into the investigation and response infrastructure.[18] Promisingly, the preliminary results from the DRC study highlight good uptake by households of all interventions. For the Ebola ring vaccination strategy for example, the ability to identify all close contacts of cases has led to stigmatization of those most at-risk, and the distribution of vaccine to selected persons has exacerbated issues of equity.[50] Thus, impressions of equity from households outside of the rings that do not receive interventions, and impressions of stigma from households inside the rings that are the target of cholera control are of high importance. Process evaluation of CATI responses, including qualitative research on community acceptance, would be useful.

Bedson et al reviewed the integration of social and behavioural responses of communities into disease modelling to improve accuracy of predictions, especially for epidemic prone diseases like Ebola, cholera, and measles where interventions like isolation can be restrictive and bring stigma to communities.[51] They found that individual models can embody differences in perspectives and behaviours related to trust and fear of the disease. CATI among sub-populations can therefore incorporate individual, community, and institutional behaviour across levels, over time and space, which can be reflected in contact patterns. While this approach is attractive, it would need to be simplified and tractable, and informed by valid social science data.

In a perverse manner, the control of cholera is severely constrained in the settings where the very disease occurs because of weakened public health systems (i.e., in humanitarian crises,

post-conflict settings, and slums). This is seen in cholera-endemic hotspots in Eastern DRC and Haiti as well as countries affected by recent crises which have led to rapid upheaval, such as Lebanon. Therefore, we can expect that complex interventions like CATI are difficult to implement with adherence to standards without a strong strategy and practical support from multiple sectors and cholera actors (governmental, non-governmental, and civil society), or alternatively a single NGO driving the strategy. This limits our modelling findings, which assume a single actor with high capacity, such as MSF, consistently carries out the intervention.

Lack of modelling detail on household WASH interventions, vaccination uptake, and occurrence of antimicrobial resistance

Lantagne and Yates note several barriers to use of Aquatabs and chlorination across settings including taste preferences which may be improved by better training and previous exposure to these interventions.[52] On the other hand, household WASH programs have showed a critical decrease in intra-household transmission, which was impossible to model here with the $100m^2$ scale used.[8,9] Household-structure models of cholera transmission and CATI's impact would shed light on the potential containment of fine-scale transmission within household. Perceptions (e.g., fear of side-effects, distrust, etc.) can mediate uptake of vaccination.[53] Given the widespread availability and use of antibiotics from private pharmacies, existing antimicrobial resistance will determine the effectiveness of doxycycline or azithromycin for chemoprophylaxis. *V. cholerae's* antibiotic resistance patterns change frequently and resistance to ciprofloxacin, cotrimoxazole, and ampicillin in recent epidemics are of particular concern.[54] While macrolide resistance is a major concern for large-scale mass azithromycin campaigns against child mortality, the small volumes distributed for CATI may carry less risk of resistance.[55]

Limited capture of unobservable phenomena (surveillance of mild and moderate cases, prior immunity/seroprevalence, asymptomatic proportion and transmission)

In a landscape of increased and variable use of the vaccine, it was difficult to incorporate realistic estimates of immunity from vaccination (or prior infection) into the various models that I used. Few serosurveys exist, and little is known about population-level coverage.[56] Similarly, little is known about mild and moderate cases that do not seek care, but may be transmissible in the community. This is a limitation for the spatiotemporal analysis in terms of non-observable cases and their transmission. However, if care-seeking cases represent a random sample of all cases, we feel that we account for population-level transmission in the clustering estimates. Finally,

models were simplified to assume that asymptomatically-infected persons do not transmit. This is another quantity that is difficult to quantify for modelling purposes. An improved understanding of the effects of asymptomatic infection on propagation of outbreaks and acquired immunity would be useful for modelling and planning interventions.

6.5. CONCLUSIONS AND RECOMMENDATIONS

This thesis has evidenced four main findings:

1. Inclusion of harmonised CATI strategies driven by WASH, antibiotics, and particularly vaccination with defined 100-600m radii in reactive responses to cholera outbreaks shows potential impact and should feature in cholera preparedness and response planning.

2. The effectiveness of CATI is critically dependent on the early detection of suspected cases and clusters, narrowed down to RDT-positive alerts. If CATI is to be implemented, I recommend increasing the capacity for early warning and event-based surveillance for cholera at the local level. Outbreak metrics can be used to evaluate this capacity with a perspective towards continual improvement of mechanisms for detection, investigation, confirmation, and early response.

3. The Global OCV Stockpile and Gavi should consider the value of a policy for proactive requests for small OCV stocks in-country to prepare for CATI. No such policy currently exists, and there is no other way to procure vaccine dedicated to CATI.

4. When CATI is deployed, operational data on implementation delays, coverage, and uptake of interventions should be collected for after action review, and to inform future pragmatic modelling studies of CATI strategies.

6.6. AGENDA FOR FUTURE RESEARCH

There are several avenues for future research:

Sensitivity analyses incorporating asymptomatic transmission and household transmission could be used to evaluate the robustness of the impacts of the CATI model.

- **Improved understanding of the role of asymptomatic infection in transmission:** Cholera modelling would benefit from robust evidence on asymptomatic (a) incidence, (b) shedding and infectiousness, (c) roles in the propagation of outbreaks in the short-term, and (c) roles in population acquired immunity in the longer-term.
- **Incorporating household transmission and household impacts of CATI:** Incorporation of household structures into individual-based or household models may highlight an advantage of rapidly-acting WASH and antibiotic interventions, especially when incorporating increased infectiousness of cases in the first 2 days of infection among household members.

Alternative CATI strategies for varied contexts can be first evaluated with modelling and then empirical study during outbreaks:

- In the pre-epidemic, dry season as a less resource-intensive strategy using fewer CATIs.[57,58]
- In population-dense, urban settings, smaller rings can be investigated for operational feasibility and their capacity for containment using a smaller geographic area.
- Modelling and empirical evaluation of combined CATI and mass vaccination could be used to investigate initial containment, with longer-term protection for larger populations. Given the longer time period, this modelling should account for migration due to fishing, trade, and forced migration and effects on propagating outbreaks and achieving long-term protection.

Improved understanding of community acceptance and uptake

- Process evaluation of CATI's implementation which probes the perceived equity of the strategy from the perspective of communities and staff should be undertaken. Where possible, surveys of knowledge, attitudes, and actual practices should be undertaken to better observe the practical uptake of WaSH interventions and hygiene promotion over time.

Cost-effectiveness of CATI versus other strategies: CATI including vaccination should be costed to understand the cost per case averted compared to modalities of mass campaigns.

6.7. CONCLUDING REMARKS

While cholera continues to be a major public health burden, much can be gained from the set of multisector interventions which have a strong evidence base and have long been used. As demonstrated by this thesis, CATI with vaccination holds much promise for rapid containment of cholera outbreaks. Targeted approaches like CATI are attractive because they appear to be more resourceful and faster to implement. However, practical experience with CATI implementation in DRC and Cameroon also indicates that CATI stands a chance to be effective only when localised public health staff and epidemiologists are trained and motivated, given adequate access to resources, and prepared for reactivity, hence reducing the delay and coverage of response and ability to measure the response. [59] Thus, while CATI is predicated on multiple interventions, health workers should be kept as the core of its preparedness.

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41. Ouamba JP, Fouda Mbarga N, Ciglenecki I, et al. Implementation of targeted cholera response activities, Cameroon. *Bulletin of the World Health Organization* 2023; **101**(03): 170-8.

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45. Ratnayake R, Checchi F, Jarvis CI, Edmunds WJ, Finger F. Inference is bliss: Simulation for power estimation for an observational study of a cholera outbreak intervention. *PLoS Negl Trop Dis* 2022; **16**(2): e0010163.

46. 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**(6): e0005652.

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56. Azman AS, Lauer SA, Bhuiyan TR, et al. Vibrio cholerae O1 transmission in Bangladesh: insights from a nationally representative serosurvey. *The Lancet Microbe* 2020; **1**(8): e336-e43.

57. Rebaudet S, Gazin P, Barrais R, et al. The dry season in haiti: a window of opportunity to eliminate cholera. *PLoS currents* 2013; **5**.

58. Camacho A, Bouhenia M, Alyusfi R, et al. Cholera epidemic in Yemen, 2016-18: an analysis of surveillance data. *Lancet Glob Health* 2018; **6**(6): e680-e90.

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7. Appendices

Appendix A: Supplementary materials for Chapter 2

A.1 Search strings

Note: The Cochrane Review Library was searched using the terms: cholera* AND efficacy OR effect* OR protect*

Date of query	Date and language restrictions	Exact Search Query (PubMed)	Exact Search Query (EMBASE)
Antibiotic chemoprophylaxis			
April 24, 2020	January 1, 2000-April 24, 2020; English, French	((antibiotic[Title/Abstract] OR antimicrobial[Title/Abstract] OR chemoprevention[Title/Abstract] OR chemoprophyla*[Title/Abstract]) AND (effect*[Title/Abstract] OR efficacy[Title/Abstract] OR protect*[Title/Abstract])) AND ((((cholera[Title/Abstract] OR vibrio cholerae[Title/Abstract] OR acute watery diarrh*[Title/Abstract]))) AND ("2000/01/01"[Date - Publication] : "3000"[Date - Publication]))	1. cholera*.ti,ab. 2. efficac*.ab,ti. 3. effect*.ab,ti. 4. protect*.ab,ti. 5. antibiotic*.ti,ab. 6. antimicrobial*.ti,ab. 7. chemoprophyla**.ti,ab. 8. chemoprevent*.ti,ab. 9. 5 or 6 or 7 or 8 10. 2 or 3 or 4 11. 1 and 9 and 10 12. limit 11 to (full text and yr="2000 -Current")
Oral cholera vaccination			
April 24, 2020	January 1, 2000-April 24, 2020; English, French	(((vaccin*[Title/Abstract]) AND (effect*[Title/Abstract] OR efficacy[Title/Abstract] OR protect*[Title/Abstract]))) AND ((((cholera[Title/Abstract] OR vibrio cholerae[Title/Abstract] OR acute watery diarrh*[Title/Abstract]))) AND ("2000/01/01"[Date - Publication] : "3000"[Date - Publication]))	13. cholera*.ti,ab. 14. efficac*.ab,ti. 15. effect*.ab,ti. 16. protect*.ab,ti. 17. vaccin*.ab,ti. 18. 1 and 5 19. 2 or 3 or 4 20. 6 and 7 21. limit 8 to (full text and yr="2000 -Current")
WASH and hygiene promotion			
April 24, 2020	January 1, 2000-April 24, 2020; English, French	(((hygiene promot*[Title/Abstract] OR “health education”[Title/Abstract] OR hygiene[Title/Abstract] OR "hygiene promotion"[Title/Abstract] OR “hand hygiene”[Title/Abstract] OR “hand-washing”[Title/Abstract] OR handwashing[Title/Abstract] OR hand disinfection*[Title/Abstract] OR health behavior*[Title/Abstract]) AND (effect*[Title/Abstract] OR efficacy[Title/Abstract] OR protect*[Title/Abstract]))) AND ((((cholera[Title/Abstract] OR vibrio cholerae[Title/Abstract] OR acute watery	1. cholera*.ti,ab. 2. efficac*.ab,ti. 3. effect*.ab,ti. 4. protect*.ab,ti. 5. 2 or 3 or 4 6. hygiene promot*.ti,ab. 7. health educ*.ti,ab. 8. hygiene promoti*.ti,ab. 9. hand hyg*.ti,ab. 10. hand-wash*.ti,ab. 11. hand disinfect*.ti,ab. 12. health behav*.ti,ab. 13. 6 or 7 or 8 or 9 or 10 or 11 or 12

		diarrh*[Title/Abstract]))) AND ("2000/01/01"[Date - Publication] : "3000"[Date - Publication]))	14. 1 and 5 and 13 15. limit 14 to (full text and yr="2000 -Current")
Water treatment			
April 24, 2020	January 1, 2000-April 24, 2020; English, French	(((water purification[Title/Abstract] OR "water treatment"[Title/Abstract] OR chlorin*[Title/Abstract] OR aquatab[Title/Abstract] OR well chlorin*[Title/Abstract] OR bucket chlorin*[Title/Abstract] OR pot chlorin*[Title/Abstract]))) AND ((((cholera[Title/Abstract] OR vibrio cholerae[Title/Abstract] OR acute watery diarrh*[Title/Abstract]))) AND ("2000/01/01"[Date - Publication] : "3000"[Date - Publication]))	1. cholera*.ti,ab. 2. efficac*.ab,ti. 3. effect*.ab,ti. 4. protect*.ab,ti. 5. 2 or 3 or 4 6. water purif*.ti,ab. 7. water treat*.ti,ab. 8. chlorin*.ti,ab. 9. aquatab.ti,ab. 10. 6 or 7 or 8 or 9 11. 1 and 5 and 10 12. limit 11 to (full text and yr="2000 -Current")
Household spraying/disinfection			
April 24, 2020	January 1, 2000-April 24, 2020; English, French *The requirement for effectiveness studies was removed since none were initially found.	(((spray*[Title/Abstract] OR household spray*[Title/Abstract] OR household clean*[Title/Abstract]))) AND ((((cholera[Title/Abstract] OR vibrio cholerae[Title/Abstract] OR acute watery diarrh*[Title/Abstract]))) AND ("2000/01/01"[Date - Publication] : "3000"[Date - Publication]))	1. cholera*.ti,ab. 2. spray*.ti,ab. 3. household spray*.ti,ab. 4. household clean*.ti,ab. 1. 2 or 3 or 4 5. 1 and 5 6. limit 10 to (full text and yr="2000 -Current")
Safe burial			
April 24, 2020	January 1, 2000-April 24, 2020; English, French *The requirement for effectiveness studies was removed since none were initially found. Date limits were removed as no relevant articles were initially found.	(funeral*[Title/Abstract] OR burial*[Title/Abstract] OR corpse*[Title/Abstract]) AND (cholera[Title/Abstract] OR vibrio cholerae[Title/Abstract] OR acute watery diarrh*[Title/Abstract])	2. cholera*.ti,ab. 3. funeral*.ti,ab. 4. burial*.ti,ab. 5. corpse*.ti,ab. 6. 2 or 3 or 4 7. 1 and 5
Case-area targeted response			
April 24, 2020	January 1, 2000-April 24, 2020; English, French	(((targeted response*[Title/Abstract] OR "targeted intervention"[Title/Abstract] OR "comprehensive targeted response"[Title/Abstract] OR "case-area targeted response"[Title/Abstract] OR "case-area targeted intervention"[Title/Abstract] OR "alert and response"[Title/Abstract] OR "rapid response"[Title/Abstract] OR "ring vaccination"[Title/Abstract] OR "community response"[Title/Abstract] OR "community-based	1. cholera*.ti,ab. 2. targeted response.ti,ab. 3. targeted intervention.ti,ab. 4. comprehensive targeted response.ti,ab. 5. case-area targeted response.ti,ab. 6. case-area targeted intervention.ti,ab. 7. "alert and response".ti,ab. 8. "rapid response".ti,ab. 9. "community response".ti,ab. 10. "community-based response".ti,ab.

		response"[Title/Abstract] OR community health workers[Title/Abstract] OR community health work*[Title/Abstract] OR community health volunteer*[Title/Abstract])))) AND ((((cholera[Title/Abstract] OR vibrio cholerae[Title/Abstract] OR acute watery diarrh*[Title/Abstract]))) AND ("2000/01/01"[Date - Publication] : "3000"[Date - Publication]))	11. "community health work".ti,ab. 12. "community health volunteer".ti,ab. 13. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 14. 1 and 13 15. limit 14 to (full text and yr="2000 -Current")
Spatiotemporal transmission			
April 24, 2020	January 1, 2000-April 24, 2020; English, French	(((communicable disease transmission[Title/Abstract] OR disease clustering[Title/Abstract] OR clustering[Title/Abstract] OR cluster*[Title/Abstract] OR cluster analysis[Title/Abstract] OR "spatial clustering"[Title/Abstract] OR spatial analysis[Title/Abstract] OR "spatial transmission"[Title/Abstract] OR spatio-temporal analysis[Title/Abstract] OR "household transmission"[Title/Abstract] OR "community transmission"[Title/Abstract] OR "neighborhood transmission"[Title/Abstract] OR "hotspot"[Title/Abstract]))) AND ((((cholera[Title/Abstract] OR vibrio cholerae[Title/Abstract] OR acute watery diarrh*[Title/Abstract]))) AND ("2000/01/01"[Date - Publication] : "3000"[Date - Publication]))	1. cholera*.ti,ab. 2. "communicable disease transmission".ti,ab. 3. "disease cluster".ti,ab. 4. cluster*.ti,ab. 5. "cluster analysis".ti,ab. 6. "spatial cluster".ti,ab. 7. "spatial analysis".ti,ab. 8. "spatial transmission".ti,ab. 9. "household transmission".ti,ab. 10. "community transmission".ti,ab. 11. "neighborhood transmission".ti,ab. 12. "neighbourhood transmission".ti,ab. 13. "hotspot".ti,ab. 14. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 15. 1 and 14 16. limit 15 to (full text and yr="2000 -Current")

A.2 Websites searched and organizations contacted

Websites searched	Organizations contacted
Global Task Force for Cholera Control Global Health Cluster Global WASH Cluster UNICEF WHO	1. Aix-Marseille University 2. Centers for Disease Control and Prevention (CDC): Emergency Response and Recovery Branch 3. Democratic Republic of Congo, Ministry of Health 4. Epicentre 5. International Centre for Diarrhoeal Disease Research, Bangladesh (icddr, b) 6. International Federation of the Red Cross and Red Crescent (IFRC) 7. International Rescue Committee (IRC) 8. International Vaccine Institute (IVI) 9. Johns Hopkins Bloomberg School of Public Health: DOVE Project 10. Mahidol-Oxford Tropical Medicine Research Unit 11. Massachusetts General Hospital Center for Global Health 12. Médecins Sans Frontières (MSF), OCA, 13. Médecins Sans Frontières (MSF), OCG 14. Norwegian Red Cross

	15. UNICEF, Public Health Emergencies 16. UNICEF, WASH 17. Universidad Miguel Hernandez 18. University of Philippines 19. Swiss Red Cross 20. Tufts University: School of Engineering 21. WHO, Cholera Branch 22. WHO, Eastern Mediterranean Regional Office (EMRO) 23. WHO, Health Emergencies Branch 24. WHO, Western Pacific Regional Office (WPRO) 25. York University: Dahdaleh Institute for Global Health Research

A.3 Data abstraction variables for CATI descriptions and evaluations

Descriptions	**Evaluations**
Setting Catchment population Transmission pattern Epidemic period Size of epidemic (suspected cases) Target (case-area or household-only) Epidemic phase when implemented Delay (weeks) Objective Modality (operational approach) Cases targeted Ring size Timing (intended) Team composition Costs	Volume (suspected cases, and/or contacts) Types of cases targeted Proportion of cholera alerts responded to Mean delay (detection to household visit) Coverage (contacts in catchment area) Impact on epidemic Study design and limitations

A.4 Retrieved articles

Interventions

	Antibiotic chemoprophylaxis	Study design	Search
1.	Grandesso F. The Use of doxycycline to prevent cholera. Journée Scientifique Epicentre/Médecins Sans Frontières - Jeudi 2 juin 2016. Paris, France: Epicentre; 2016. p. 14. (unpublished abstract)	Cohort study	CATI request
2.	Khan WA, Saha D, Rahman A, Salam MA, Bogaerts J, Bennish ML. Comparison of single-dose azithromycin and 12-dose, 3-day erythromycin for childhood cholera: a randomised, double-blind trial. *Lancet* 2002; **360**(9347): 1722-7.	Randomized control trial (treatment)	ACP
3.	Leibovici-Weissman Y, Neuberger A, Bitterman R, Sinclair D, Salam MA, Paul M. Antimicrobial drugs for treating cholera. *Cochrane Database Syst Rev* 2014; (6): CD008625.	Meta-analysis (treatment)	ACP
4.	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**(11): e27060.	Meta-analysis (chemoprophylaxis)	ACP
	Oral cholera vaccination	**Study design**	**Search**
5.	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**(11): e1001901.	Case study (two doses)	Manual (Ref 8)
6.	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**(11): e856-e63.	Case-cohort study (one dose)	OCV
7.	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**(10): 1080-8.	Meta-analysis (one dose, two doses)	OCV
8.	Date KA, Vicari A, Hyde TB, et al. Considerations for oral cholera vaccine use during outbreak after earthquake in Haiti, 2010-2011. *Emerging infectious diseases* 2011; **17**(11): 2105-12.	Case study	Manual (Ref 17)
9.	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**(6): 577-9.	Case-control study (one dose)	OCV
10.	Hsiao A, Desai SN, Mogasale V, Excler JL, Digilio L. Lessons learnt from 12 oral cholera vaccine campaigns in resource-poor settings. *Bull World Health Organ* 2017; **95**(4): 303-12.	Literature review (two doses)	OCV
11.	Iyer AS, Bouhenia M, Rumunu J, et al. Immune Responses to an Oral Cholera Vaccine in Internally Displaced Persons in South Sudan. *Sci Rep* 2016; **6**: 35742.	Cohort study (one-dose, two doses)	OCV
12.	Lopez AL, Deen J, Azman AS, et al. Immunogenicity and Protection From a Single Dose of Internationally Available Killed Oral Cholera Vaccine: A Systematic Review and Metaanalysis. *Clin Infect Dis* 2018; **66**(12): 1960-71.	Meta-analysis (one dose)	OCV
13.	Parker LA, Rumunu J, Jamet C, et al. Adapting to the global shortage of cholera vaccines: targeted single dose cholera vaccine in response to an outbreak in South Sudan. *Lancet Infect Dis* 2017; **17**(4): e123-e7.	Case study (one-dose)	OCV
14.	Poncin M, Zulu G, Voute C, et al. Implementation research: reactive mass vaccination with single-dose oral cholera vaccine, Zambia. *Bull World Health Organ* 2018; **96**(2): 86-93.	Case study	OCV
15.	Qadri F, Ali M, Lynch J, et al. Efficacy of a single-dose regimen of inactivated whole-cell oral cholera vaccine: results from 2 years of follow-up of a randomised trial. *Lancet Infect Dis* 2018; 18(6): 666-74.	Randomized control trial (one dose)	OCV
16.	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**(18): 1723-32.	Randomized control trial (one dose)	OCV
17.	Spiegel P, Ratnayake R, Hellman N, et al. Responding to epidemics in large-scale humanitarian crises: a case study of the cholera response in Yemen, 2016–2018. *BMJ Global Health* 2019; **4**(4): e001709.	Case study	Trans
	Water, sanitation, and hygiene (WASH)	**Study design**	**Search**
	WASH reviews		
18.	Fewtrell L, Kaufmann RB, Kay D, Enanoria W, Haller L, Colford JM, Jr. Water, sanitation, and hygiene interventions to reduce diarrhoea in less developed countries: a systematic review and meta-analysis. *Lancet Infect Dis* 2005; **5**(1): 42-52.	Meta-analysis (diarrhea)	Manual (Ref 40)

19.	Taylor DL, Kahawita TM, Cairncross S, Ensink JH. The Impact of Water, Sanitation and Hygiene Interventions to Control Cholera: A Systematic Review. *PLoS One* 2015; **10**(8): e0135676	Systematic review (WASH interventions)	WT
20.	Wolfe M, Kaur M, Yates T, Woodin M, Lantagne D. A Systematic Review and Meta-Analysis of the Association between Water, Sanitation, and Hygiene Exposures and Cholera in Case-Control Studies. *Am J Trop Med Hyg* 2018; **99**(2): 534-45.	Meta-analysis (case-control studies)	Hyg Pr
21.	Yates T, Vujcic JA, Joseph ML, Gallandat K, Lantagne D. Water, sanitation, and hygiene interventions in outbreak response: a synthesis of evidence. *Waterlines* 2018; **37**(1): 5-30.	Systematic review (WASH interventions)	Manual (Ref 19)
Water treatment (also includes WASH reviews, above)			
22.	Lantagne D, Yates T. Household Water Treatment and Cholera Control. *J Infect Dis* 2018; **218**(suppl_3): S147-S53.	Systematic review (household treatment)	WT
23.	Roberts L, Chartier Y, Chartier O, Malenga G, Toole M, Rodka H. Keeping clean water clean in a Malawi refugee camp: arandomized intervention trial. *Bull World Health Organ* 2001; **79**(4): 280-7.	Randomized control trial (safe storage)	WT
Household spraying and hygiene kits (also includes WASH reviews, above)			
24.	Gallandat K, String G, Lantagne D. Effectiveness evaluation of household spraying in cholera outbreaks. 9th Emergency Environmental Health Forum: 18-19 June 2019. Geneva, Switzerland; 2019. (unpublished abstract)	Exploratory study	CATI request
25.	Gartley M, Valeh P, de Lange R, et al. Uptake of household disinfection kits as an additional measure in response to a cholera outbreak in urban areas of Haiti. *J Water Health* 2013; **11**(4): 623-8.	Program evaluation	WT
Safe burial			
26.	Gunnlaugsson G, Einarsdottir J, Angulo FJ, Mentambanar SA, Passa A, Tauxe RV. Funerals during the 1994 cholera epidemic in Guinea-Bissau, West Africa: the need for disinfection of bodies of persons dying of cholera. *Epidemiol Infect* 1998; **120**(1): 7-15.	Observational study	Safe burial
Hygiene promotion (also includes WASH reviews, above)			
27.	Childs L, Francois J, Choudhury A, et al. Evaluation of Knowledge and Practices Regarding Cholera, Water Treatment, Hygiene, and Sanitation Before and After an Oral Cholera Vaccination Campaign-Haiti, 2013-2014. *Am J Trop Med Hyg* 2016; **95**(6): 1305-13.	Cross-sectional surveys	WT
28.	Lilje J, Kessely H, Mosler HJ. Factors determining water treatment behavior for the prevention of cholera in Chad. *Am J Trop Med Hyg* 2015; **93**(1): 57-65.	Cross-sectional surveys	WT

Spatiotemporal transmission

Spatiotemporal transmission		**Study design**	**Search**
29.	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**(9): e1002120.	Epidemiological model	Trans
30.	Azman AS, Luquero FJ, Salje H, et al. Micro-Hotspots of Risk in Urban Cholera Epidemics. *J Infect Dis* 2018; **218**(7): 1164-8.	Epidemiological model	Manual (Ref 40)
31.	Debes AK, Ali M, Azman AS, Yunus M, Sack DA. Cholera cases cluster in time and space in Matlab, Bangladesh: implications for targeted preventive interventions. *Int J Epidemiol* 2016; **45**(6): 2134-9.	Epidemiological model	Trans
Spatial-only transmission		**Study design**	
32.	Ali M, Kim DR, Kanungo S, et al. Use of oral cholera vaccine as a vaccine probe to define the geographical dimensions of person-to-person transmission of cholera. *Int J Infect Dis* 2018; **66**: 90-5.	Epidemiological model	OCV
33.	Ali M, Sur D, You YA, et al. Herd protection by a bivalent killed whole-cell oral cholera vaccine in the slums of Kolkata, India. *Clin Infect Dis* 2013; **56**(8): 1123-31.	Epidemiological model	Trans
34.	Bi Q, Azman AS, Satter SM, et al. Micro-scale Spatial Clustering of Cholera Risk Factors in Urban Bangladesh. *PLoS Negl Trop Dis* 2016; **10**(2): e0004400.	Epidemiological model	Trans

Household-transmission		Study design	
35.	Richterman A, Sainvilien DR, Eberly L, Ivers LC. Individual and Household Risk Factors for Symptomatic Cholera Infection: A Systematic Review and Meta-analysis. The Journal of infectious diseases 2018; 218: S154-S64.	Meta-analysis	WT
36.	Sugimoto JD, Koepke AA, Kenah EE, et al. Household Transmission of Vibrio cholerae in Bangladesh. *PLoS Negl Trop Dis* 2014; **8**(11): e3314.	Cohort study	Trans
37.	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**(4): 738-42.	Cohort study	Manual (Ref 36)
38.	Weil AA, Khan AI, Chowdhury F, et al. Clinical outcomes in household contacts of patients with cholera in Bangladesh. *Clin Infect Dis* 2009; **49**(10): 1473-9.	Cohort study	Manual (Ref 40)

Case-area targeted intervention (CATI)

CATI		Study design	Search
39.	Bompangue D, Moore S, Taty N, Impouma, Sudre B, Manda R, Balde T, Mboussou F, Vandevelde T. Description of the targeted water supply and hygiene response strategy implemented during the cholera outbreak of 2017–2018 in Kinshasa, DRC. *BMC Med* 2020; 20(226): 10.1186/s12879-020-4916-0	Observational study	WT
40.	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**(2): e1002509.	Mathematical model	OCV
41.	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**(2): 233-41. (see associated studies below)	Randomized control trial (individual)	WT
42.	George CM, Biswas S, Jung D, et al. Psychosocial Factors Mediating the Effect of the CHoBI7 Intervention on Handwashing With Soap: A Randomized Controlled Trial. *Health Educ Behav* 2017; **44**(4): 613-25.		Hyg Pr
43.	George CM, Jung DS, Saif-Ur-Rahman KM, et al. Sustained Uptake of a Hospital-Based Handwashing with Soap and Water Treatment Intervention (Cholera-Hospital-Based Intervention for 7 Days [CHoBI7]): A Randomized Controlled Trial. *Am J Trop Med Hyg* 2016; **94**(2): 428-36.		WT
44.	Burrowes V, Perin J, Monira S, et al. Risk Factors for Household Transmission of Vibrio cholerae in Dhaka, Bangladesh (CHoBI7 Trial). *Am J Trop Med Hyg* 2017; **96**(6): 1382-7.		WT
45.	Guevart E, Noeske J, Solle J, Mouangue A, Bikoti JM. [Large-scale selective antibiotic prophylaxis during the 2004 cholera outbreak in Douala (Cameroon)]. *Sante* 2007; **17**(2): 63-8. (see associated study below)	Observational study (routine data)	Manual (Ref 40)
46.	Noeske J, Guevart E, Kuaban C, et al. Routine use of antimicrobial drugs during the 2004 cholera epidemic in Douala, Cameroon. *East Afr Med J* 2006; **83**(11): 596-601.		Manual (Ref 45)
47.	Michel E, Gaudart J, Beaulieu S, et al. Estimating effectiveness of case-area targeted response interventions against cholera in Haiti. *Elife* 2019; **8**. (see associated study below)	Quasi-experimental evaluation	CATI
48.	Saif-Ur-Rahman KM, Parvin T, Bhuyian SI, et al. Promotion of Cholera Awareness Among Households of Cholera Patients: A Randomized Controlled Trial of the Cholera-Hospital-Based-Intervention-for-7 Days (CHoBI7) Intervention. *Am J Trop Med Hyg* 2016; **95**(6): 1292-8.		Hyg Pr
49.	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**(6): e0005652.	Program evaluation (cross-sectional survey)	OCV
50.	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.	Program evaluation (routine data)	CATI request
51.	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**(4): e0007263.		CATI
52.	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**(5): 1088-97.	Program evaluation (cross-sectional survey)	CATI
53.	Santa-Olalla P, Gayer M, Magloire R, et al. Implementation of an alert and response system in Haiti during the early stage of the response to the cholera epidemic. *Am J Trop Med Hyg* 2013; **89**(4): 688-97.	Program description	CATI

A.5 Risk of Bias Assessment

Author	Year	Design	Domain	Selection bias and confounding	Spillover and contamination	Incomplete outcome	Selective reporting	Other biases	Overall	Notes
Bompangue et al	2020	NE	CATI (eval)	High	Low	Low	Low	High	High	Based only on routinely collected data with no bias assessment
Burrowes et al	2017	E	CATI (eval)	Low	Low	Low	Low	Low	Low	Bias unlikely due to study design
George et al	2017	E	CATI (eval)	Low	Low	Low	Low	Low	Low	Bias unlikely due to study design
George, Jung et al	2016b	E	CATI (eval)	Low	Low	Low	Low	Low	Low	Despite following up intervention and control groups later, the groups remained similar.
George, Monira et al	2016a	E	CATI (eval)	Low	Low	Low	Low	Low	Low	Bias unlikely due to study design
Guevart et al	2007	NE	CATI (eval)	High	High	Unclear	Unclear	High	High	Based only on routinely collected data with no bias assessment
Michel et al	2019	QE	CATI (eval)	Low	High	Low	Low	High	Medium	Unmeasured confounders due to design; inconsistent exposure to ACP
Noeske et al	2006	NE	CATI (eval)	High	High	Unclear	Unclear	High	High	Based only on routinely collected data with no bias assessment
Ramos et al	2019	NE	CATI (eval)	High	High	Unclear	Unclear	High	High	Based only on routinely collected data with no bias assessment
Rebaudet et al	2018	QE	CATI (eval)	Low	High	Low	Low	High	Medium	Unmeasured confounders due to design; inconsistent exposure to ACP
Roskosky et al	2019	NE	CATI (eval)	High	High	Low	Low	Low	Medium	Weak coverage evaluation due to gap between intervention and survey
Saif-Ur-Rahman et al	2016	E	CATI (eval)	Low	Low	Low	Low	Low	Low	Bias unlikely due to study design
Grandesso	2016	NE	I: ACP	High	High	Unclear	Unclear	Unclear	Unclear	Unclear, as source was an abstract with limited information
Khan et al	2002	E	I: ACP	Low	Low	Low	Low	Low	Low	Bias unlikely due to study design
Childs et al	2012	E	I: HP	Low	Low	Low	Low	Low	Low	Bias unlikely due to study design
Gallandat et al	2019	NE	I: HP	High	Low	High	Unclear	High	High	Source is abstract with limited information; small sample size
Gartley et al	2013	NE	I: HP	High	High	Unclear	High	High	High	Non-systematic sampling method
Gunnlaugsson et al	1998	NE	I: HP	High	High	Unclear	Unclear	High	High	Based only on routinely collected surveillance data with no bias assessment
Lilje et al	2015	NE	I: HP	High	Low	Low	Low	High	Medium	Desirability bias since asking about self-reported behaviours
Azman et al	2016	NE	I: OCV	Low	Medium	Low	Low	Low	Medium	Potential bias related to ascertainment of vaccination through self-report
Ferreras et al	2018	NE	I: OCV	Low	Medium	Low	Low	Low	Medium	Potential bias related to ascertainment of vaccination through self-report
Iyer et al	2016	NE	I: OCV	High	Low	Low	Low	High	Medium	Non-systematic sampling method
Qadri et al	2016	E	I: OCV	Low	Low	Low	Low	Low	Low	Bias unlikely due to study design
Qadri et al	2018	E	I: OCV	Low	Low	Low	Low	Low	Low	Bias unlikely due to study design
Roberts et al	2001	E	I: Water	Low	Low	Unclear	Low	High	Medium	Those lost to follow-up were significantly different.

E, experimental; QE, quasi-experimental; NE, non-experimental; ACP, antibiotic chemoprophylaxis; OCV, oral cholera vaccination; HP, hygiene promotion; CATI, case-area targeted intervention. Excluded Parker et al, 2017b and Santa-Ollala et al, 2013 because of the lack of evaluative study design.

A.6 Estimates of the effectiveness of individual interventions against infection and/or development of symptoms (Table S1)

Intervention	References (cholera-specific)	References (all-cause diarrhea)	Relative risk reduction [1-RR, 95% CI]	Days to protection	Duration of protection (days)
Antibiotic chemoprophylaxis (for reduction of symptoms among infected persons)	Finger, 2017[1] based on: Lewnard, 2016[2] (meta-analysis) Echevarria, 1995[3] (ciprofloxacin) Reveiz, 2011[4] (multiple drugs)*	-	0·96 [0·70, 0·999]*	0	2·74 [95% CI 2·40, 3·07] [5] (mean reduction in days of shedding)
Antibiotic chemoprophylaxis (for protection against infection among uninfected persons)	Reveiz, 2011[4] (multiple drugs)* Grandesso, 2016[6] (doxycycline)	-	0·66 [0·34, 0·82]* 0·68 [0·29, 0·87]*	0	2[7] (azithromycin) 1[8,9] (doxycycline)
OCV (1-dose, <12m) OCV (1-dose, 2m, endemic) OCV (1-dose, 2m, naïve)	Bi, 2017 [10] (meta-analysis) Azman, 2015 (case-cohort, 2m) [11] Ferreras, 2019 (case-control, 2m) [12]	-	0·69 [0·35, 0·85]* 0·87 [0·70, 1.0]‡ 0·89 [0·43, 0·98]*	2-12[11]	≥365[10]
Point of use water treatment	Lantagne and Yates, 2018[13] (systematic review) (no RR reported)	Fewtrell, 2005[14] (meta-analysis)	0·26 [0·15, 0·35]*	0	▪ As long as sustained ▪ Limited by compliance
Safe water storage	Lantagne and Yates, 2018[13] Taylor, 2015[15] (systematic review) (no RR reported)	Roberts, 2001 (RCT) [16]	0·21 [-0·03, 0·38]*	0	▪ As long as sustained ▪ Limited by compliance
Water treatment of local collection sources	Taylor, 2015[15] (no RR reported)	Fewtrell, 2005[14]	0·11 [-0·90, 0·58]*	0	▪ As long as sustained ▪ Limited by compliance
Hygiene interventions focusing on handwashing	Taylor, 2015[15] NR (no RR reported)	Fewtrell, 2005[14]	0·44 [0·07—0·67]	0	▪ As long as sustained ▪ Limited by compliance

Shaded cells represent studies that were used to derive the RR estimates. (*) direct effect; (‡) indirect effect; multiple drugs = tetracycline, doxycycline, ciprofloxacin, sulfadoxine; OCV=oral cholera vaccination; RR=relative risk.

A.7 Spatiotemporal studies of cholera infection risk. (Table S2)

Setting	Epidemic year	Design	Distance and time increments (range)	Spatial window limits (m)	Time limit (d)	RR [95% CI]
Spatiotemporal models						
Matlab, Bangladesh[17]	1991-2000	Epi. model	50 m (0-500 m) 3 d (0-30 d)	≤ 50 m ≤ 150 m	1-3 d 4-6 d ≤ 23 d	35·74 [22·92–55·72]; Sig. RR ≤450 m (RR 1·71 [1·22-2·40]) 28·20 [16·55-48·02]; Sig. RR ≤400 m (RR 1·46 [1·03-2·06]) 1·81 [1·30—2·51]
Kolkata, India[18]	2006-2011	Epi. model using RCT data	10 m (0-55 m) 7 d (0-42 d)	≤10 m	≤ 7 d ≤ 14 d	11·44 [6·89—19]; Sig. RR ≤50 m (RR 2·52 [1·69-3·78]) 8·84 [2·09—37·36]
N'Djamena, Chad[19]	2011	Epi. model	10 m (0-500 m) 1 d (0-30 d)	≤ 40 m ≤ 40 m 75-125 m 75-125 m	1 d 5 d 1 d 5 d	55·4 [42·3–72·4]; Sig. RR ≤340 m 32·4 [25·3—41] 5·9 [3·8–8·7] 3·9 [2·7—5·4]
Kalemie, DRC[19]	2013-2014	Epi. model	10 m (0-500 m) 1 d (0-30 d)	≤ 40 m ≤ 40 m 75-125 m 75-125 m	1 d 5 d 1 d 5 d	189·7 [139·7—261·9]; Sig. RR ≤80 m 121·1 [89·7—164·8] 1·9 [0·7–3·6] 2·0 [1·0—3·2]
Spatial models						
Kolkata, India[20]	2006-2009	Epi. model using RCT data	50 m (0-500 m)	≤ 150 m	-	-
Dhaka, Bangladesh[21]	2013	Epi. model	N/A (0-780 m)	≤ 400 m	-	-
Matlab, Bangladesh[20]	1985-1986	Epi. model using RCT data	100 m (0-700 m)	≤ 500 m	-	-

*Epi. model = regression model comparing incidence of cases among a cohort of contacts of cases, and controls. Sig. RR = RR and 95% confidence intervals are greater than 1.

A.8 References

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Appendix B: Supplementary materials for Chapter 3

B.1 Countries investigated

Fragile and conflict-affected states[1]	Refugee-hosting country and/or borders one or more fragile state[b]
Afghanistan	Benin
Angola	Ethiopia
Burundi	Kenya
Cambodia	Niger
Cameroon	Nigeria
Central African Republic	Tanzania
Chad	Uganda
Congo, Dem. Rep.	Zambia
Congo, Rep.	
Côte d'Ivoire	
Djibouti	
Eritrea	
Gambia, The	
Guinea	
Guinea-Bissau	
Haiti	
Iraq[a]	
Lao, PDR	
Liberia	
Madagascar	
Mali	
Mozambique	
Myanmar[a]	
Nepal	
Papua New Guinea	
Sierra Leone	
Somalia	
South Sudan	
Sudan	
Syrian Arab Republic[a]	
Tajikistan	
Timor-Leste	
Togo	
Yemen, Rep.	
Zimbabwe	

[a]These fragile states[1] did not appear on the list of the Global Task Force for Cholera Control list of cholera-affected countries[2], but were included as they are known to have had cholera outbreaks from 2008-2019.

[b]These countries did not meet the criteria set for fragile states (appearing ≥2 times during 2008-2019 on the World Bank's Harmonized List of Fragile Situations).[1] However, these countries were included as they are considered cholera-affected using the Global Task Force for Cholera Control list of cholera-affected countries[2] and are either (a) a refugee-hosting country and/or (b) are bordering a fragile or conflict-affected state.

B.2 Outbreaks by country, date of onset, delays (detection, investigation, response), signal, source, and description of investigation and response

ID	Country, area	Date onset (DOS)	DOS to detection (days)	DOS to investigation (days)	DOS to response (days)	Signal	Source (system)	Investigation and response
1	**Afghanistan**, Nawa district, Ghazni province [1, 2]	Aug 2010	6	6	6	Cluster of 60 suspect cases in a remote and insecure district	Formal alert (DEWS)	Through DEWS, an alert, investigation, and response was linked on the same day that the alert was issued, involving distribution of medical supplies and training of NGO workers with access to the site in investigation and control. The outbreak was reported as contained by Sept 2010.
2	**Afghanistan**, Giro district, Ghazni province [3, 4]	Apr 2011	21	21	--	Multiple clusters in a remote and insecure district	Formal alert (DEWS)	Through DEWS, surveillance officers investigated rumours of multiple clusters and recorded 255 cases of AWD with dehydration. In parallel, they carried out a rapid response. The first case was traced back two weeks before the outbreak was detected. The outbreak was reported as contained by Jul 2011.
3	**Angola**, Soyo City, Zaire Province [5-7]	Dec 2016	13	--	32	Multiple clusters in two towns in provinces bordering DRC	NR	The two clusters appeared close in time, and were judged to be linked to a larger outbreak in Kongo, Central Province, DRC. Linked transmission in Luanda was identified in January 2017.
4	**Angola**, Tchizo neighborhood, Cabinda Province [5, 7, 8]	Dec 2016	5	--	17	Multiple clusters in two towns in provinces bordering DRC	NR	
5	**Angola**, Uige Town, Uige Province [5, 9, 10]	Dec 2017	5	--	10	Two suspect cases presenting to a health facility in urban area	NR	Two cases with travel history to Kimpangu, DRC presented close in time to a health facility. The outbreak was linked to the ongoing outbreak in DRC.
6	**Benin**, Littoral Department (outskirts of Cotonou) [11]	Jul 2008	5	--	8	Single suspect case presented to a health facility in an urban area	NR	The same health facility opened a CTC shortly after.
7	**Benin**, So-Tchanhoue village, So Ava Commune, Atlantique Department [12-14]	Feb 2016	5	8	--	Single suspect case presented to a health facility in a rural area	Formal alert (routine surveillance with immediate notification)	The health facility alerted public health officials immediately, without waiting for the weekly epidemiological report. The response was driven by community health program and occurred rapidly.
8	**Benin**, Dekanme, So Ava commune, Atlantique Department [14-16]	Aug 2016	13	13	18	Single suspect death presented at	Formal alert (routine surveillance	Routine surveillance was the source of the alert of a suspected cholera death, with one week's delay. Response was

						a health facility in a rural area	through weekly report)	enabled by the pre-positioning of cholera kits in affected districts and a locally-driven strategy with community health workers.
9	**Burundi**, Rumonge, Bururi province [17, 18]	Jul 2011	7	--	20	Multiple suspect cases presented to a health facility in a town on Lake Tanganika	NR	The outbreak spread from Rumonge town to multiple provinces including Bujumbura Rural. CTCs were setup in response.
10	**Burundi**, Bujumbura town and Bujumbura Rural [19, 20]	Sept 2012	5	--	9	Multiple suspect cases were reported in an urban area and the wider province.	NR	A community-focused response was setup.
11	**Burundi**, District Sanitaire Nyanza-Lac, Makemba Province [21, 22]	Aug 2017	5	--	5	Single suspect case presented to a health facility in a rural area	Formal alert (routine surveillance with immediate notification)	The case was immediately notified and transferred to a hospital for isolation and diagnostics. A CTC and community-based activities were setup.
12	**Burundi**, Rumonge, Bururi Province [23, 24]	Dec 2018	0	3	6	Multiple suspect cases presented to a health facility in a single health district on Lake Tanganika.	NR	Three suspected cases presented to a health facility in a single health district within two days. A CTC was opened immediately.
13	**Cameroon**, Mora town, Mora and Maroua Districts [24]	Apr 2016	5	5	5	Single cluster of 69 suspect cases reported after several cases presented to a hospital	Formal alert (routine surveillance with immediate notification)	This was a false alert of a cholera signal (likely food poisoning) linked to a rapid investigation and response. A rumour of a large cluster was reported through the surveillance system. RDT tests that were positive were culture negative. Red Cross volunteers did household disinfection and community activities during the investigation period.
14	**Cameroon**, Boko health district, Littoral Department [25]	May 2016	5	5	--	Multiple suspect cases and one death among under 5 children	Informal alert (rumour form community member)	This was a false alert of a cholera signal (likely rotavirus) linked to a rapid investigation and response. A rumour from a community leader involving suspect cases and a death among children closely in time was reported to public health authorities. On the same day, investigation and response was undertaken.
15	**Cameroon**, Guirviza health area and Doumo health area, Maya Oulo health zone [26]	May 2018	6	6	11	Multiple suspect cases from two rural areas	Formal alert (routine surveillance	Cultures were taken on the same day, indicating an immediate alert to public health authorities. The investigation determined the cases were linked to

							with immediate notification)	travel to Nigeria, where there was an ongoing outbreak. Response included community activities, chlorination of water points, and training in case management.
16	**Central African Republic**, villages along the Ubangui River, 80 km south of Bangui [27-29]	Sept 2011	13	15	20	Multiple suspect cases (and a death) in villages on the Ubangui River close to the capital	Informal alert (rumour of a death reported from community)	Response required declaration by government and mobilization of international partners. Transmission to Bangui was registered within one month.
17	**Central African Republic**, Mourou-Fleuve village, Ndjoukou subprefecture [30, 31]	Jul 2016	5	5	14	Multiple suspect cases in villages along a river, bordering DRC	Formal alert (community-based surveillance)	Red Cross community volunteers detected and provided an immediate formal alert to the first cases. The outbreak was linked to another outbreak in DRC.
18	**Chad**, District Sanitaire Fianga, Mayo-Kebbi [32]	Jun 2011	5	--	79	Multiple suspect cases in a rural area	NR	11-week delay in response due to poor mobilization of non-governmental support.
19	**Chad**, Marrena village, District Sanitaire Koukou, Sila Region [33-36]	Aug 2017	5	6	6	Two suspect cases (resulting in deaths) among children presented to a health facility	Formal alert (immediate notification and investigation)	Two children presented and died upon admission with further cases from a remote village. Investigation on the same day (immediate formal notification) through the health facility found 50 cases and 13 deaths in Marena. Rapid response occurred the next day.
20	**Chad**, District Sanitaire Koukou, Sila Region [33, 34]	Aug 2017	5	5	11	Multiple suspect cases (and deaths) presented to a health facility in a rural area bordering Sudan	Formal alert (immediate notification and investigation)	Health facility reported multiple suspect cases and two deaths from villages near the border with Sudan. Response within 3 days occurred.
21	**Chad**, Angarana, District Sanitaire Koukou, Sila Region [33]	Aug 2017	5	--	10	NR	NR	NR
22	**Chad**, d'AmTiman, District Sanitaire d'AmTiman, Salamat Region [33]	Sept 2017	5	--	7	NR	NR	NR
23	**Chad**, Youe health district, Mayo Kebbi [37]	Jul 2019	5	--	10	Multiple suspect cases (including 1 death) from 1 neighbourhood presented to a health facility	NR	NR
24	**Congo**, Assemblee camp, Mbanou Island, Talangai Health District [38]	Aug 2016	6	7	7	Multiple suspect cases were notified from a work camp	NR	Six suspected cases from a work camp among persons from DRC were notified. Investigation and response was rapid, and included disinfection of camp and

								health centre, chlorination activities, and community mobilization. By mid-Sept, no further cases were reported.
25	**Congo**, Likouala Department [39]	Mar 2018	5	19	19	Multiple suspect cases from a village presented to a health facility	Informal alert (immediate investigation and review of retrospective data)	Retrospective review of health facility records found 3 cases of AWD managed in previous week. A national rapid response team was deployed two weeks after notification to conduct investigations and a comprehensive response.
26	**Cote d'Ivoire**, Zimbabwe neighborhood, Abidjan [40, 41]	Sept 2014	5	--	6	Multiple suspect cases presented to health facility on an island close to the capital	NR	Eight Ghananian fisherman sought care on an island close to Abidjan.
27	**DRC**, Kinshasa (Camp Luka, Binza Meteo, Limete and Kintambo Health Zones) [42]	Nov 2017	5	--	37	Sudden increase in trend for AWD in urban area	Formal alert (data analysis of case numbers)	Through IDSR, following intensive rains and flooding, a formal alert (data analysis of case numbers) showed an increase from <5 to >100 weekly suspect cases. A logistically-intensive and comprehensive CATI-like strategy was used for response. No further cases reported by late-Dec 2017.
28	**Ethiopia**, Moyale town and surrounding kebeles, Moyale Oromia and Moyale-Somali [43-46]	Nov 2015	1	51	51	Large cluster of AWD cases in urban area	Formal alert (data analysis of case numbers via EWARS)	In an area of displacement between Somalia and Ethiopia, WHO deployed a rapid response team to strengthen the outbreak response almost two months following detection of an AWD outbreak which had grown to 268 cases. A rapid decline in caseload was reported following the rapid response.
29	**Ethiopia**, Degah-ad Kabele, Danbal Woreda, Sitti Zone (near Jijiga city) [47]	Jun 2017	5	6	6	Cluster of suspect cases near an urban area	Informal alert (rumour of suspect cases via EWARS)	Rumour from community of 31 suspect cases in a community. Rapid response team in Jijiga City trained on case management and IPC; supported scale up of surveillance and community WASH measures.
30	**Guinea**, fishing village, Khounyi, Kabak Island, Forecariah [48]	Feb 2012	3	4	--	Cluster of suspect cases in a single fishing village	Formal alert (immediate notification of a cluster)	Cluster of suspect cases in a single village alerted by a CHW carrying out vaccination as part of the sentinel surveillance system.
31	**Guinea-Bissau**, Tombali village, Tombali region [49-51]	Apr 2008	5	--	20	Cluster of suspect cases in a remote fishing village	NR	This outbreak was thought to be contained in Tombali village but linked transmission was detected in Bissau in Jul 2008. There was a notable delay in detection of the outbreak of 2 weeks.

32	**Haiti**, Mirebalais, Artibonite Department [52, 53]	Oct 2010	7	9	9	Sudden increase in trend for AWD and dehydration in urban areas	Formal alert (data analysis of case numbers)	Ministry of Health notified of unusually high peaks of AWD and dehydration cases (>1,000 cases), and some deaths from Centre and Artibonite departments
33	**Iraq**, Al-Auzeir town, Maysan Governorate [54-57]	Aug 2008	12	--	31	Single suspect case (death) among a child in a town, followed by other case reports	Formal alert (data analysis of case numbers through national diarrhoea surveillance)	A child died of suspected cholera. Initial laboratory tests were inconclusive. A delay in laboratory confirmation and notification to the central authority delayed comprehensive outbreak response activities.
34	**Iraq**, Najaf City, Baghdad Governorate [58]	Aug 2015	9	14	15	Sudden increase in trend for AWD in urban area	Formal alert (data analysis of case numbers)	Single suspect case detected at Najaf Hospital but routine analysis of diarrheal cases from district served as alert of increase in diarrheal cases and earlier cases traced back to a week before. Field investigation and a preliminary local response was rapidly conducted.
35	**Kenya,** Kakuma refugee camp, Turkana District [59]	Sept 2009	5	--	18	Sudden increase in trend for AWD in refugee camp	Formal alert (data analysis of case numbers)	Incidence of AWD among camp residents increased sharply in Sept 2009, at same time of first clinical encounters with suspect cases. The context was a larger outbreak in Turkana District since Aug 2009. Large-scale response started in Oct 2009.
36	**Kenya,** Hagadera refugee camp, Dadaab complex, Garissa District [60]	Mar 2019	5	--	7	NR	NR	The delay between reporting of the index case and notification was due to surveillance challenges. A CTC was setup shortly after the first case reports.
37	**Liberia**, Maryland and Grand Kru counties [61, 62]	Nov 2007	7	--	23	Sudden increase in AWD (and deaths) reported, mostly from one hospital in an urban area	NR	Suspect cases detected between early Dec 2007 and Jan 2008. The response (development of an CTU at the hospital) occurred 2 weeks after presentation of the first cases.
38	**Liberia**, Tapitta district, Nimba County [63, 64]	Mar 2017	5	7	7	Single suspect case died en-route to health facility in urban area	Formal alert (immediate notification through IDSR)	The outbreak was detected within 2 days of the first case (a death among an adolescent) presenting to a health facility. A rapid response team was dispatched on the same day. The outbreak was reported as contained within the same week.
39	**Mali,** Wabaria District, Gao region [65]	Jun 2012	5	7	7	Single cluster reported in a rural village	NR	Sudden appearance of 32 suspected cases. Response included implementation of a CTC by ICRC, who was already present, and use of Red Cross volunteers for community mobilization.

40	**Mozambique** (Cyclone Idai), Beira city and districts of Nhamatanda, Dondo, Buzi, Sofola Province [66-68]	Mar 2019	5	--	12	NR	Formal alert (immediate notification using EWARS)	Vigilance and rapid detection of an outbreak following Cyclone Idai, and rapid growth, followed by rapid response involving OCV.
41	**Mozambique** (Cyclone Kenneth), Pemba city and Mecufi district [69]	Apr 2019	5	--	9	Multiple clusters reported in two areas	Formal alert (immediate notification using EWARS)	Vigilance for cholera due to prior experience with Cyclone Idai. The first suspect case observed on 27 April 2019 and outbreak declared after multiple clusters in Pemba city and Mecúfi district. Rapid response within four days of detecting the first case.
42	**Nepal,** Tilathi VDC [70]	Oct 2011	5	6	6	Single cluster (with deaths) in an urban area	Formal alert (immediate notification via early warning function)	District public health authorities notified of a cluster in an urban area. The next day, the outbreak control team investigated and responded.
43	**Nepal,** Kathmandu Valley [71, 72]	Jun 2016	5	--	9	Single suspect case presented to a health facility in an urban area	Formal alert (immediate notification using sentinel surveillance and RDTs)	Sentinel site surveillance of AWD using RDT was used after the earthquake in Nepal. Rapid response team respond to suspect cases.
44	**Nepal,** Gaidataar, Chandranigahpur VDC-3 and 4 [73]	Apr 2017	5	6	6	Sudden increase in trend for AWD in urban area	Formal alert (immediate notification using EWARS)	Via EWARS, increase of AWD detected mid-Apr 2017. On same evening, two suspect cases admitted to hospital. The next day, a rapid response team sent to investigate and control.
45	**Niger**, Bella village, Dosso Health District [74, 75]	Oct 2016	5	11	--	Single cluster (with 9 deaths) in a rural village	Informal alert (rumour of suspect cases and deaths)	A rumour of gastroenteritis cases from one village, including 9 community and health facility deaths. An MoH, WHO, and UNICEF investigation team was sent within a week.
46	**Niger**, Madarounfa, Maradi District [76]	Jun 2018	7	7	--	Single cluster (one death) among one family presenting to a health facility in a rural village	Informal alert (rumour of suspect cases and deaths)	A suspected cluster was notified among a family of cases admitted to a health facility. Investigation found travel history to Nigeria during exposure period.
47	**Nigeria**, Gomani settlement, Kundu ward of Kwali LGA, Federal Capital Territory [77]	Oct 2014	13	13	13	Single cluster presenting to a health facility	Formal alert (immediate notification via early warning function)	Health facility reported to surveillance officer an increase in suspect cases in a single village. The investigation traced back an index case to 2 weeks earlier that the date of detection. The outbreak was reported as contained within a week.
48	**Nigeria**, Muna Garage IDP camp, Jere LGA, Borno State [78-80]	Aug 2017	2	2	9	Single suspect case of AWD in a refugee camp	Formal alert	First case was notified by MSF via phone call to EWARS, triggering an investigation on the same day. The delay

							(immediate notification using EWARS)	in laboratory confirmation (declared negative at local labpratpry and positive by national laboratory weeks later) delayed a comprehensive response.
49	**Nigeria**, Doro Ward, Kukawa LGA, Borno State [81]	Feb 2018	5	13	14	Single cluster in an urban area	NR	NR
50	**Pakistan,** Mingora, Swat Valley [82-84]	Jul 2010	5	--	5	Gradual increase in trend for AWD across flood-affected area	Formal alert (data analysis of case numbers)	One case was confirmed in Mingora, Swat Valley. Suspect cases were detected, and the response assumed cholera. A trend in confirmed cases was identified.
51	**Pakistan,** Amarpura, Rawalpindi [85]	Jul 2017	0	3	--	Single case confirmed among a paediatric patient already admitted in hospital	Formal alert (immediate notification)	Health facility notified of a confirmed case among a pediatric patient already admitted to hospital. Following an investigation, no further cases were reported. Response included chlorination of water tanks in households and community, isolation of cases, and active case finding.
52	**Papua New Guinea,** Nambariwa, Morobe province [86, 87]	Jul 2009	15	22	22	Single cluster in a remote village	Informal alert (rumour from community)	A physician visiting family reported an outbreak of AWD associated with death of his father and 4 persons from two villages. Response included active case-finding, isolation, and improvement of WASH.
53	**Sierra Leone,** Island of Yeliboya, Kambia [48, 88]	Jan 2012	5	8	8	Single cluster of AWD in an island	Formal alert (immediate notification)	Physician notified central public health authorities of increase in AWD trend. Investigation occurred within two days of notification. Confirmation took one month (at laboratory in Burkina Faso).
54	**Somalia,** Luuq and Belet Xawa, Gedo Region [89]	Nov 2008	5	66	--	NR	NR	Outbreak remained undetected over 12 weeks causing relatively high mortality and morbidity. Long time lag between submission of samples and confirmation, and a comprehensive response.
55	**Somalia,** Belet Xaawo (Belet Hawa) [90]	Apr 2016	5	--	14	Single cluster at a health facility in urban area	Formal alert (immediate notification via early warning function)	A district hospital alerted other health facilities to an increase in AWD trend when the hospital admitted the first suspected case. Response included community prevention measures.
56	**Somalia,** Beletweyne district, Hiraan region [91, 92]	Dec 2018	5	5	19	Sudden increase in trend for AWD in urban area	Formal alert (data analysis via EWARS)	Increased trend in AWD was notified via EWARS and confirmed rapidly, Response including opening a CTC and training CHWs on community case management of cholera.
57	**South Sudan,** Yei town [93-96]	Feb 2008	29	34	34	Multiple suspect cases presenting	NR	The response appeared delayed for 3 weeks due to a need for external non-

						to a health facility in a remote and insecure area		governmental support (Medair provided support for the response).
58	**South Sudan,** Juba 3 IDP camp, Gudelle 2 [97-99]	Apr 2014	6	6	22	Single suspect case presenting to a health facility in a camp	Formal alert (immediate notification via EWARS)	A single suspect case was notified by MSF on the day of presentation. Confirmation was achieved in a week, and a comprehensive response followed. OCV had been deployed preventatively in Juba 2 months before.
59	**South Sudan,** 50 villages in seven payams of Juba County [94, 100]	May 2015	8	9	9	Multiple suspect cases presenting to health facility in a camp	Formal alert (immediate notification via EWARS)	Investigation of the initial cases occurred the day following case presentation.
60	**South Sudan**, 11 villages in 6 payams in Juba [94, 101]	Jun 2016	0	15	15	Multiple suspect cases reported from multiple locations	Formal alert (immediate notification via EWARS and RDT testing)	RDT testing used for alerts issued through EWARS. Cases first observed in host community, then among IDPs.
61	**South Sudan,** Tonj East and Tonj North Counties, Warrap State [102]	May 2017	11	12	15	Single cluster in a rural payam	Formal alert (immediate notification via EWARS)	District-level public health authorities notified of a cluster in a rural payam. WHO supported a rapid response
62	**Sudan,** Ganees Shareg area of El Roseires locality, Blue Nile State [103-106]	Aug 2019	5	--	5	Single cluster (including 1 death) at a single hospital in an urban area	Formal alert (immediate notification via early warning function)	El Roseires hospital notified of 5 suspect cases (and a death). The comprehensive response started <2 weeks later.
63	**Syria,** Aleppo Governorate, Eastern Rural [107, 108]	Oct 2015	2	2	--	Single suspect case (leading to death) in a rural and insecure area	Formal alert (immediate notification via EWARN and RDT testing)	Via EWARN, a five year old child with AWD and dehydration was reported after being admitted to hospital (and death). Case was RDT+ but died before stool sample could be taken. Field investigation showed no symptomatic persons among household members. No formal response.
64	**Syria,** Zogra camp, near Jarabulus City, Aleppo [109, 110]	Oct 2017	5	5	--	Single suspect case in a camp in an insecure area	Formal alert (immediate notification via EWARN and RDT testing)	This suspect case was likely a false alert. Via EWARN, alert of a suspected case among an infant of 4 months with AWD. Child was treatment and discharged; further investigation of the case showed that symptoms did not fit the case definition for cholera. No formal investigation in community or response.
65	**Tanzania,** Dar es Salaam (Kinondoni district) [111, 112]	Aug 2015	5	5	8	Single cluster (and death) primarily among one family in an urban area	Formal alert (immediate notification)	Unknown source notified MoH of a suspect case of AWD with severe dehydration. Four family members identified as suspect cases with 1 death.

								Response was targeted to neighbourhood of cases.
66	**Tanzania,** Kigoma on Lake Tanganyika, in the nearby villages of Kagunga and Nyarugusu [113, 114]	May 2015	5	7	9	Single cluster of two suspect cases (leading to death) in a refugee camp	Formal alert (immediate notification)	Two adults died, with symptoms of diarrhea and vomiting. AWD cases were considered suspect cholera, though cultures were initially testing negative for cholera. Active case-finding initiated and UNHCR sent treatment supplies.
67	**Uganda,** psychiatric hospital, Kampala [115]	Oct 2008	2	2	3	Single cluster (and death) in a psychiatric hospital in an urban area	Formal alert (immediate notification)	Cluster of patients in same ward developed AWD and died rapidly. The hospital team suspected cholera and initiated control measures immediately including case management and antibiotic chemoprophylaxis.
68	**Uganda,** Bwere sub-county, Kasese District [116]	Mar 2015	22	84	84	Single suspect case among a child presented to a heath facility	Formal alert (immediate notification with RDT)	The district health officer notified MoH of a RDT-positive suspect case with travel history to DRC. Despite local efforts, the outbreak continued to expand. Two months later, a comprehensive response was organized by the MoH. The investigation found suspect cases traced back to a month before outbreak detection. The outbreak lasted for 6 weeks with 183 suspect cases.
69	**Uganda,** Katwe village, Kasese District [117]	Jun 2015	4	6	6	Single suspect case among a fisherman who presented to a hospital in a fishing village	Formal alert (immediate notification with RDT)	Rapid control was initiated with community hygiene measures, household chlorination and investigation. Outbreak reported contained within one month, with 61 suspect cases.
70	**Uganda,** Kyangwali refugee settlements, Hoima district [118]	Feb 2018	0	--	6	Single cluster (with deaths) among refugees at a reception centre	Informal alert	Cluster of suspect cases (and deaths) alerted from a refugee reception centre in a short time period. Outbreak coordination set up rapidly.
71	**Yemen,** Alshat and Ras Alara districts, Lahj Governorate [119]	Jun 2010	5	--	10	NR	NR	Outbreak started at the end of Jun 2010, with a large number (n=300) of suspect cases including 4 deaths. Comprehensive control measures including case management, we chlorination initiated by the MoH.
72	**Yemen,** Al-Razi hospital, Shokra Hospital, Abyan Governorate [120-122]	Apr 2011	5	60	70	Sudden increase in trend for AWD in urban area	Formal alert (data analysis via routine surveillance)	During an armed conflict, routine surveillance system detected a large increase in diarrheal cases in Abyan governorate. At detection, the outbreak was large (n=343 suspect cases). WHO supported a comprehensive response within 2 months.

73	**Yemen,** Sana'a (Al-Nasr neighbourhood of the Sho'ob district) [123, 124]	Oct 2016	5	6	14	Multiple clusters detected in Sana'a City though presentation to a hospital	Formal alert (immediate notification with RDT)	MoH declared 8 confirmed cases admitted to a hospital in Sana'a, possibly from the same family. A WHO-supported rapid response team investigated and tested the cases. Shortly after, multiple villages in Al-Beyda district report suspect cases including deaths. Confirmation occurs a few days later.
74	**Zambia,** Chipata sub-district, Lusaka, and spreading to Kanyama sub-district around Oct 9, 2017 [125-128]	Oct 2017	8	--	17	Single cluster of two suspect cases presented to a health facility in an urban area	NR	Two patients had presented at an urban clinic with symptoms. Coordination efforts occur shortly after.
75	**Zambia,** Nsumbu, Nsama District, Northern Province [129]	Mar 2019	0	0	0	Multiple clusters (and deaths) from multiple villages in a rural area reported	NR	Index case among a child presented to a health facility and was isolated, but left prematurely. A traditional healer who later saw the child referred the child back to the health facility (died in transit). Multiple cases from the same household and a neighbouring village presented and were isolated. Outbreak was reported as contained.
76	**Zambia,** Mpulungu District, Northern Province [128]	Apr 2019	5	5	--	Single case presented to health facility in urban area.	NR	Index case among a child presented to the health facility with AWD, vomiting, and dehydration and deteriorated. Patient isolated and public health authorities alerted. Culture-positive results returned with delay a month later.
77	**Zimbabwe,** St Mary's and Zengeza sections of Chitungwiza city, Harare Province [130-132]	Aug 2008	3	--	15	NR	NR	MoH and MSF rapidly set up two CTCs in a hospital and in the community. Outbreak was reported as contained, but two months after this outbreak, a second wave of cases was reported across Harare suburbs and eventually in every province in the country.
78	**Zimbabwe,** Harare [133-135]	Sept 2018	4	4	5	Single, large cluster (with deaths) presented to a hospital in an urban area	Formal alert (immediate notification with RDT)	At detection, a large cluster of 25 suspect cases were admitted to hospital. A concurrent typhoid outbreak in Harare stretched response capacity.
79	**Zimbabwe,** Chegutu municipality, Mashonland West Province [136-138]	Jan 2018	13	16	16	Single cluster (with deaths) presented to a health facility in an urban area	Formal alert (immediate notification via early warning function)	A small cluster of 5 suspect cases admitted to hospital, and 3/5 cases died within hours of admission. On the same day, public health authorities were notified of a suspected outbreak and investigated. A case in a woman who died at home after seeking treatment at

		a private clinic was retrospectively identified. Her funeral provided the epidemiological link to the current caseload. A rapid response team was sent to the Chegutu area to carry out a comprehensive response. The outbreak was reported as contained.

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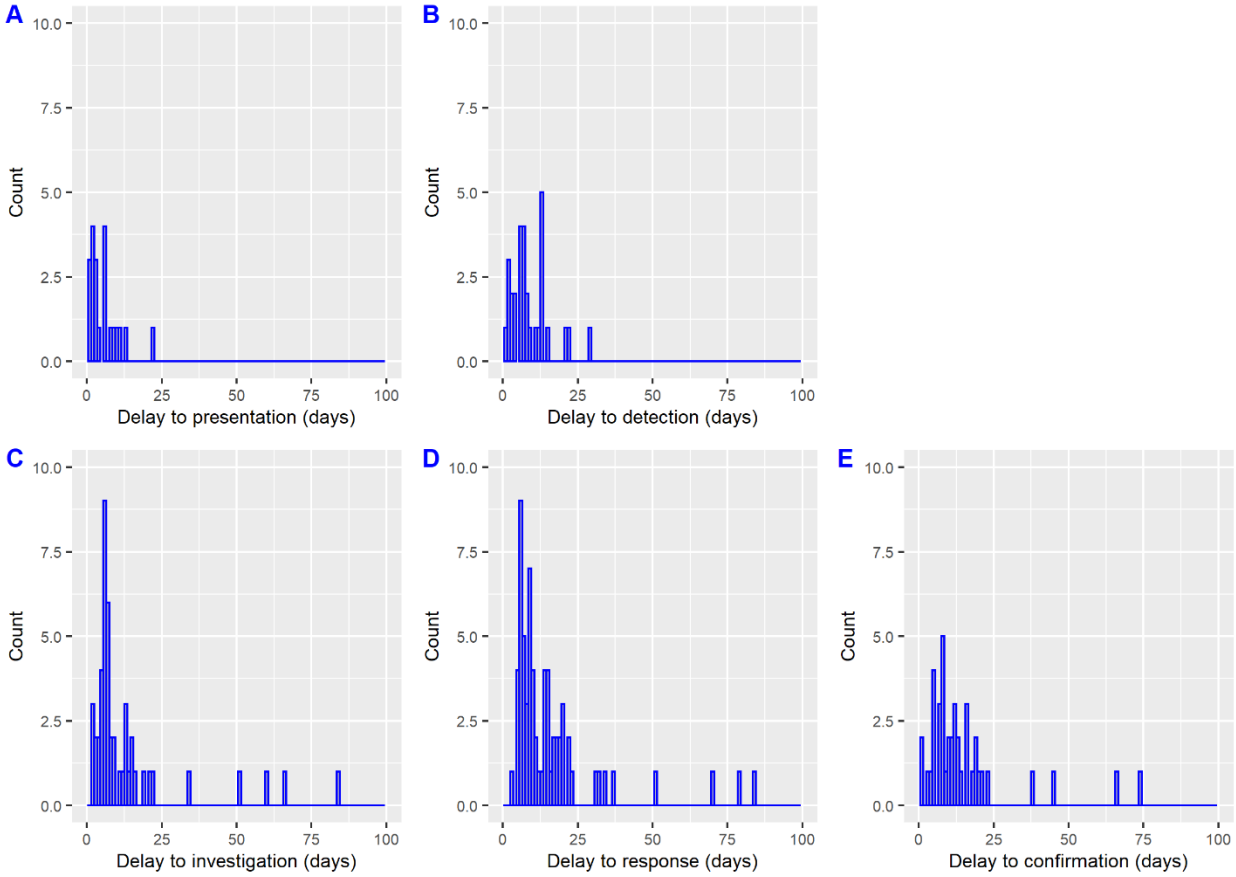
B.3 Histograms of delays from symptom onset to (A) case presentation, (B) outbreak detection, (C) investigation, (D) response, and (E) confirmation



B.4 Overview of alternative models for the main analyses

Main analyses: model selection using Akaike Information Criterion (AIC)

Model	Signal	Year	Region	Context	Crisis	Parameters	AIC
m1	0	1	1	1	1	4	-33.2
m2	0	1	0	1	1	3	-39.0
m3	0	1	0	1	0	2	-41.7
m4*	0	1	0	0	0	1	-45.6

*Model used in the main analysis.

Model parameters (Y= delay from onset of symptoms to response)

Model	N_Y	X	N_X	Est	% change	% LCI	% UCI	SE	*p*, Est	Adj. r^2	F-stat	*p*, F-stat
m4	67	Year	76	-0.05	-5.18	-9.61	-0.52	0.02	0.03	0.06	4.90	0.03
m5	67	Alert	49	-0.50	-40.24	-60.99	-5.67	0.22	0.03	0.08	5.19	0.03

LCI, lower 95% confidence interval, UCI, upper 95% confidence interval, SE, standard error

B.5 Model parameters for additional delay analyses (X=year)

Model parameters for additional delay analyses (X=year)

Model (Y)	N_Y	N_X	Est	% change	% LCI	% UCI	SE	*p*, Est	Adj. r^2	F-stat	*p*, F-stat
Presentation	76	76	-0.02	-1.87	-5.40	1.80	0.02	0.31	0.00	1.05	0.31
Detection	76	76	-0.05	-4.66	-8.46	-0.69	0.02	0.02	0.06	5.43	0.02
Investigation	48	76	-0.10	-9.42	-15.88	-2.47	0.04	0.01	0.12	7.25	0.01
Response	67	76	-0.05	-5.18	-9.61	-0.52	0.02	0.03	0.06	4.90	0.03
Confirmation	41	76	-0.10	-9.57	-16.10	-2.53	0.04	0.01	0.14	7.37	0.01

LCI, lower 95% confidence interval, UCI, upper 95% confidence interval, SE, standard error

B.6. Delays calculated using outbreaks with date of symptom onset of primary case (N=25)

Delay from date of symptom onset	Median delay (IQR) (days) N=25 outbreaks	Median delay (IQR) (days) N=76 outbreaks*
Case presentation	4 (1—6)	5 (5—5)
Outbreak detection	4 (1.5—8)	5 (5—6)
Investigation	6 (3—13.5)	7 (5.8—13.3)
Response	9 (6—15.5)	10 (7—18)
Confirmation	8.5 (3.25—13)	11 (7—16)

* Date of onset of symptoms of the primary case is assumed based on available data.

Appendix C: Supplementary material for Chapter 4

Technical Appendix for *Spatiotemporal modelling of cholera and implications for its control, Uvira, Democratic Republic of the Congo*

Ruwan Ratnayake, Jacqueline Knee, Oliver Cumming, Jaime Mufitini Saidi, Baron Bashige Rumedeka, Flavio Finger, Andrew S. Azman, W. John Edmunds, Francesco Checchi, Karin Gallandat

C.1 Statistical framework for local and global clustering statistics

Methods for the space-time scan statistic (1, 2)

For a given cylinder consisting of a radius centered on an avenue-centroid and height of the temporal window of interest, ***c*** is the observed number of cases inside the cylinder, ***E[c]*** is the expected number of cases for any given cylinder, and ***C*** is the total number of cases in Uvira, with RR given by:

$$RR = \frac{\frac{c}{E[c]}}{\frac{(C - c)}{(C - E[c])}}$$

During the scan, a circular scanning window of varying radii and duration moves over the geographical area, so that each avenue-centroid is at the center of several candidate clusters of differing radii and heights. At each cylinder location, the number of cases inside the cylinder is compared with the expected number, under a null hypothesis of no clustering (i.e., cases are randomly distributed). To find the most likely cluster, candidate clusters are ordered by a log-likelihood ratio (LLR) where the cluster with the largest LLR is the least likely to be due to chance and therefore, the most likely cluster. The significance of each cluster was evaluated using Monte Carlo simulation to compare the original dataset with 999 random replicates produced under the null hypothesis.

Methods for the τ statistic (3-5)

$\hat{\tau}(d_1, d_2)$ as an RR is approximated by dividing the odds that cases within the band are transmission-related $\hat{\theta}(d_1, d_2)$ by the same odds among cases in the general population, regardless of distance $\hat{\theta}(0, \infty)$.

The τ equation is given by: $\hat{\tau}(d_1, d_2) = \frac{\hat{\theta}(d_1, d_2)}{\hat{\theta}(0, \infty)}$

The odds for numerator $\hat{\theta}(d_1, d_2)$ are given by: $\hat{\theta}(d_1, d_2) = \frac{\sum i \sum j * I_1(i,j)}{\sum i \sum j * I_2(i,j)}$

The numerator tallies the number of case-pairs (i-j) within the given distance band that are transmission-related (within 0—4 days) (using indicator variable $I_1(i,j)$=1 for notation). The denominator tallies the number of case-pairs (i-j) within the given distance band that are not transmission-related (occurring after 4 days) (using indicator variable $I_2(i,j)$=1 for notation). The equivalent odds $\hat{\theta}(0,\infty)$ is estimated for the entire population.

C.2 Simulations to compare centroid-geotagged cases with cases with simulated individual household locations

The case data used in this study are geocoded by X/Y coordinates of the centroid of the 216 avenues (or streets) of the case's residence (Appendix Figure 1 displays the avenue boundaries and their centroids). In this simulation, we assess whether using centroids versus simulated individual household locations affects trends in the tau statistic, and to what extent.

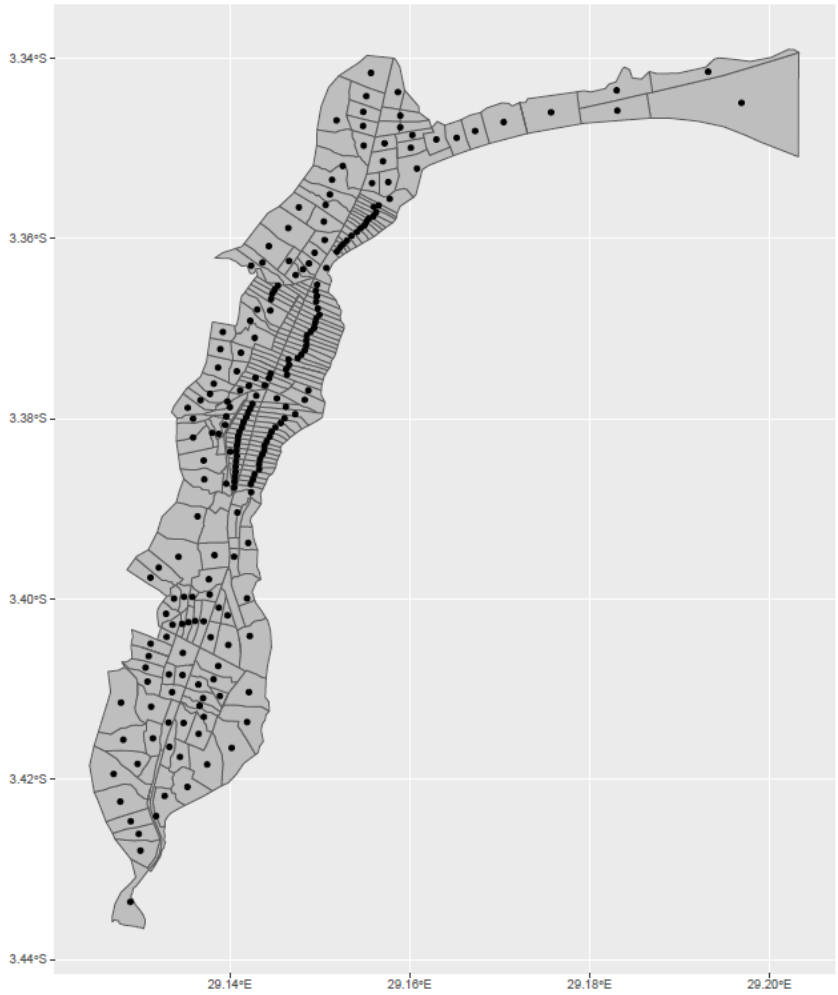


Figure C2.1: Map of the centroid locations and borders of Uvira's 216 avenues

Methods

We used the dataset of 1493 rapid diagnostic test (RDT) positive cholera cases from 2016—2020 (displayed in space and time in Appendix Figure 2). The X/Y coordinates in this dataset were perturbed randomly by adding a random normal distribution with an

arbitrarily-defined standard deviation of 100. The points were plotted as maps to visually compare the spatial spread of cases between datasets 1 and 2 (Appendix Figure 3). The main τ analysis was run for each dataset. This produced the τ statistic (relative risk and 95% CIs) of the next case being within a specific distance to another case (y-axis) compared with the risk of the case occurring anywhere else during days 0—4 for RDT-positive cases. A moving average was applied in distance spans of 10m, 25m, and 50m to smooth fluctuations. To assess the similarity between the datasets, the trendlines were evaluated visually by graphing and by comparing Pearson correlations.

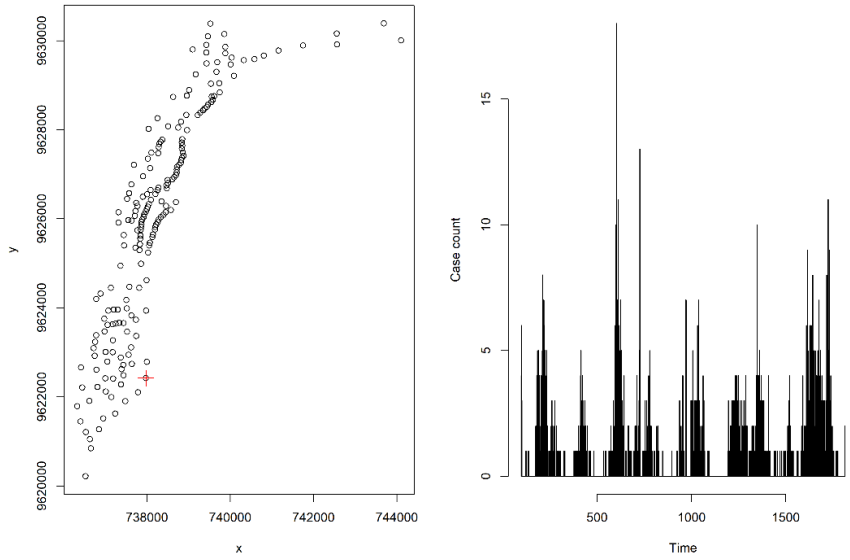


Figure C2.2: Uvira 2016—2020 dataset of rapid diagnostic positive cases with avenue centroids of cases (index case in red)

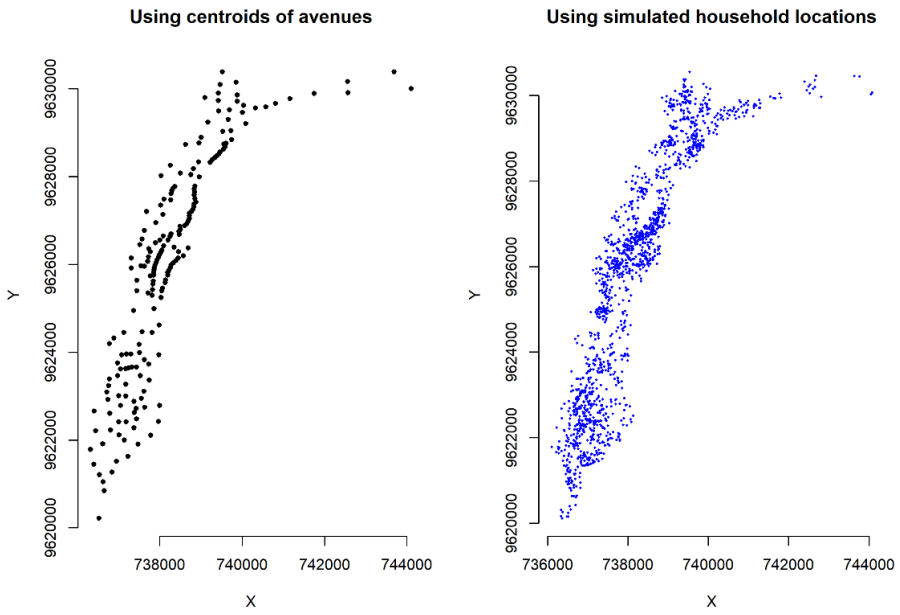


Figure C2.3: Case centroid locations (black) and simulated household locations (blue)

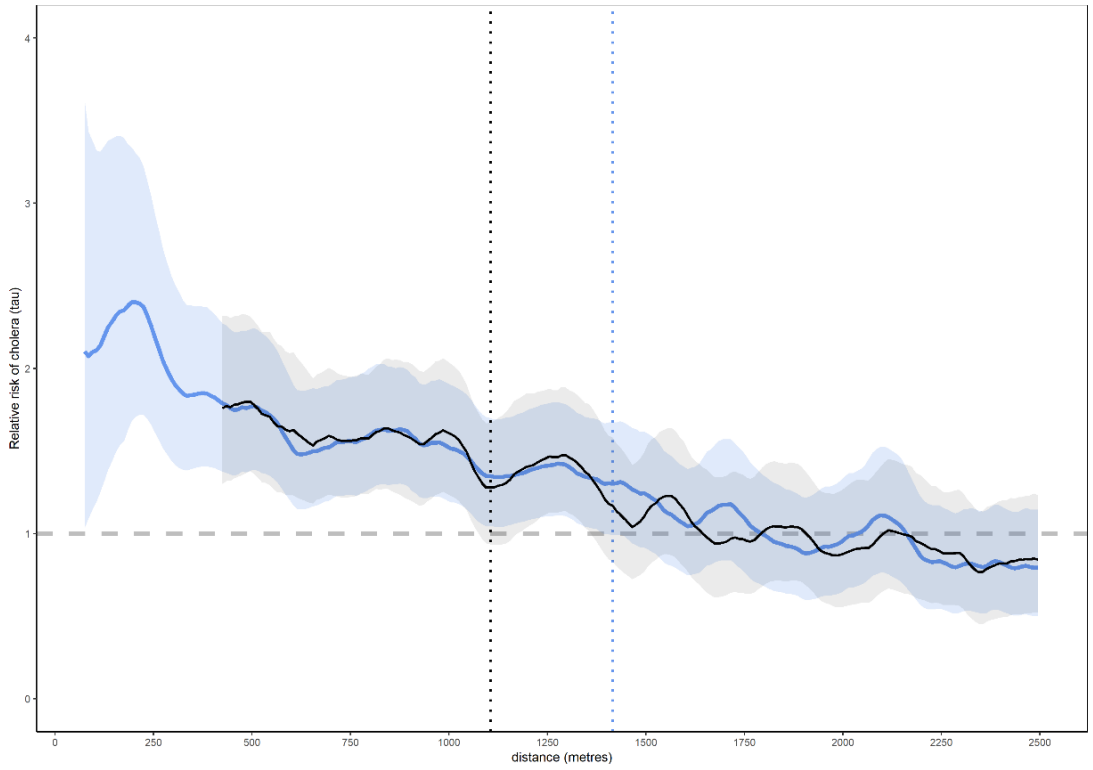


Figure C2.4: Moving average of point estimates and 95% confidence intervals for tau τ statistic for RDT-positive cholera cases (75—2500m) of the centroids (black, starting at 420m) and the household locations (blue, starting at 75 m) (Appendix Figure 4). The dashed line is where the lower confidence interval for the moving average crosses 1.0 three times consecutively.

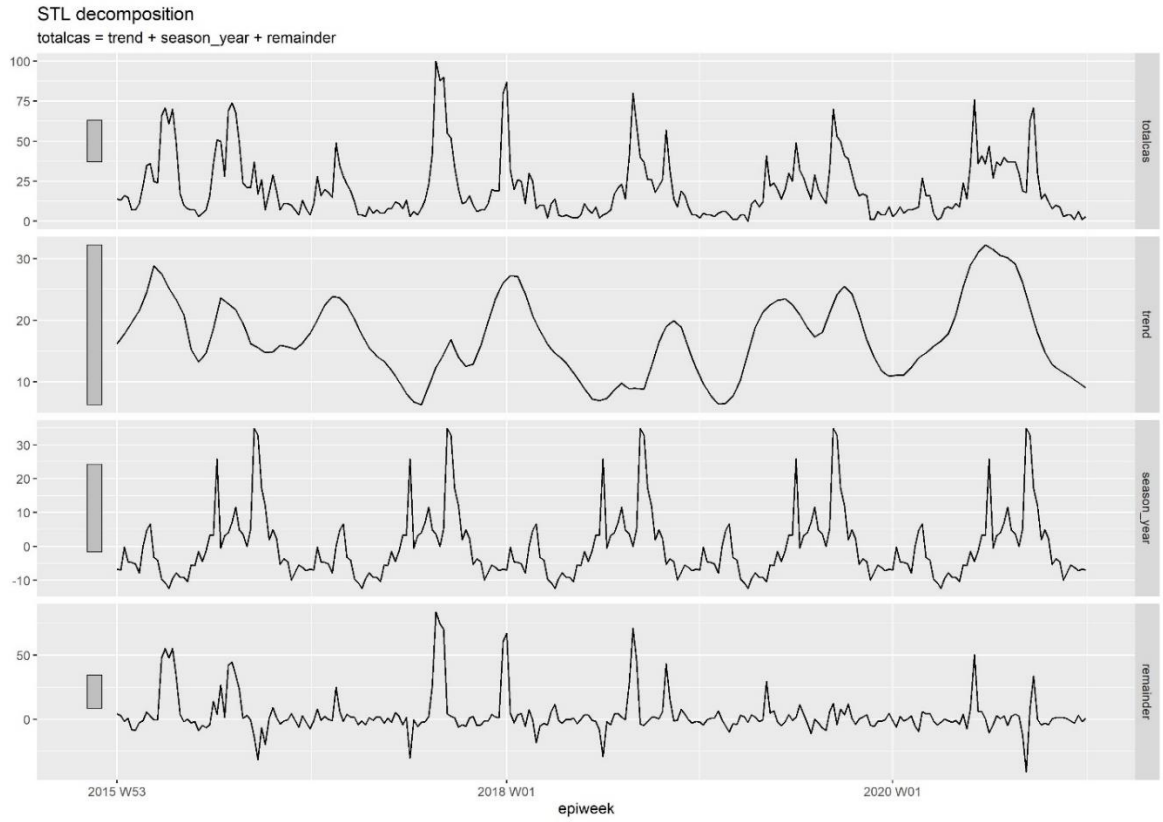
Findings and interpretation

The two datasets showed similar τ trends (Appendix Figure 4). Both for lower CIs of the moving average τ and for the moving average τ point estimates where τ crossed 1.0 twice consecutively differed between the centroid dataset and the household dataset (Appendix Table 1). The Pearson correlation coefficients were significant and nearly identical.

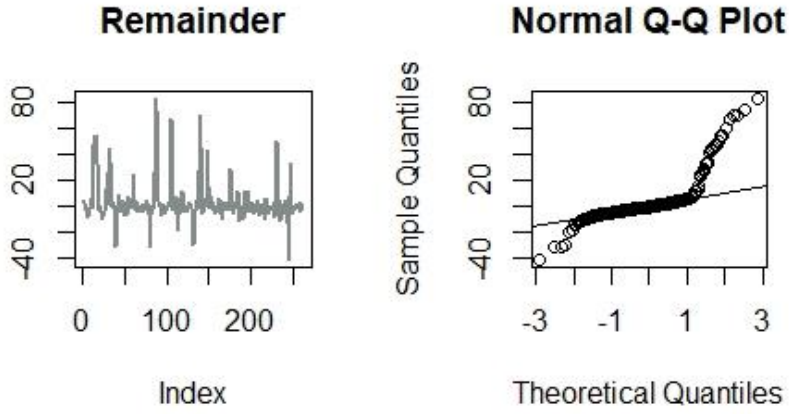
Table C2.1: Differences in points where τ crosses RR=1.0 twice consecutively

Dataset	Min τ	Max τ	Mean τ	Moving average τ <1.0 (3 times)	Moving average τ LCI <1.0 (3 times)	Pearson correlation coefficient
Centroid	0.52	3.01	1.01	1665m	1105m	-0.87 (95% CI -0.89, -0.85)
Simulated household	0.55	2.40	1.05	1815m	1415m	-0.88 (95% CI -0.90, -0.86)

Overall, the centroid dataset showed a similar descending trend in risk over distance, central tendencies and correlation coefficients, as compared with the simulated household dataset. The centroid dataset however showed a lower τ threshold estimate for the moving average τ point estimate (by 8.3%) and lower 95% CI moving average (by 21.9%). Notably, the simulated households had the highest moving average τ estimate (equivalent to 2.0 < RR < 2.5) from 75—275m, which was unmeasured in the centroid dataset.



C.3 Trend, season and remainder decomposition using a trend window for smoothing of 14 days and seasonal window for smoothing including the entire period

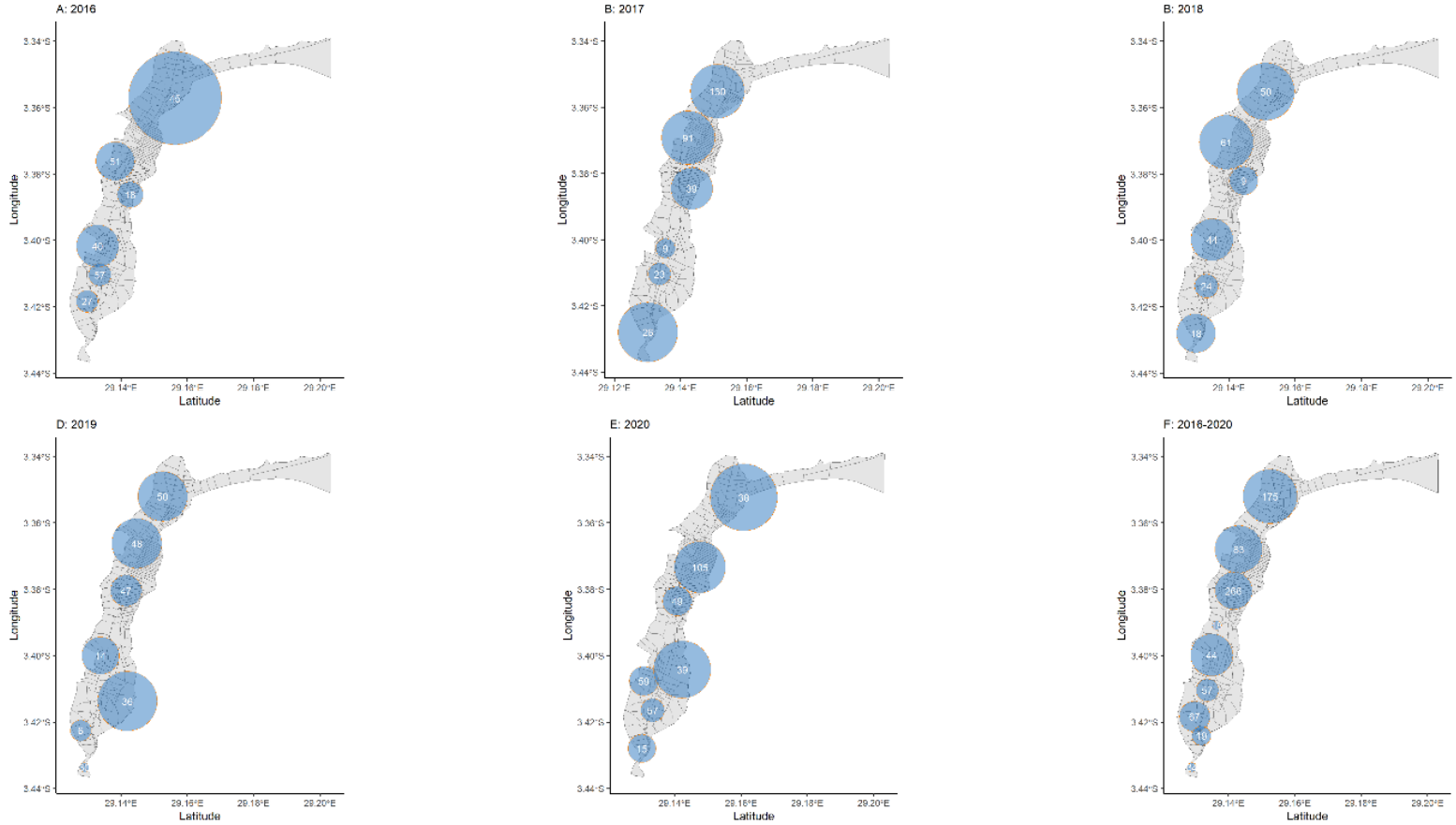


C.4: Normal Q-Q plot of residuals (remainder) and verification of a heavy-tailed skew approaching a normal distribution of residuals (indicating a mix of structure and noise)

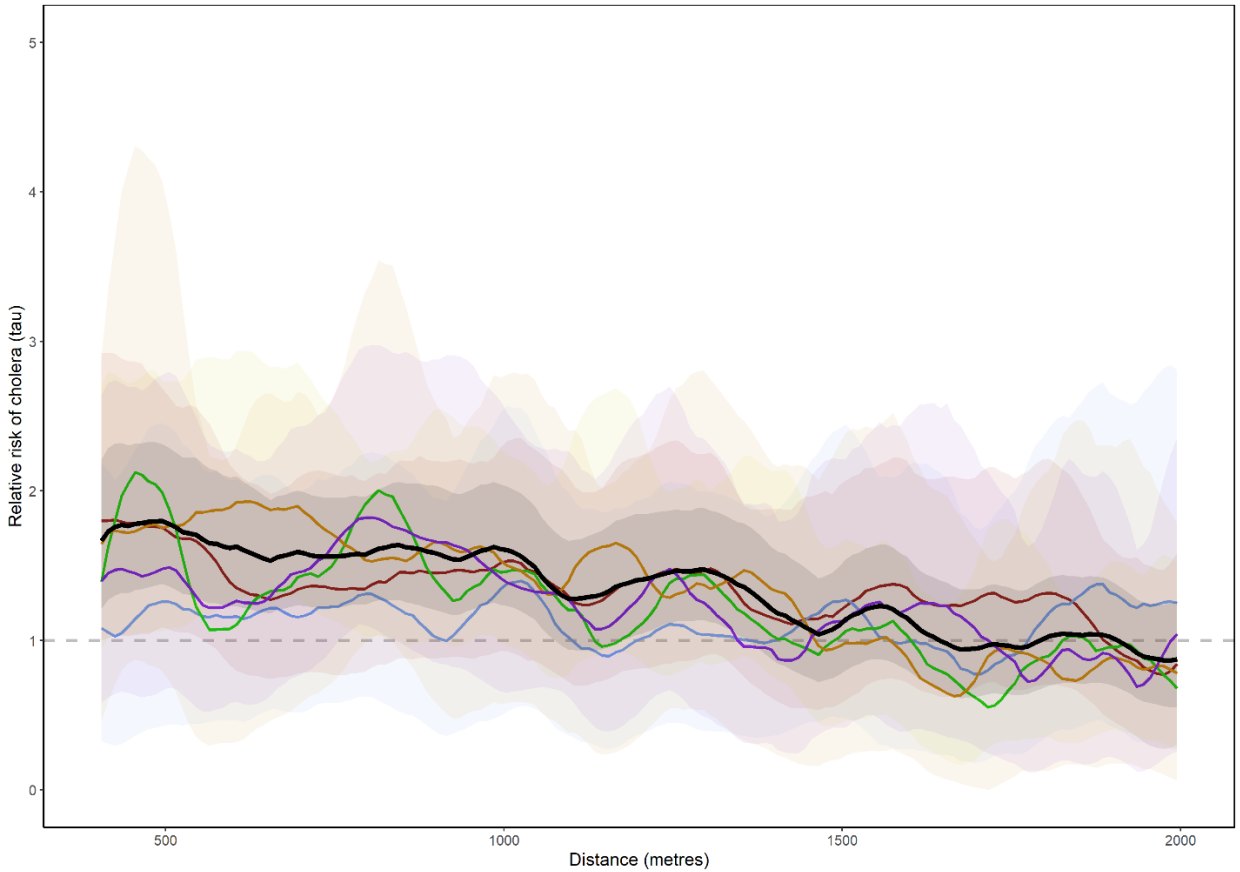
C.5 Sensitivity analysis: spatiotemporal clusters of suspected cholera cases, Uvira, 2016—2020

Year	No.	Cases observed	Cases expected	Population at-risk	RR	Radius (m)	Start date (mm/dd)	Duration (days)
2016	1	57	5	177122	10.8	378	04/07	15
	2	51	4	187076	12.1	647	03/24	11
	3	45	6	183225	7.2	1557	08/06	17
	4	27	3	120498	8.4	368	04/09	13
	5	40	9	147424	4.6	709	07/22	30
	6	18	2	29390	7.8	436	02/18	40
2017	1	130	13	148014	10.8	908	08/07	43
	2	91	16	150104	5.9	897	08/19	52
	3	39	6	88959	6.6	704	08/29	32
	4	23	2	134147	10.6	378	12/24	7
	5	26	5	143948	5.2	1001	08/23	16
	6	9	1	42275	17.3	331	02/14	5
2018	1	50	3	130673	15.3	963	10/26	12
	2	24	2	134311	15.1	397	01/01	5
	3	61	15	132515	4.2	906	07/29	56
	4	44	10	128631	4.5	708	08/21	38
	5	18	3	70142	5.9	653	10/30	21
	6	9	1	52203	14.4	477	02/17	5
2019	1	50	4	93453	14.3	831	09/10	18
	2	30	2	21965	13.9	0	09/01	48
	3	47	7	105035	7.1	524	04/27	31
	4	48	10	115699	5.0	836	09/07	41
	5	36	8	120197	4.7	995	06/08	31
	6	14	2	40341	7.4**	626	06/23	22
	7	6	0	45292	32.2	350	09/20	1
2020	1	105	17	159204	6.7	860	07/29	59
	2	59	11	141671	5.8	488	05/31	41
	3	38	5	106256	8.6	1121	02/20	23
	4	57	13	155765	4.6	395	05/30	46
	5	49	13	120618	3.9	490	07/27	59
	6	39	10	159261	4.0	959	05/30	34
	7	15	2	44366	10.1	468	09/10	18

* p-value < 0.001 ≥ p-value <0.01; ** p-value < 0.001. † RR, relative risk. ‡ Signal delay indicates the number of days between retrospective detection date with all available data and the earliest prospective detection date.



C.6 Sensitivity analyses of prospectively detected spatiotemporal clusters of suspected cholera cases, 2016—2020. The size of the orange circle depicts the radius with the number of suspected cases (in white).



C7: Cholera, Uvira, 2016—2020: Annual and aggregated moving average estimates of τ (relative risk) and 95% CIs (solid line and shading) for days 0—4. 2016—2020 in black, 2016 in purple, 2017 in orange, 2018 in green, 2019 in blue, 202 in red

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SECTION A – Student Details

Student ID Number	071663	**Title**	Mr.
First Name(s)	Ruwan		
Surname/Family Name	Ratnayake		
Thesis Title	Case-area targeted intervention for the control of cholera epidemics in crises: from spatial mathematical modelling to field evaluation		
Primary Supervisor	Prof. Francesco Checchi		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PLOS Neglected Tropical Diseases		
When was the work published?	February 16, 2022		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	Not published prior to registration		
Have you retained the copyright for the work?*	Yes	Was the work subject to academic peer review?	Yes

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Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived of the work, devised the methodlogy, led the analysis, wrote the original draft of the manuscript, prepared the tables and figures, interpreted the data and revised the manuscript.

SECTION E

Student Signature	[redacted]
Date	September 18, 2023

Supervisor Signature	[redacted]
Date	18 September 2023

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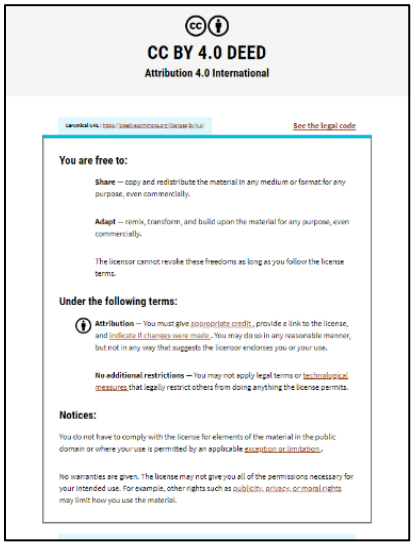

Appendix D: Inference is bliss: Simulation for power estimation for an observational study of a cholera outbreak intervention (non-thesis article)

Inference is bliss: Simulation for power estimation for an observational study of a cholera outbreak intervention

Published in *PLOS Neglected Tropical Diseases*, Volume 16, Issue 2, e0010163, February 2022.

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ABSTRACT

Background: The evaluation of ring vaccination and other outbreak-containment interventions during severe and rapidly-evolving epidemics presents a challenge for the choice of a feasible study design, and subsequently, for the estimation of statistical power. To support a future evaluation of a *case-area targeted intervention* against cholera, we have proposed a prospective observational study design to estimate the association between the strength of implementation of this intervention across several small outbreaks (occurring within geographically delineated clusters around primary and secondary cases named 'rings') and its effectiveness (defined as a reduction in cholera incidence). We describe here a strategy combining mathematical modelling and simulation to estimate power for a prospective observational study.

Methodology and Principal Findings: The strategy combines stochastic modelling of transmission and the direct and indirect effects of the intervention in a set of rings, with a simulation of the study analysis on the model results. We found that targeting 80 to 100 rings was required to achieve power ≥80%, using a basic reproduction number of 2.0 and a dispersion coefficient of 1.0—1.5.

Conclusions: This power estimation strategy is feasible to implement for observational study designs which aim to evaluate outbreak containment for other pathogens in geographically or socially defined rings.

AUTHOR SUMMARY

From Ebola virus disease outbreaks to the COVID-19 pandemic, the use of real-time evaluations of interventions to contain outbreaks is vital for rapidly estimating impact during the outbreak itself. Such evaluations must be both epidemiologically rigorous and logistically feasible to justify their conduct during an outbreak. In this short report, we report on the process (with R code) and the results of a simulation strategy that we devised for power estimation for a prospective observational study of a novel intervention ("case-area targeted intervention") to contain cholera case clusters that present at the start of a new outbreak. We used simulation in two ways: mathematical modelling to simulate the impacts of a cholera outbreak and the intervention, and simulation of the study analysis on the model results. The strategy provided estimates of the sample sizes of study units required to achieve 80% and 90% power. Our findings reinforce that this process is feasible to implement for similar observational study designs which aim to evaluate outbreak containment for other pathogens in geographically or socially defined rings.

INTRODUCTION

Fast and efficient disease control approaches are critical for controlling cholera epidemics. Case area-targeted interventions (CATI) aim to interrupt transmission within small cholera outbreaks by rapidly addressing different routes of infection with multiple interventions (i.e., antibiotic chemoprophylaxis, household water treatment, and oral vaccination) in geographical 'rings' of 100—250 metres around the household of the index case. [1, 2] Such containment strategies for small outbreaks target people at the highest risk of infection and may be less resource-intensive and more effective than mass, community-wide campaigns over large geographical areas. [1]

We designed an observational study to measure the effects of CATI during a future cholera epidemic response, to be conducted by Médecins Sans Frontières. The evaluation of CATI presents several challenges for the choice of a feasible study design and subsequently, for the estimation of statistical power. Randomizing individuals or communities to different interventions or a placebo is often not feasible and ethically problematic during a demanding epidemic response in a low-resource setting. For the evaluation of ring vaccination with a new vaccine during the 2016 Ebola epidemic in Guinea, an adapted cluster randomized-controlled trial (RCT) design was developed wherein each ring of contacts of confirmed cases was randomized to a different delay to implementation, thereby producing intervention and control groups. [3] During a cholera outbreak, where a package of routine rather than novel interventions is applied, the

objective is to assess the allocation strategy. For this question, an RCT design may not always be appropriate or feasible.

Here, a prospective observational study design is considered, where participants or groups are not randomized and the outcome is measured prospectively. [4] In our example, the measurement of effectiveness (i.e., incidence) is related to the strength of implementation of the intervention across small outbreaks rather than an assigned presence or absence of the exposure (i.e., CATI). The strength of implementation is represented by the natural delay between case notification and the implementation of CATI, which may differ across several small outbreaks. This results in CATI rings categorized by the delay between case notification and implementation. Two interrelated challenges emerge, which do not fit well with a classical statistical approach for study design. First, the analysis does not conform to the conventional formulae for sample size and power estimation given the presence of several 'natural' control groups. Second, the non-independence of infection risk between persons drives the incidence and is difficult to estimate *a priori*. [5] The interventions produce direct and indirect effects on infection and transmission, with infection prevention, infection, and/or treatment of one person affecting the outcome of another person. [6] Moreover, the cumulative effects of a package of interventions are difficult to predict.

In this report, we describe a strategy to estimate power for a prospective observational study across a range of sample sizes. This approach combines stochastic simulation

modelling of small outbreaks and the direct and indirect effects of the intervention, with a simulation study of the study analysis based on model results. While simulation studies are often conducted to estimate power for RCTs, there is little documentation of (a) simulation used for other study designs and (b) mathematical modelling to simulate transmission dynamics for power estimation. [7-9] We provide details of the approach, and R code, as a foundation for further application to outbreak intervention studies of other pathogens.

METHODS

We describe the study design for which we are calculating power. We then describe the simulation study using the *Aim, Data Generating Mechanism, Estimand, Methods, Performance Measures* (ADEMP) framework for the coherent reporting of simulation studies. [7]

Summary of the prospective observational study design

The impact of CATI (which includes single-dose oral cholera vaccination (OCV), point-of-use water treatment, and antibiotic chemoprophylaxis) will be measured by the reduction in the incidence of cholera around the index cases of small outbreaks through direct and indirect protection, as a function of the time to implementation of CATI (Fig 1). The intervention is triggered when a suspected case is detected and tests positive by an enriched rapid diagnostic test (RDT). [10] Then, a 100—250 metre radius around the index case's household is outlined (hereafter, the 'ring'), wherein CATI is rapidly implemented. While the first outbreak clusters may be responded to very rapidly, as the

size of the epidemic increases logistical barriers for field teams are anticipated to result in delays to implementation in new rings of up to 7 days, thus creating natural control groups. The ring is the unit of analysis. A regression analysis will model the observed incidence of enriched RDT-positive cholera in rings relative to the time to response (in days) and coverage. The regression function quantifying the association between timeliness/coverage and incidence provides a measure of effectiveness at different levels of performance.

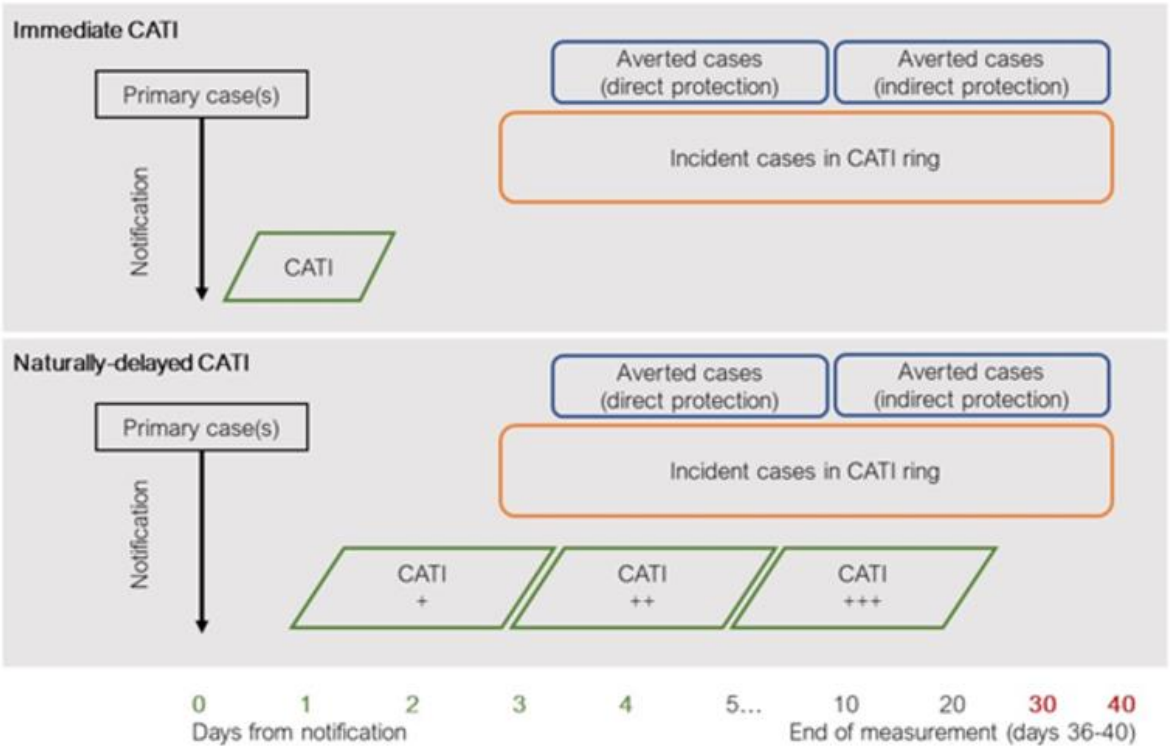

Fig 1. Diagram of the s**tudy design.** Delays to implementation of CATI give rise to natural controls. A regression analysis is used to model the observed incidence of enriched rapid diagnostic test-positive cholera in rings (outcome) as a function of the delay to response. CATI=case-area targeted intervention.

Summary and rationale for the simulation

The study design rests on the assumption that the regression analysis will have sufficient power to detect an association between CATI performance and the incidence of cholera, i.e. that data from a sufficient number of rings of given size and characteristics (e.g. transmissibility of cholera within the rings) will be available. The **aim** of the simulation study is to explore these sample size requirements. We chose as a **data-generating mechanism** a stochastic transmission model to predict the incidence and the direct and indirect effects of CATI, applied with varied delays, on transmission across a large set of rings during a 30-day period. This mechanistic model of transmission and the predicted effect of the intervention is driven by transmission dynamics and is therefore more realistic than the assignment of an effect size, as typically used in statistical simulations. [5] The basic reproduction number for cholera, R_0, is varied in the modelling scenarios. The **estimand** is the incidence of suspected cholera in each ring in the first 30 days after presentation of the index case. The **method** used for simulation involves a regression applied to each set of simulated data to estimate the association of CATI performance and cholera incidence, while tracking *p-values* for the association. For each combination of simulation parameters, the mechanistic model and regression on the resulting simulated data are replicated by an assigned number of simulations (n_{sim}) by randomly sampling without replacement over the anticipated number of rings in the study (n_{rings}). The proportion of runs in which the regression yields a significant association provides a measure of power given that a sample of n_{rings} are available. A

range of n_{sim} (1000—3000) is used to assess the stability of power estimates. The **performance measure** is the predicted power.

All analyses were carried out in R version 4.0.5, using the following packages: `bpmodels` [11] for branching process modelling, `lme4` for generalized linear mixed modelling, and the `map_dfr()` function of the `purrr` package to repetitively apply functions for the simulation coding. [12] In the following sections, we describe each step in detail, which together with the code provided, can be used to replicate the simulation (https://github.com/ruwanepi/CATI-power-sim-shared.git).

Stochastic transmission model

Using the `bpmodels` package, we applied a branching process model which generated infected persons and accounted for the depletion of susceptible persons to produce the incidence for each of 100,000 rings in the first 30 days after notification of the index case. The population size of the ring (normal distribution with mean 500, SD 50) was within the range of the number of people living in a 100—250 metre radius in major African cities including N'Djamena, Conakry, and Lumumbashi (mean 295, range 55—456 persons). [2] People were assumed to mix homogeneously. Given the efficiency of person-to-person and environmentally-mediated cholera transmission within households, there is potential for exponential growth, mediated by the depletion of susceptibles, before effective control measures are implemented. [13] We assumed that

the first notified index case was the true primary case for the outbreak and that all infectious cases were symptomatic and detectable, with some delay. Infection-to-reporting delays before and after CATI implementation were set as Poisson-distributed. The main outcomes of the model were, by ring, (a) cumulative incidence at day 30, and (b) a random effect accounting for the varying delay from infection to reporting of the primary case in the model (categorized as 0, 1, ≥1 days), as a proxy of the surveillance capacity by geographic area.

To model transmission, the parameters listed in Table 1 were used, and were either sampled from the underlying distributions or fixed. All persons were assumed to be susceptible without immunity derived from previous vaccination or exposure to *V. cholerae*. An outbreak started with a single seed case and each case generated a number of secondary cases drawn from a negative binomial distribution $Z \sim NegB(R_0, k)$. The mean is equal to the basic reproduction number at the early phase of the outbreak among an unvaccinated population (R_0=1.5, R_0=2.0).[14,15] Heterogeneity in the number of new infections produced by each individual is represented by a dispersion coefficient (D=1.0, D=1.5), which relates to the dispersion parameter of the negative binomial distribution, *k* $\left(k = \frac{R_0}{D-1}\right)$. [14-17] Each potential new infection was assigned a time of infection drawn from the serial interval distribution, $S \sim gamma\ (shape = 0.5, rate = 0.1)$. [14] The number of susceptible persons in the population was progressively reduced due to infection or immunity, reducing the mean of the negative binomial offspring distribution by a factor n/N, where n is the number of remaining susceptible

and N is the total population, while keeping the dispersion coefficient constant, and truncating the distribution at n. We assumed that no other interventions were implemented before CATI. Four scenarios using high and low R_0 and *D* were modelled (Table 1).

CATI interventions were then simulated, with a delay from notification of the index case as determined by a Poisson distribution, and the upper limit approximately based on the 75th percentile of the median delay from symptom onset to case presentation derived from a meta-analysis of cholera outbreaks (0 to 5 days), assuming that the surveillance set-up for CATI will prevent longer delays. [18] We assumed that implementation took one day and the population-based coverage was 80%. [19, 20] CATI included distribution of (1) water, sanitation, and hygiene (WASH) materials including chlorine tablets and a narrow-neck container so that the efficacy in reducing bacterial concentration via household water treatment (26%) and safe storage (21%) remained consistent for the 30-day period (cumulative efficacy, 41.5%). [21, 22]; single-dose, oral antibiotic chemoprophylaxis against infection so that the efficacy in preventing infection (66%) was maintained for the first 2 days, whereafter it loses effect due to its biological half-life [2, 23]; and single-dose, oral cholera vaccination (OCV) prevented infection with an efficacy of 87% over a 2-month period, taking effect 7-11 days after administration when peak vibriocidal response is reached. [24] The effectiveness *(efficacy*coverage)* was calculated in three phases over the 30 days reflecting the plausible timespan over which the relative effects of each intervention would manifest: (1) days 1 to 2: WASH and

antibiotic chemoprophylaxis, (2) days 3 to 6: WASH only, (3) days 7 to 30: WASH and vaccination. The combined effect of concurrent interventions was computed as (*1 - ((1-effect.A)*(1-effect.B)*…*(1-effect.Z)))*.

We conducted two sensitivity analyses to explore the main assumptions of rapid 1-day duration of implementation and population coverage of 80%. We evaluated a longer duration of implementation of 2 days and lower population-based coverage estimates of 50%, 60%, and 75%, based on findings from field studies. [19, 20]

Parameter	Values	Reference
Sampled	**Mean (SD)**	
Serial interval, days	5 (8), by negative binomial distribution	Azman et al, 2016 [14]
Reporting delay (before CATI), days	1 (0.9), by Poisson distribution (λ=1)	Assumed
Reporting delay (after CATI), days	0.5 (0.7), by Poisson distribution (λ=0.5)	Assumed
Implementation delay, days	3 (1.9), by Poisson distribution (λ=1.4)	Ratnayake et al, 2020 [18]
Population size of ring ± SD	500 (50), by normal distribution	Finger et al, 2019 [2]
Fixed	**Values**	
Basic reproduction number for index cases, R_0	1.5, 2.0	Azman et al, 2016[14] Camacho et al, 2018 [14]
Dispersion coefficient, *D*	1.0, 1.5	Emch et al, 2008 [16]
Initial immune, persons, %	0%	Assumed
Implementation duration, days	1 (main analysis), 2	Ouamba et al, 2021 [20]
Population coverage, %	80% (main analysis), 50%, 60%, 70%	Parker et al, 2017 [19]
Efficacy of antibiotics, %	66%	Reveiz et al, 2001 [23]
Efficacy of water treatment, %	26%	Fewtrell et al, 2005 [21]
Efficacy of safe water storage, %	21%	Roberts et al, 2001 [22]
Efficacy of vaccination, %	87%	Azman et al, 2016 [24]
During each simulation, sampled values are probabilistically sampled and fixed values remain constant. Median (SD), single values, or proportion efficacy are given. Efficacy measures are summarized in Ratnayake et al, 2021. [1]		

Table 1. Parameters for the stochastic transmission model

Simulation method

A generalized linear mixed model (GLMM) was used to estimate the response variable (cumulative incidence rate) as a function of time to implementation. A negative binomial

distribution accounted for overdispersion. Fixed effects quantified the main explanatory variable: the overall effect of time from case presentation to CATI implementation. The logarithm of the ring population was used as an offset to produce an incidence rate ratio (IRR). A random effect accounted for the delay from infection to presentation of the index case, which was categorized into 3 classes (0, 1, ≥1 days). For simplicity, other potential confounders that would require explicit measurement of geographical locations of rings were not considered (e.g., distance between the ring and the base of the field team). Model fit was assessed using the ratio of sum of squares of Pearson residuals to the residual degrees of freedom (to estimate overdispersion), inspection of the width of confidence intervals, and plotting of response by random effect levels (to estimate the benefit of including the random effect, as compared to using a generalized linear model (GLM)).

As the health of individuals in the same ring may be correlated, regression modeling approaches that account for the clustered nature of the data should be used for the study analysis. This includes GLMM, generalized estimating equations (GEE) and generalized additive models (GAM). GLMM uses random effects to account for contextual factors from the rings that alter the relationship between the exposure and the population effect, while GEEs infer the population-averaged effect across all rings. [25] As we expect there will be variance between rings and we may want to explore it further, GLMMs are preferred over GEEs for this study. GAMs add together the non-parametric and parametric fits of separate regressors into a transformed regression. [26]

In this study, GAMs may be used if the observed relationship between delay to response and incidence offers a better fit than a purely parametric GLMM model. Regardless of model choice, the effect estimates should remain similar and unbiased.

The expected power was estimated for a range of sample sizes (n_{rings} = 50—150 rings), based on recent CATI experiences during large epidemics in Nepal and Haiti, with a target of 80% power. [27, 28] We simulated 100,000 CATI rings using the above-described method. We then conducted a simulation study by randomly sampling a set number of rings (n_{rings}), a set number of times (n_{sim}). A negative binomial GLMM was run on each set of n_{rings}. Power was assessed as the number of simulations with a significative effect of delay to CATI implementation *($p<0.05$),* considered to be true positives, divided by the number of n_{sim}. n_{rings} was varied to assess the effect of the number of rings in each study on power. Table 2 lists the simulation parameters including the range of n_{sim} values used to demonstrate consistency in results. For each set of n_{rings} rings randomly sampled without replacement from the 100,000 rings simulated by the stochastic model, 500—3,000 simulations were run to evaluate the reliability of the results.

Parameter	Value	Reference
Number of rings produced by stochastic model	100,000	Assumed
Number of rings randomly sampled (n_{rings})	50, 75, 100, 125, 150	Roskosky et al, 2019 [27] Michel et al, 2019 [28]
Number of simulations run for each value of n_{obs} (n_{sim})	500, 1,000, 3,000	Morris et al, 2019 [7]

Table 2. Parameters for the simulation study

FINDINGS

Using R_0=2.0, D=1.5 and n_{sim}=100,000, the mean caseload increased with each single day from 12 cases (with delays of 0 days) to 59 cases (with delays of 7 days). A higher proportion of outbreaks were extinct by day 30 for the ≤3-day category versus the >3-day category. An IRR of 1.27 (95% CI 1.25—1.29) was produced, demonstrating a 27% increase in the incidence rate per single day increase in the delay of implementation of CATI (visualized in Fig 2). The model fit is described in S1 Text.

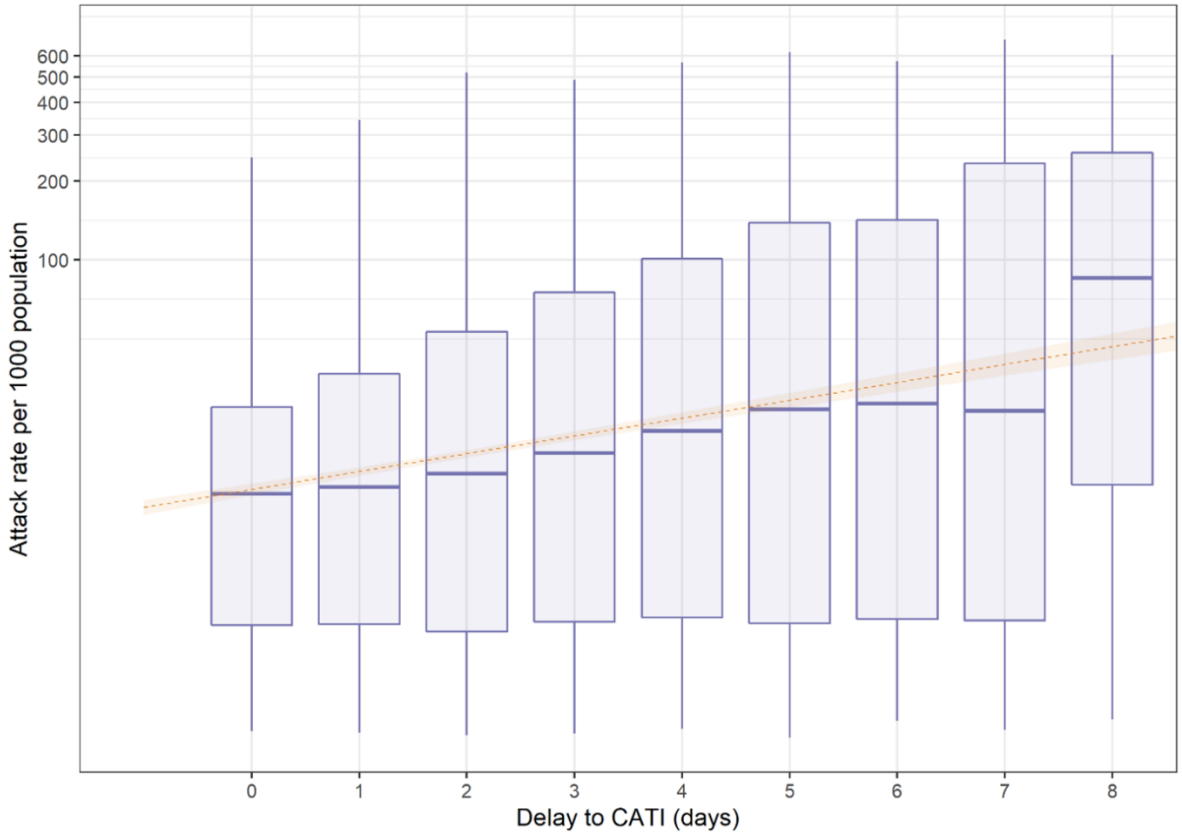

Fig 2. Boxplots of the attack rate of cholera cases (per 1000 population, on a log10 scale) categorized by the delay to CATI implementation (in days) using 100,000 rings (with generalized linear model of the association outlined in orange)

The compiled power estimates are presented in Table 3 and the main power estimations where R_0, D, and n_{rings} were varied are displayed in Fig 3 (additional graphs are found in Figs A—D, S1 Text). Using the main model (R_0=2.0 and D=1.5), the simulation returned 80.6% (95% CI 71.2—87.6) power with n_{rings}=100; 73.7% power with n_{rings}=80; and, 88.7% power with n_{rings}=125 (Fig 3). Using R_0=2.0 and D=1.0, the simulation reached 81.2% (95% CI 71.9—88.1) power with n_{rings}=80. With R_0=1.5 and D=1.5, the power was reduced substantially wherein n_{rings}=150 produced 62.8% power. The model for R_0=1.5 and D=1.0 did not converge for any number of rings tested and is omitted from Fig 3. The results were generally consistent when n_{sim} was varied.

Sensitivity analyses

Applying a slower duration of implementation of 2 days meant that 80% power is reached with >125 rings. Using lower population coverage of 50% and 60% increased the sample size required to >100 rings to reach 80% power. Lowering slightly the population coverage to 75% resulted in 79.1% power reached with 100 rings, which is close to the target of 80% power.

				Number of rings					
R₀	**D**	**Duration**	**Coverage**	**50**	**75**	**80**	**100**	**125**	**150**
2	1.5	1	80%	52.4	71.7	73.7	80.6	88.7	94.7
2	1	1	80%	57.3	77.1	81.2	85.8	92.7	96.2
1.5	1.5	1	80%	33.6	37.4	49.5	49.7	58.3	62.8
2	1.5	2	80%	44.4	60.4	60.5	69.5	78.7	84.7
2	1.5	1	50%	52.9	64.2	68.9	77.5	85.9	92.4
2	1.5	1	60%	51.3	64.6	70.6	76.8	85.3	92.3
2	1.5	1	75%	53.6	68.0	72.8	79.1	84.7	92.1

Table 3. Power estimates from main simulations and sensitivity analyses. Shading indicates the variable that was changed (grey), and where power estimates were farthest from the 80% target (≤69%, in orange), close to the target (≥70 to 79%, in light green), and at or above the target (≥80%, in dark green).

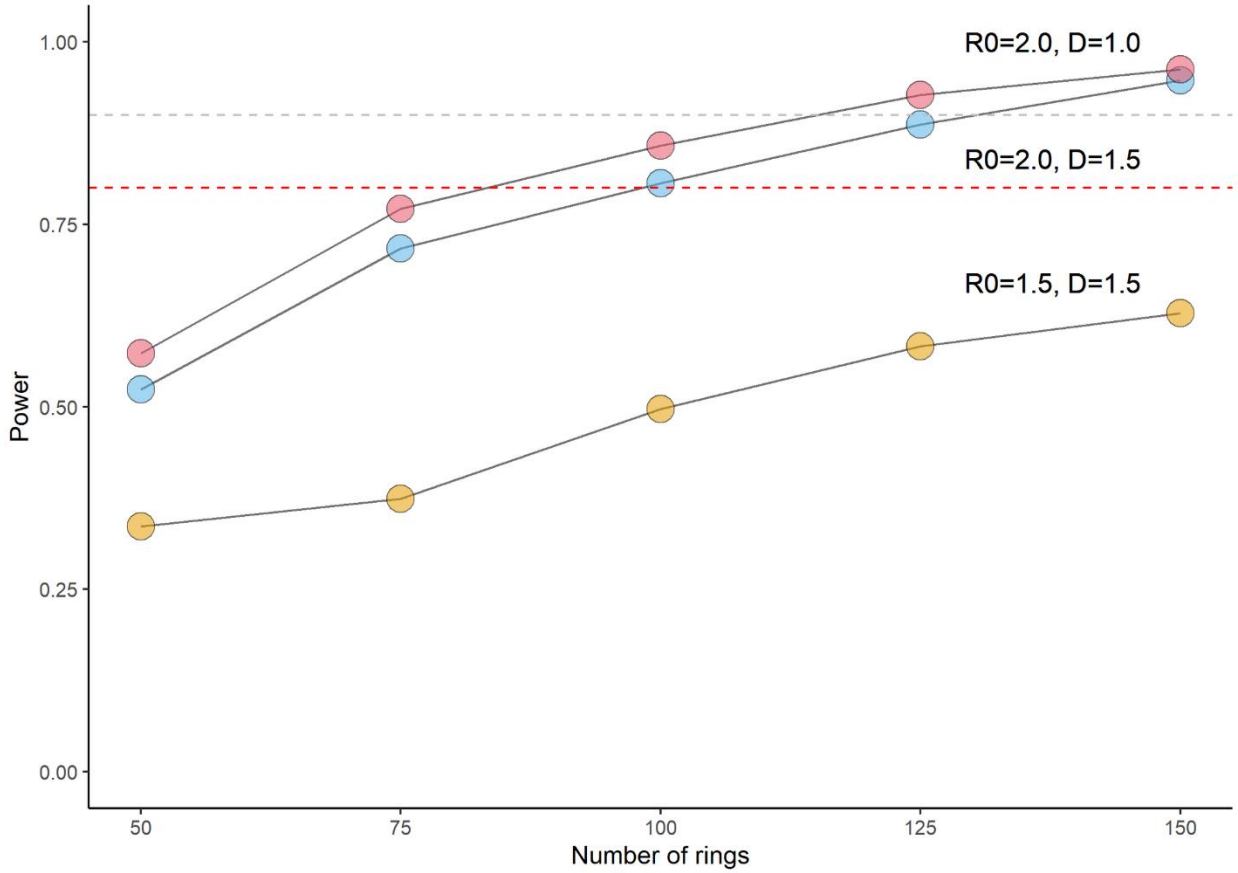

Fig 3. Power estimation by the number of rings: (A) $R_0 = 2.0$, D=1.0 (RED), (B) $R_0 = 2.0$, D=1.5 (BLUE), (C) $R_0 = 1.5$, D=1.5 (YELLOW). Power thresholds are indicated by the red dashed line (80%) and the grey dashed line (90%). R_0, basic reproduction number, D, dispersion coefficient.

DISCUSSION

Our simulation strategy provided a relatively simple means of estimating power and associated sample sizes for an observational study of CATI. Based on an R_0 of 2.0, the sample size required to reach 80% power was 80—100 rings, which was generally maintained when population coverage decreased from 80% to 75%. This would have been feasible during recent experiences in implementing CATI during large epidemics in Kathmandu Valley, Nepal (169 rings in 7 months), and Centre Department, Haiti (238

rings in 24 months). [27, 28] Alternately, where CATI was used to suppress the tails of large outbreaks though only at the end of mass vaccination campaigns in Juba, South Sudan and Kribi, Cameroon, the sample size would far exceed the number of rings that are typically implemented. [19, 20] As cholera epidemics frequently remain small due to the burn-out of the susceptible pool [18], overdispersion of R_0 leading to extinction [16, 17], or the impact of the interventions themselves, a pooled analysis of multiple epidemics within a country implementing the same CATI package could be a more secure prospect to attain the required sample size.

A strength of this simulation strategy is the inclusion of a realistic depiction of CATI implementation which models the relative effects of its composite interventions over time. This accounted for the time-limited effects of antibiotics (~ 2 days) and the 7—11 day delay to a measurable immune response after administration of vaccination. [2, 24] Another strength was that the stochastic model accounted for the depletion of susceptible persons to provide a plausible representation of early epidemic growth in a small population. This approach can be adjusted using the real-time estimates of the effective reproduction number (R_E) to update sample size estimation. It is also computationally-light, as the process takes less than 2 hours to run without the use of parallel computing.

There are key limitations to our methodology and its simplifying assumptions. The mean population size of 500 persons reflects urban settings. However, cholera epidemics can occur across urban and rural areas simultaneously and would include smaller rings with lower intra-cluster variation in incidence. As such, a larger sample size may be required to reach 80% power. For the stochastic model, several parameters relating to the early growth of a cholera epidemic are uncertain. The main model used a relatively high R_0 (2.0) sourced from early epidemic growth in unvaccinated populations in South Sudan and Yemen; considerably lower power was achieved with $R_0 = 1.5$. [9, 14] In addition, we assumed the entire population was susceptible at the start of the outbreak, which may not be the case in cholera-endemic or previously-vaccinated areas, lowering the R_E and the measurable effect of CATI. The stochastic model is not spatially-explicit, so transmission between communities is not accounted for, nor is the force of infection external to a given ring which could represent long-distance transmission from outside the community or contamination of the local water supply. [2] A duration of implementation of a single day has been shown in Cameroon and South Sudan [19, 20], but this may not be sufficient to cover the entire ring. This potentially leads to an overestimation of the effect, with the sensitivity analysis finding higher sample size requirements. Outbreak simulations are right censored at 30 days, and thus we cannot determine from the 30 day analysis alone whether outbreaks are fully extinct. How the delay to case detection was parameterized as a random effect may not truly represent the surveillance capacity, indicating that it must be accounted for empirically in the actual analysis of the study. Similarly, key co-variates that are thought to be influential on

ring incidence (i.e., coverage, average rainfall, distance from roads) could not be simulated realistically without a more complex, spatially-explicit transmission model.

Despite its limitations, the strategy demonstrates a relatively simple and efficient approach to integrating dynamic modeling of a cholera outbreak with study simulation to guide the design of a prospective observational study that we intend to implement. The approach can be used to provide power estimates for evaluations of similar highly targeted interventions for epidemic-prone diseases delivered rapidly to high-risk communities during an outbreak.

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Technical Appendix for *Simulation for power estimation for an observational study of a cholera outbreak intervention*

1. Model fitting

The plot of standardized residuals versus fitted values was skewed left, showing some independence of the residuals from the fitted value and unequal variance. The random effect for the delay to detection of the index case, did not appear to substantially improve on the fit of the GLMM on the GLM, as the marginal R-squared (R^2_m=0.12, which represents the variance of fixed effects) was similar to the conditional R-squared (R^2_c=0.13, which represents the variance of fixed and random effects). This may have resulted from the simulated delay to detection of the index case failing to capture a realistic gradient in surveillance system sensitivity. Accordingly, little variance among the random effect levels was shown in the plot of fitted random effect values versus residuals. The GLMM and GLM (without random effects) produced similar effect sizes and variance.

2. Sensitivity analyses

Power estimates are shown in Table A and sensitivity analyses are visualized in Figures A—D.

				Number of rings					
R₀	**D**	**Duration**	**Coverage**	**50**	**75**	**80**	**100**	**125**	**150**
2	1.5	1	80%	52.4	71.7	73.7	80.6	88.7	94.7
2	1	1	80%	57.3	77.1	81.2	85.8	92.7	96.2
1.5	1.5	1	80%	33.6	37.4	49.5	49.7	58.3	62.8
2	1.5	2	80%	44.4	60.4	60.5	69.5	78.7	84.7
2	1.5	1	50%	52.9	64.2	68.9	77.5	85.9	92.4
2	1.5	1	60%	51.3	64.6	70.6	76.8	85.3	92.3
2	1.5	1	75%	53.6	68.0	72.8	79.1	84.7	92.1

Table A. Power estimates from main simulations and sensitivity analyses. Shading indicates the variable that was changed (grey), and where power estimates were farthest from the 80% target (≤69%, in orange), close to the target (≥70 to 79%, in light green), and at or above the target (≥80%, in dark green).

Fig A: power estimates using a duration of implementation of two days

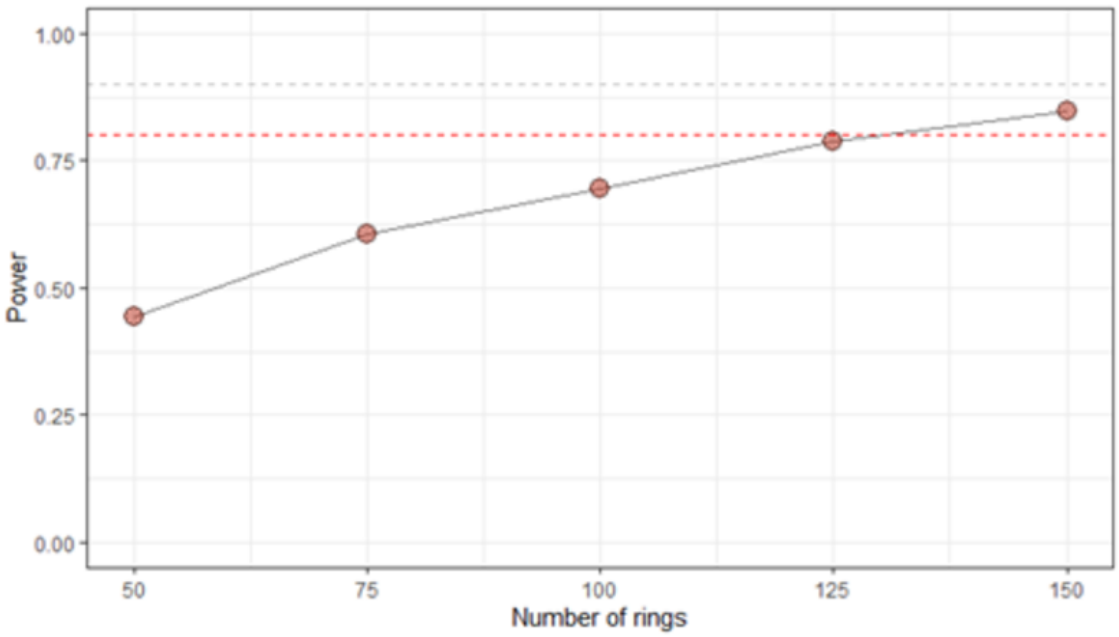


Fig B: power estimates using a population coverage of 50%

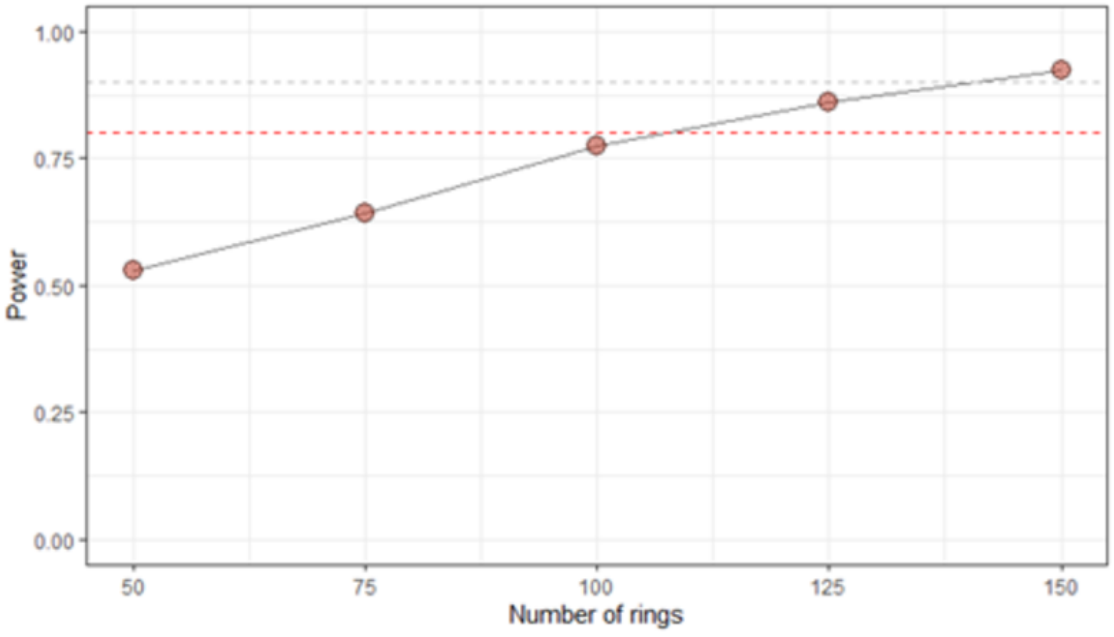


Fig C: power estimates using a population coverage of 60%

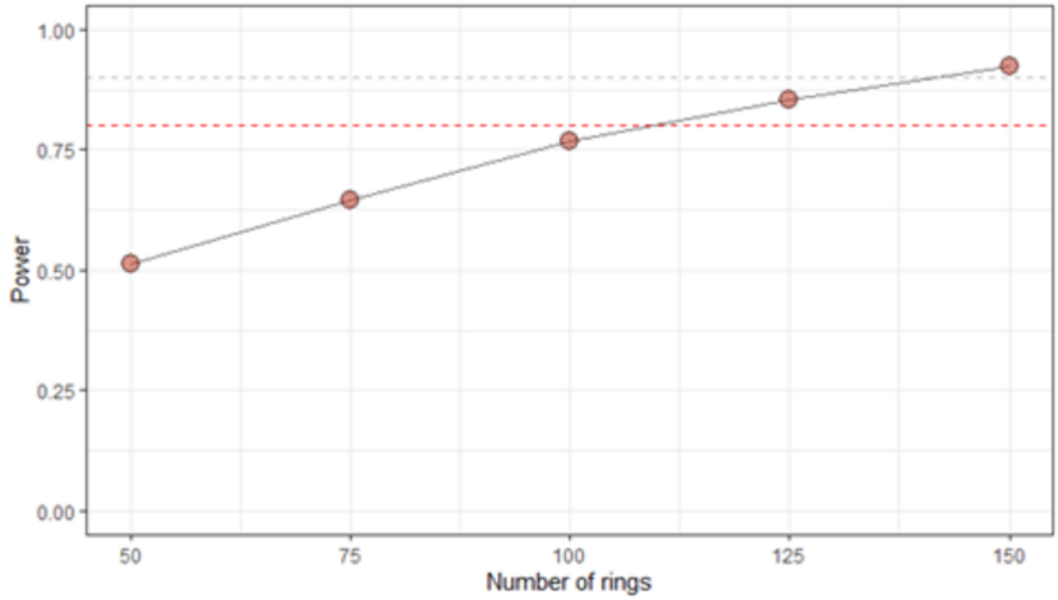
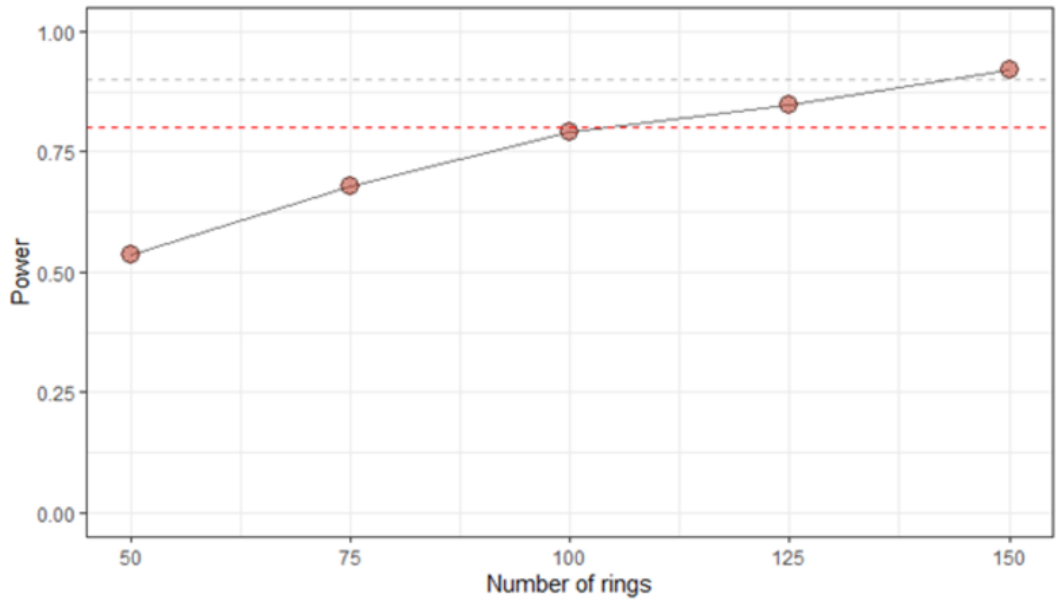


Fig D: power estimates using a population coverage of 75%



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Thesis Title	Case-area targeted intervention for the control of cholera epidemics in crises: from spatial mathematical modelling to field evaluation		
Primary Supervisor	Prof. Francesco Checchi		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BMJ Open		
When was the work published?	Published online: July 6, 2022		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived of the study, devised the methodology, drafted the paper, and led the revisions of the paper.

SECTION E

Student Signature	[redacted]
Date	September 18, 2023

Supervisor Signature	[redacted]
Date	18 September 2023

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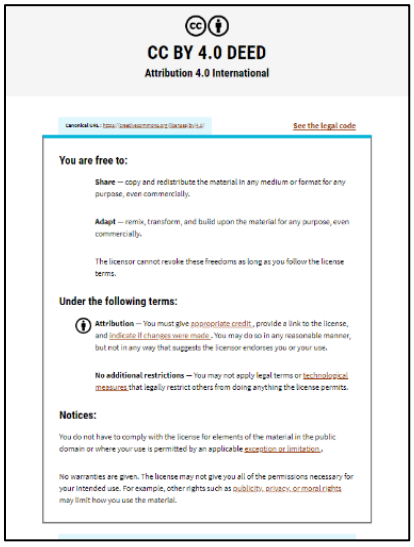

Appendix E: The Effectiveness of case-area targeted interventions including vaccination on the control of epidemic cholera: protocol for a prospective observational study (non-thesis article)

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

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Abstract

Introduction: Cholera outbreaks in fragile settings are prone to rapid expansion. Case-area targeted interventions (CATI) 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 (e.g., water, sanitation, and hygiene interventions, vaccination, and antibiotic chemoprophylaxis) to households in a 100—250 meter '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 upon 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 using meetings and policy briefs, to the scientific community using journal articles and the network of the Global Task Force for Cholera Control, and to communities via community meetings.

Strengths and limitations of this study

This is the first effectiveness study of case-area targeted interventions (CATI) that includes oral cholera vaccination during a cholera outbreak.

The prospective observational study design will provide rigorous measurement of exposures and outcomes whereas a randomized 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 sub-studies 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 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 (e.g., in Democratic Republic of the Congo (DRC), Haiti), transmission has ceased (e.g., in South Sudan), and in some settings, transmission has remained high (e.g., 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 health care 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 fecal contamination of drinking water.[12] Another strategy, case-area targeted intervention (CATI), involves the early detection of primary outbreak cases and delivery of a rapid response to households in a 100—250 meter ‘ring’ around the case’s household to halt or substantially reduce transmission.[13 14] To increase the capacity to differentiate cholera from other diarrhea, 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 (i.e., point-of-use water treatment, hygiene promotion with soap distribution, and antibiotic chemoprophylaxis) and longer-term (i.e., 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 emphasizing hand-washing with soap, and antibiotic chemoprophylaxis adapted to household delivery shows promise for the rapid reduction of localized 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 43–98).[17-20] A high-risk spatiotemporal zone of 100—250 meters 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-meter 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—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 (i.e., 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 randomized trial, would require randomizing 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, randomization would not be logistically-feasible during the acute phase of an emergency response.[37 38] To improve upon the drawbacks of prior observational studies of CATI, we propose (a) prospective data collection of exposures and outcomes based on a scenario where CATI is administered using (b) a standardized intervention package which represents a standardized exposure (i.e. a uniform intervention package and ring-radius), and (c) 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

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 upon 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 have 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 two days (i.e., the upper limit of cholera's median incubation period [1-2 days]).[40]

In addition to the main study on effectiveness, three sub-studies will be undertaken:

Household coverage sub-study: 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.

Household transmission sub-study: 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.

Antimicrobial resistance (AMR) sub-study: The potential for increasing AMR using azithromycin is greater than for doxycycline (see Supplementary Information 1 for the rationale underlying this approach). If doxycycline is used, only routine AMR monitoring in V. 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.

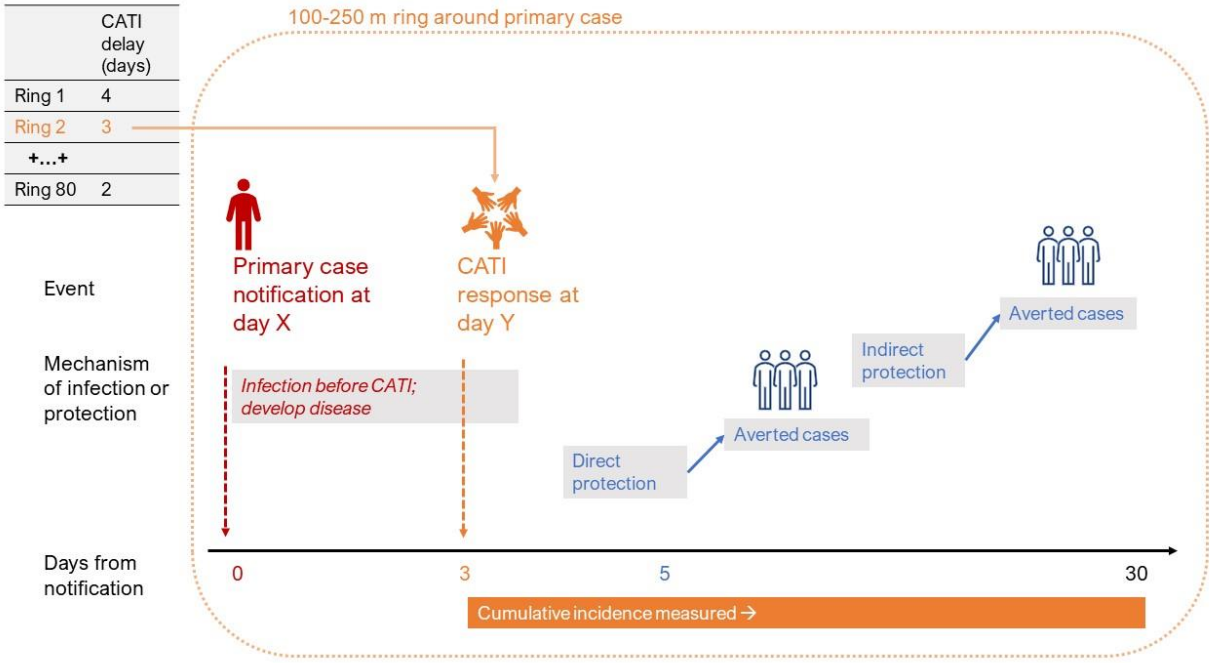

Figure 1. Infection, CATI response, and measurement in a study ring, inspired by [36]. This figure describes the study design, events and interventions, mechanisms of infection and infection prevention, and measurements. In a set of rings [table in top left corner], a given ring has a first delay for 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 to 30 days post-implementation will contribute to the cumulative incidence. The cumulative incidence across rings is compared between rings as a function of delay to response.

Aims and objectives

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

The secondary objectives are:

To evaluate the effectiveness of CATI in reducing the cumulative incidence of deaths in the rings ("main study")

To estimate the coverage of individual components of CATI (household coverage sub-study)

To evaluate the effectiveness of CATI in reducing the intra-household transmission (household transmission sub-study)

If chemoprophylaxis is included in the CATI package, to describe the presence or changes of AMR in *V. cholerae* and/or indicator *Enterobacteriae* (AMR sub-study)

To describe the overall spatiotemporal transmission patterns of the outbreak.

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 (e.g., Ituri, Nord Kivu, Sud Kivu, Tanganyika, Haut Lomami, Haut Katanga) and cholera-free areas where outbreaks have recently appeared (e.g., Kasai, Sankuru).[43 44] MSF has prepared to implement CATI where it has sufficient capacity for a robust response (i.e., 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 WASH strategy ("quadrillage")

to increase water supply and quality and hygiene promotion in a 500-metre 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 pre-positioned in health facilities for rapid verification of alerts. [46] CATI will be implemented in rings of 100—250 meters (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 signaled by a single suspected case testing positive by enriched RDT. The RDT result will be confirmed by culture or polymerase chain reaction (PCR). The target is to implement CATI within a maximum 5 to 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.

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] [47] [48]	Hygiene kit that includes: [12] Jerrycan (10—20 L) for water collection and storage Point of use water treatment products (e.g., chlorine/Aquatabs, flocculant if water has high turbidity) Soap Handwashing device (10 L bucket with tap) The kit will contain consumables sufficient for one month's use.

Antibiotic chemoprophylaxis to prevent or clear infection among household members and direct neighbours of cases (loses effect within two days due to its biological half-life); [13 49-51]	Single-dose, oral doxycycline delivered to members of primary case household and directly adjacent households. Adults (≥15 years): doxycycline, 300 mg, p.o. Children (1-12 years): doxycycline, 4 mg/kg, p.o. 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 52]	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.

Table 1. Intervention package for CATI 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).[53 54] 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 (i.e., 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 modeling results. The power was estimated for a range of sample sizes of rings (i.e., 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 to 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.

Study procedures

Recruitment

A schedule of the implementation and data collection is shown in Table 1. Upon 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 meter ring around the case-household, which is automatically visualized and can be adjusted 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 sub-studies, an information note will be read to the household contacts (household and AMR sub-studies) and head of household (household coverage sub-study) 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.

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).

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/neighborhood								
Community leader approval for intervention/study								
GIS delineation of ring								
Enumeration of ring								
CATI delivered in ring								
Stool sample collection (sub studies only)								
Coverage survey conducted								
Data analysis and reporting								

Table 1. Schedule of study interventions and data collection activities

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 (CHW) will be trained to use a community case definition to detect and immediately refer suspected cases to health facilities.[55] 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 hospitalization, 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 (CHIRPS) dataset).[56-58] In addition, 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 sub-study

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 (e.g. chlorine tablets, soap, containers), observations of their placement as a proxy for uptake (e.g. soap 1-metre away from a kitchen and latrine) and individual uptake (vaccination coverage).[12 27 59 60] Drinking water will be tested for free residual chlorine concentration using a pool tester and for turbidity using a turbidity tube.[61] Absent households will be visited twice during the day, and if still absent, replaced with another randomly-sampled household.

Household transmission and AMR sub-studies

The sub-studies 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 and colleagues (2014).[62] 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 sub-study will only be conducted if azithromycin is used in the CATI interventions (see Supplementary 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 5 adjacent households that received chemoprophylaxis will be included. From each of the 6 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 sub-study 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 to 6 hours at ambient temperature before RDT testing.[15 16] RDTs used will be Crystal VC™, Arkray Healthcare Pvt Ltd., Surat, India and/or SD Bioline, Standard Diagnostics Inc., 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—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.[63 64] 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.[65] The system aims to link primary cases, ring linelists, testing results, and sub-study 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 Limited) 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 and colleagues.[32] That is, every ring that receives CATI will be categorized 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).[66] It will include fixed effect terms for the exposure variable (i.e., delay to CATI as a continuous variable) and potential confounder variables (i.e., 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.

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, $\boldsymbol{time}$ (delay to CATI implementation), $\boldsymbol{dist}$ (distance to nearest health facility), $\boldsymbol{pop\_dens}$ (population density), $\boldsymbol{cov}$ (proportion of households who received CATI), and $\boldsymbol{rain}$ (average daily rainfall); $\boldsymbol{[\![effect]\!]\_ring}$ is the ring-specific random effect (deviation in cumulative incidence for a given ring), as an additional source of variance; ∈ is the error that is assumed to be normally distributed with standard deviation, $\boldsymbol{\sigma}$.

Given the absence of the randomization of rings to the intervention, the differences in the outcome may reflect 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.[67] 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, 2019)[32], distance to site, population density, and prior OCV coverage (see Data Collection

section above for a full set of confounders).[68] The generalized propensity score can be calculated by linear regression with the delay to response as the independent variable and the confounders as the covariates.[69] Rings will be grouped into a set of ≥5 strata. Balance between confounders among strata will be checked (e.g. standardized 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.[70] 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 to a reference value, of observing cases in a spatio-temporal window compared to a situation where the co-occurrence of cases is independent in space and time (using varying space-time windows from 15—250 meters from primary cases and 1-7 days).[21 71 72] 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 to 7)

For the household coverage sub-study (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 generalized linear model with a logarithmic link function. For the household transmission sub-study (Objective 4), the incidence of infection (asymptomatic and symptomatic) and 95% CIs will be calculated. A multivariate logistic regression using generalized estimating equations (GEE) of

predictors (e.g., 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 sub-study (Objective 5), the change in prevalence of carriers of azithromycin-resistant *Enterobacteriaceae* will be estimated for days 0, 7, and 30.[73 74] Chi-squared 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 71] Direct and indirect costs will be analyzed and pro-rated for the intervention period to derive cost-efficiency estimates (Objective 7).[75]

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.[76] 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.[77-79] 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.[80] These challenges can be countered, to some extent, through pre-consultation 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 to 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.[81]

Evaluating a complex intervention with multiple interacting components will be demanding. A holistic approach to understanding the pathway to impact through interrogation of multiple sub-studies (e.g. importance of household versus 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 stigmatization of primary cases and their households.[82] 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 (e.g., 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 organizations 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.

Multiple ethics committees have approved the study protocol. The ethics review boards of MSF and LSHTM have approved the generic protocol (MSF Protocol n° 2074, LSHTM Protocol n° 22976), a DRC-specific version of the protocol (MSF Protocol n° 2074a, LSHTM Protocol n° 22976–1). The DRC-specific protocol was approved by the MOH's ethics review board (Comité National d'Éthique de la Santé, Protocol n° 249) and administrative approval was granted by the PNECHOL-MD and the Programme Élargi de Vaccination (PEV/EPI, Extended Programme of Immunization). 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 neighborhood leaders. Verbal informed consent for the primary case data, household and AMR sub-studies and household coverage sub-study 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 (a) the potential for the population in remote cholera-affected areas to have limited literacy and the compounded problem of finding a literate witnesses, (b) the collection of this data and stool samples are not considered to be invasive procedures, and (c) 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.

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AUTHORS CONTRIBUTIONS

RR, FF, FL, FC, WJE, NP, IC, EG, ML, ASA, PG, JPO, 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 PWO, 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 paper. 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.

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SUPPLEMENT 1: Rationale underlying the AMR monitoring strategy

The GTFCC recommends that any studies of antibiotic chemoprophylaxis for cholera requires evidence that considers the emergence of antibiotic resistance.[1] Doxycycline has been frequently used for seasonal (mass) malaria chemoprophylaxis in Africa, and resulting increased levels of resistance among parasites have not been documented in current studies at clinically-relevant levels.[2] Doxycycline's impact on extended-spectrum beta-lactamases (ESBL) producing *Enterobacteriaceae* is considered negligible as compared to azithromycin. For mass chemoprophylaxis with azithromycin for trachoma and prevention of child mortality, transient increases in AMR among *Enterobacteriaceae* were detected.[3 4]. Therefore, if antibiotic chemoprophylaxis with azithromycin is used in CATI, a nested cohort study of AMR will be undertaken. A description of presence of AMR at baseline and post-administration (in *Enterobacteriae*) will be performed among persons receiving antibiotics in a subset of rings. In addition, if doxycycline or azithromycin are used, routine systematic AMR monitoring in *V. cholerae* isolates will be undertaken.[5] Given concerns of rapidly-increasing resistance specific to ciprofloxacin, we do not recommend its use for selective chemoprophylaxis.[1 6]

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1. Global Task Force on Cholera Control (Case Management Working Group). Interim Technical Note: Use of antibiotics for the treatment and control of cholera Geneva, Switzerland: WHO,; 2018 [Available from: http://www.who.int/cholera/task_force/use-of-antibiotics-for-the-treatment-of-cholera.pdf?ua=1.

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3. Keenan JD, Arzika AM, Maliki R, et al. Longer-Term Assessment of Azithromycin for Reducing Childhood Mortality in Africa. *N Engl J Med* 2019;380(23):2207-14. doi: 10.1056/NEJMoa1817213

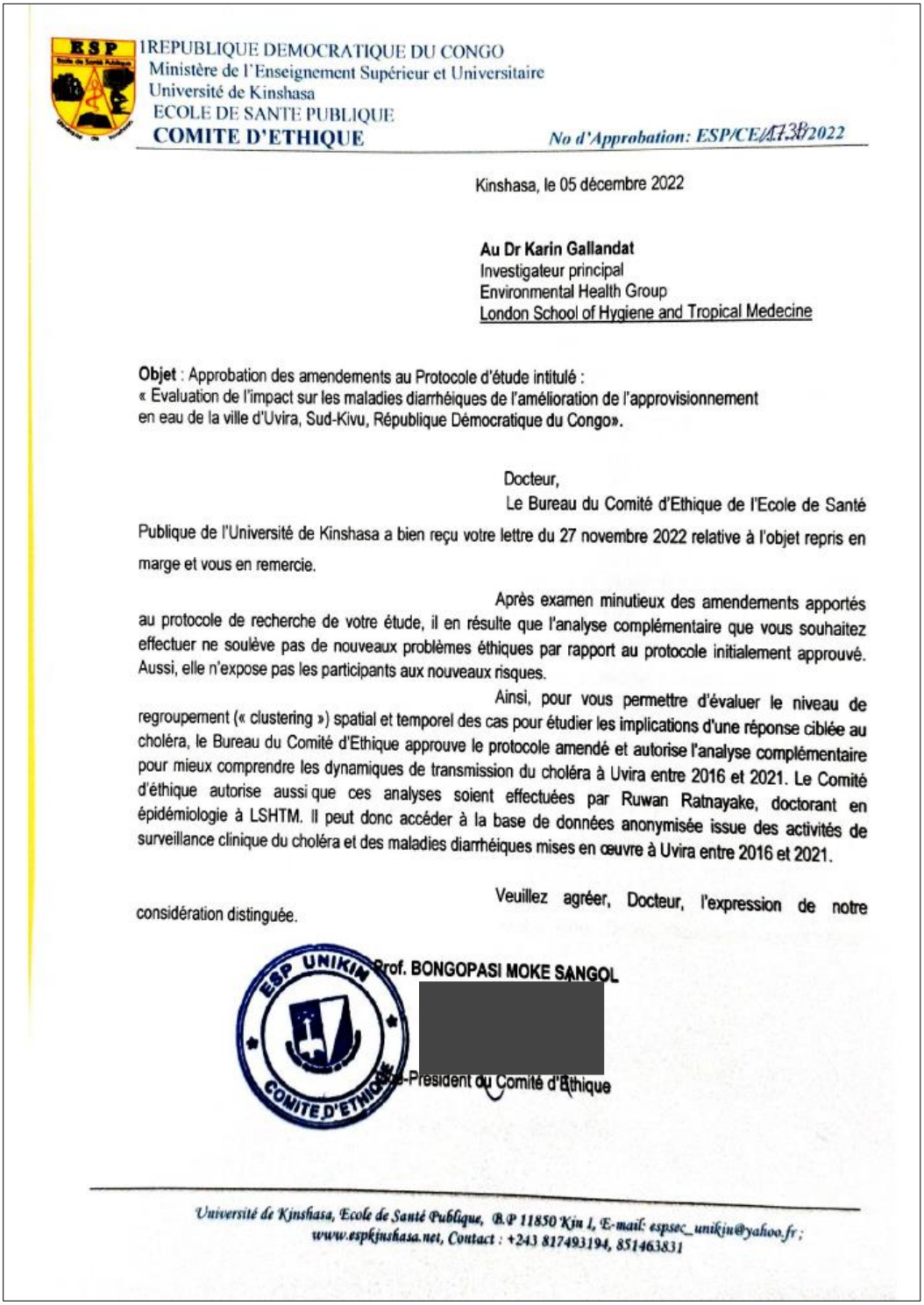
4. Doan T, Arzika AM, Hinterwirth A, et al. Macrolide Resistance in MORDOR I - A Cluster-Randomized Trial in Niger. *N Engl J Med* 2019;380(23):2271-73. doi: 10.1056/NEJMc1901535

5. Global Task Force for Cholera Control. Antimicrobial Susceptibility Testing for Treatment and Control of Cholera 2021 [Available from: https://www.gtfcc.org/wp-content/uploads/2021/04/gtfcc-job-aid-antimicrobial-susceptibility-testing-for-treatment-and-control-of-cholera.pdf.

6. Mashe T, Domman D, Tarupiwa A, et al. Highly Resistant Cholera Outbreak Strain in Zimbabwe. *N Engl J Med* 2020;383(7):687-89. doi: 10.1056/NEJMc2004773 [published Online First: 2020/08/14]

APPENDIX F: ETHICS APPROVAL CERTIFICATES

F.1 Approval letter: University of Kinshasa School of Public Health



REPUBLIQUE DEMOCRATIQUE DU CONGO
Ministère de l'Enseignement Supérieur et Universitaire
Université de Kinshasa
ECOLE DE SANTE PUBLIQUE
COMITE D'ETHIQUE

No d'Approbation: ESP/CE/473/2022

Kinshasa, le 05 décembre 2022

Au Dr Karin Gallandat
Investigateur principal
Environmental Health Group
London School of Hygiene and Tropical Medecine

Objet : Approbation des amendements au Protocole d'étude intitulé :
« Evaluation de l'impact sur les maladies diarrhéiques de l'amélioration de l'approvisionnement en eau de la ville d'Uvira, Sud-Kivu, République Démocratique du Congo».

Docteur,

Le Bureau du Comité d'Ethique de l'Ecole de Santé Publique de l'Université de Kinshasa a bien reçu votre lettre du 27 novembre 2022 relative à l'objet repris en marge et vous en remercie.

Après examen minutieux des amendements apportés au protocole de recherche de votre étude, il en résulte que l'analyse complémentaire que vous souhaitez effectuer ne soulève pas de nouveaux problèmes éthiques par rapport au protocole initialement approuvé. Aussi, elle n'expose pas les participants aux nouveaux risques.

Ainsi, pour vous permettre d'évaluer le niveau de regroupement (« clustering ») spatial et temporel des cas pour étudier les implications d'une réponse ciblée au choléra, le Bureau du Comité d'Ethique approuve le protocole amendé et autorise l'analyse complémentaire pour mieux comprendre les dynamiques de transmission du choléra à Uvira entre 2016 et 2021. Le Comité d'éthique autorise aussi que ces analyses soient effectuées par Ruwan Ratnayake, doctorant en épidémiologie à LSHTM. Il peut donc accéder à la base de données anonymisée issue des activités de surveillance clinique du choléra et des maladies diarrhéiques mises en œuvre à Uvira entre 2016 et 2021.

Veuillez agréer, Docteur, l'expression de notre considération distinguée.

Prof. BONGOPASI MOKE SANGOL
[redacted]
Vice-Président du Comité d'Ethique

Université de Kinshasa, Ecole de Santé Publique, B.P 11850 Kin 1, E-mail: espsec_unikin@yahoo.fr ; www.espkinshasa.net, Contact : +243 817493194, 851463831

F.2 Approval letter: LSHTM

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www.lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Mr Oliver Cumming

LSHTM

21 December 2022

Dear Mr Oliver

Study Title: Cholera confirmation amongst patients admitted to the Cholera Treatment Centre in Uvira, DR Congo

LSHTM Ethics Ref: 10603 - 5

Thank you for your application for the above amendment to the existing ethically approved study and submitting revised documentation. The amendment application has been considered by the Observational Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above amendment to research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval for the amendment having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Other	RRatnayake_2022	04/11/2022	1
Other	Ratnayake 204_Protecting Human Subject Research Participants_2017	04/11/2022	1
Other	Addendum to the protocol_Uvira_v3.0	27/11/2022	3.0

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

Professor David Leon and Professor Clare Gilbert
Co-Chairs

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/