Highly-targeted spatiotemporal interventions against cholera epidemics, 2000-2019: a scoping review

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Key points (Panel)

1. 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.

2. 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.

3. A high-risk spatiotemporal ring of 50 to 100 metres across 7 days in urban and rural contexts, specifies an appropriate implementation radius. This is likely due to intense household transmission and shared risk factors among neighbouring households.

4. Two controlled evaluations of CATI in Haiti and Bangladesh demonstrated respectively a reduction in the size of case-clusters, and infection among household contacts, and uncontrolled evaluations in Cameroon and the Democratic Republic of Congo suggested reductions in transmission.

5. While CATI shows promise for outbreak control, it is critically-dependent on early detection capacity and requires further evaluation to evaluate the effectiveness of combinations of interventions.

Search strategy and selection criteria (Panel)

We searched the PubMed, EMBASE, and Cochrane Databases for articles published from January, 2000, to April 23, 2020, with the following terms in the title or abstract:

- ("cholera" or "*Vibrio cholerae*", or "acute watery diarrhea") and,
- ("effect" or "efficacy" or "protect") and ("antibiotic" or "antimicrobial" or "chemoprevention" or "chemoprophylaxis") or "vaccine" or ("hygiene promotion" or "health education" or "hand hygiene" or "hand washing" or "hand disinfection" or "health behaviour") or ("water purification" or "water treatment" or "chlorination" or "Aquatab" or "well chlorination" or "bucket chlorination" or "pot chlorination")* or ("spraying" or "household spraying" or "household cleaning")* or ("funeral" or "burial" or "corpse")*,ǂ or,
- ("communicable disease transmission" or "disease clustering" or "clustering" or "spatial analysis" or "spatial transmission" or "spatio-temporal analysis" or "household transmission" or "community transmission" or "neighborhood transmission" or "hotspot") or,
- ("targeted response" or, "targeted intervention" or "comprehensive targeted response" or "case-area targeted response" or "case-area targeted intervention" or "alert and response" or "rapid response" or "ring vaccination" or "community response" or "community-based response" or "community health workers" or community health volunteer)

*The requirement for effectiveness studies was removed since none were initially found; ǂDate limits were removed as no relevant articles were initially found.

Unpublished reports on case-area targeted intervention were sought by searching agency websites and contacting experts in cholera response. We checked reference lists of retrieved references. Selection was based on relevance to the objectives and publication in English or French.

SUMMARY

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 conducted a scoping review to investigate the effectiveness of interventions delivered through case-area targeted intervention (CATI), its optimal spatiotemporal scale, and its effectiveness in reducing transmission. Fifty-three 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 could extend the duration of protection within the radius of households. Current evidence supports a high-risk spatiotemporal zone of 100-meters around case-households, for 7 days. Two evaluations separately demonstrated reductions in household transmission when targeting case-households, and in size and duration of case-clusters when targeting radii. While CATI shows promise for outbreak control, it is critically-dependent on early detection capacity and requires prospective evaluation of intervention packages.

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INTRODUCTION

In Africa and the Middle East, 126 million people live in cholera hotspots where outbreaks recur.[1,2] From 2017 to 2018, the largest epidemics (range, 16,000 to 1.3 million reported cases) occurred during humanitarian crises in Yemen, Democratic Republic of Congo (DRC), 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, population displacement and overcrowding, and compromised immunity due to malnutrition.[5-8] This results 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 of several days to two 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 to environment-to-human transmission were 45·4% (Haiti) and 82·7% (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 (GTFCC) proposed a strategy which emphasized the use of rapid response teams (RRT) 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, geographical scale) are not well-studied. We conducted 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 via person-to-person and environmentally-mediated sources. Second, we investigated the spatiotemporal dimensions of transmission to outline CATI's appropriate spatial scale and timing. Third, we evaluated CATI's feasibility and effectiveness during epidemics.

METHODS

The review followed the Preferred Reporting Items for Systematic Review and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines.[16]

Search strategy and selection criteria

Separate searches were conducted for each objective. For objective 1 (interventions), meta-analyses, systematic reviews, and studies of the impact of health and water, sanitation, and hygiene (WASH) interventions which primarily aim to reduce transmission at the household or community-level were retrieved (Table 1). For objective 2 (spatiotemporal risk), studies providing estimates of spatiotemporal scales of transmission were found. For objective 3 (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, and/or population coverage measured through a household survey or administrative data. Studies published in English or French between January, 2000 and April 24, 2020 were included.

Table 1. Health and WASH interventions to reduce *V. 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 *Often delivered through hygiene kits which may include chlorine tablets, soap, bleach for disinfection, and/or hygiene promotion materials.	Hygiene kit distribution
Health	Antibiotic chemoprophylaxis of household contacts Oral cholera vaccination	Supportive care Isolation and hospitalization Antibiotic treatment of mildly- and moderately-dehydrated cases

Information sources

The PubMed, EMBASE, and the Cochrane Review Library databases were searched (search strings are listed in appendix p 1-3). Unpublished reports on CATI were sought using searches of agency websites and by e-mailing 40 experts in cholera response (appendix p 4). Ratnayake conducted the literature searches and screening.

Data abstraction

For objective 1, RR (and uncertainty intervals) 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/or community level was documented. For objective 2, spatial (in meters) and temporal dimensions (in days) and RR (and uncertainty intervals) were extracted. For objective 3, operational data on resources, procedures, and costs were extracted (see list in appendix p 5). For evaluations, study objectives, design, sample size, RR or odds ratios (OR, and uncertainty intervals), and coverage indicators were extracted. The quality of evaluations was assessed using a Cochrane Collaboration Risk of Bias tool (e.g., selection bias, confounding, spillover and contamination, incomplete outcomes, and selective reporting) (appendix p 9).[17]

Conceptual framework

We developed a conceptual framework to integrate the findings into a pathway for rapidly reducing transmission within the ring. We integrated evidence on the optimal spatiotemporal

window and positioning of interventions at the primary case-household(s), adjacent households and ring according to the speed and magnitude of biological effect, and the logistical burden.

Role of the funding source

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

RESULTS

Across searches, 3,601 records were retrieved. After de-duplication and screening titles for relevance, 2,698 and 56 records remained, respectively. Screening by abstract yielded 41 articles. After reviewing reference lists and reports sent from experts, 12 studies were added (9 articles from reference lists, 2 abstracts, and one UNICEF report). In total, 53 articles met inclusion criteria for objective 1 (n=28)[18-45], objective 2 (n=10)[46-55], and objective 3 (n=15)[56-70] (appendix p 6-8).

Interventions to rapidly limit transmission

We summarized the potential for interventions to rapidly limit transmission, their estimated effectiveness, and potential delivery approaches through CATI (Table 2).

Table 2. Theoretical effects on transmission of CATI interventions

Intervention description, objectives, and potential delivery approach through CATI	Theoretical effect (host)
Antibiotic chemoprophylaxis (ACP) ACP acts to rapidly clear *V. cholerae* among infected persons or protect against infection among uninfected persons. 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 persons.[21,61,63] ACP has been delivered as single-dose doxycycline. The GTFCC only recommends selective ACP for closed populations at high risk of infection **(e.g. 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)
Oral cholera vaccination (OCV) Two killed oral cholera vaccines (kOCV), specific to O1 and O139 *V. cholerae*, are available from the global OCV stockpile (Shanchol and Euvichol). 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 organizations.[28]	Reduce susceptibility (uninfected host)
Point of use water treatment in household (POUWT) delivered to the household POUWT, in the form of disinfectant (e.g., 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 minutes.[40] Delivery to ring households may avoid recontamination of water in the household by soiled hands.[40] POUWT may 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, for example 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 and/or 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. While it lacks evidence for reducing contamination or reducing transmission, it 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. It encourages behaviour change to facilitate handwashing, use of safe water and safe food handling measures, and excreta disposal practices. Intensive hygiene promotion at case-households can be undertaken by a hygiene promoter once or repeatedly over a short time period. It is optimally facilitated by providing persons with access to treated water, safe storage, and soap to facilitate actions.[60] Mass messaging in the community can be undertaken 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 persons are disinfected with chlorine to prevent leakage of infectious fluids.[45] Additional measures should be undertaken to promote safe food handling and hand-washing during funeral gatherings.	Facilitate reduction in susceptibility through safe corpse management and food handling (uninfected host)

Effectiveness and potential delivery through CATI

We summarized estimates of effect sizes, delay to onset of effects, and duration of effects for interventions (Table S1, appendix p 10). For ACP, a 2011 meta-analysis of different antibiotics (tetracycline, doxycycline, ciprofloxacin, 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 diarrhea (68%, 95% CI 29—87) (Grandesso, unpublished).[21] The effectiveness of ACP in preventing symptoms among infected persons has been estimated as 96% (95% CI 70—99) with a 2·74 day (95% CI 3·1—2·4) mean reduction in shedding duration.[18-20,57,75,76] ACP's effects are short-lived. Doxycycline's half-life is estimated as 20 hours and a single-dose of azithromycin can maintain a concentration adequate to eliminate *V. cholerae* for two days.[18,77,78] *V. cholerae*'s antibiotic resistance patterns change frequently. Circulating strains from recent epidemics in DRC, Haiti, Nepal, Tanzania, Yemen, and Zambia have shown susceptibility (doxycycline[62,79,80], azithromycin[79], tetracyclines[80,81]), fluctuating resistance (ciprofloxacin[80,82,83], cotrimoxazole[80,82], ampicillin[81,82]), and complete resistance (nalidixic acid[81-84]) to common antibiotics. Doxycycline resistance was not detected among cholera cases when ACP was used in Cameroon (2004) and Haiti (2015-7).[61,63,66] While no updated trial using a particular antibiotic class is available, meta-analysed evidence across classes suggests that ACP, for which several antibiotics remain sensitive, 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 (kOCV) 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] Twelve-month effectiveness is similar for single-dose (69%, 95% CI 15—65) and two-dose (83%, 95% CI 70—91) regimens, but neither show adequate protection for children under five years.[24,26,27,31,33] High single-dose effectiveness at two-months were found during outbreaks among an immunologically-naïve population in Lusaka, Zambia (89%, 95% CI 43—98) and, among a population exposed to cholera a year prior in Juba, South Sudan (87%, 95% CI 70—100; includes indirect effects) where a single dose may have acted as a booster after exposure.[24,25,30] Peak vibriocidal antibody response occurs 7-11 days post-

administration.[24,85] While single-dose kOCV may prevent transmission minimally during the first week, it could offer longer protection during subsequent generations of transmission in the ring as compared to other interventions. Shanchol is approved to be kept out of the cold chain for up to 14 days without exceeding 40°C, allowing staff to pack more vaccine to cover more persons per day (Euvichol is expected to be approved soon).[73,86,87]

Concerns are commonly raised about the equitable distribution of limited vaccines, feasibility of campaigns during humanitarian crises, and concerns of offsetting WASH activities, as demonstrated by delays in use 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 initiated a one-dose reactive campaign within two 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—24 days) and from arrival to the start of campaign was 15 days (range, -2—87 days).[90] To support CATI's rapid response, these timelines emphasize 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 diarrhea, the effectiveness of POUWT and source water treatment in preventing diarrhea was estimated as 26% (95% CI 15—35) and 11% (95% CI -90—58), respectively (while noting the likely attenuation of uptake outside of an outbreak).[35] Use of POUWT for cholera was highly-variable (range, 7—87%) in DRC, Haiti, Kenya, Nepal, South Sudan, and Zimbabwe, with prior familiarity with products and hygiene promotion by community health workers (CHW) influencing uptake.[40] Water treatment at collection sources may prevent re-contamination during transport. To maintain protection of treated water in the household, the use of narrow-neck containers is optimal.[40] A randomized controlled trial (RCT) of narrow-neck container without POUWT showed inconclusive protection against diarrhea of 21% (-0.03—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—0·8).[37]

Hygiene promotion of hand-washing and safe food handling is considered a critical 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 cholera-affected populations 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 of an exploratory study found that spraying chlorine solution on household surfaces (e.g. dirt walls) until visibly wets lead to a rapid reduction of *V. cholerae* 30 minutes post-spraying, which was sometimes followed by re-contamination (Gallandat, unpublished).[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]

While WASH interventions for cholera are under-researched, there is substantial knowledge about improving rapid uptake using simple interventions that can be rapidly deployed, improving preparedness, and facilitating delivery through 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 summarized studies that evaluated the risk of infection among persons exposed to suspected cholera cases within spatiotemporal (or spatial-only) windows (e.g., within 25-metres of the primary case household, 3 days after onset), compared to any other person in the population outside this window (Table S2, appendix, p 11).[46-55]

Spatial-only studies demonstrated increased risk extending to ≤150-metres in Kolkata and 500-metres in Matlab.[47] In urban Kalemie, DRC 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 20-metres (RR>20, commensurate with the household and its immediately-surrounding area) to a threshold of 220-metres and 330-metres, respectively.[49] A re-analysis of data from an OCV

cluster RCT in Kolkata, India, limited to maximum 55-metre radii around index cases, found a gradient of elevated risk during 7 days up to a threshold of 50-metres (RR 2·5, 95% CI 1·7—3·8) and the highest risk within 25-metres (RR 4·8, 95% CI 2·8—8·8) of the primary case.[46] The elevated risk decreased after 7 days and 100-metres 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 50-metres, found a gradient of elevated risk up to 400-metres, 6 days after a primary case visited a health facility (RR 1·5, 95% CI 1—2·1).[51] High risk existed up to 50-metres from 3 days (RR 35, 95% 22·5—54·6) to 6 days (RR 28·2, 95% CI 16·6-48).[51] This suggests a spatiotemporal window extending to 7 days and a 50 meters around the primary case.[51]

Shared risk factors and behaviors among neighboring households may underpin the risk presented by the spatiotemporal windows. In Dhaka, type of water source, distance to water source, intermittent water supply, sharing a latrine, and soap availability were clustered among case-households and neighboring households, with clustering of water sources extending to 400-metres.[50] Prospective studies in Dhaka, Bangladesh estimated a high risk of household transmission, via cross-contaminated water or food.[52-54] Infection through household transmission has been measured as 2-4 fold higher than through community sources.[52] In another study, 49% of household contacts developed diarrhea and 21% were culture-positive during a 21-day study period.[54] A meta-analysis also showed a 3-fold 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 (2010-1 and 2013-7), Bangladesh (Dhaka), South Sudan (Juba), Nepal (Kathmandu Valley), Yemen, and DRC (Kinshasa) (Table 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 two weeks of detection, CATI provided early detection of cholera-related events to inform rapid response.[69] This was followed by an intensive program where case-households and their 50-100-metre 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 RRTs.[67] In Yemen, to direct resources 10-months into a large national epidemic, WASH and health interventions were organized by RRTs to deliver CATI.[65] In Juba, CATI was used at the end of a mass vaccination campaign to reduce transmission around sporadic cases.[64]

Trigger events

Triggering occurred after cases sought care for diarrhea at health facilities. In Douala and Kinshasa, suspect cases were exhaustively responded to.[61,63,70] CATIs in Juba, Kathmandu, and Dhaka were launched for cases testing positive by rapid diagnostic test (RDT) or culture (Nepal).[60,64,67] In Haiti and Yemen, case-clusters with above-threshold levels of suspect 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 urban Douala and Kinshasa, adjacent households were considered at high risk given population density, and therefore ACP with WASH was prioritized 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]

Table 3. Implementation of CATI 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-[65]	Kinshasa, DRC, 2017-2018[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 (months)	Jan-Aug 2004 (8m)	Nov 2010-11 (12m)	Jun 2013-Nov 2014 (17m)	Aug 2015 (1m)	Jun-Nov 2016 (6m)	Jul 2013-2017 (48m)	Oct 2016-present	Nov 2017-Nov 2018
Size (cases)	8,005	519,690	Not reported	1,818	169	177,709	>1 million	1,712
Epidemic phase	Early	Early	Not applicable (RCT)	Tail of epidemic	Early	Midway	Midway	Early
Delay (weeks)	Within 1 week	~2 weeks	Not applicable (RCT)	~1 (post-OCV campaign)	0	Not applicable	Not applicable	Within 1 week
Intended timing (days)	Same or following day	Within 24h of alert	Within 36h of alert	NR	Within 48h of case presentation	Within 48h of case presentation	Within 24h of alert	Within 1 week
Cases targeted	Suspected cases from CTUs	Alerts of increased caseload/deaths	Culture+ cases only	RDT+ (enriched) cases only	Culture+ cases only	Alerts of increased caseloads/deaths	Alerts of increased caseloads/deaths	Suspected cases from CTUs in most affected health zones
Ring size targeted	Directly-adjacent households	Neighborhood related to alert	Case household only	Neighborhood around a case household	100m 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	**Case-HH:** ▪ ACP ▪ HHS **Adjacent-HHs:** ▪ ACP ▪ HP ▪ WCT (wells) **Guardians in hospital:** ▪ ACP	EBS	▪ HP (HH visits daily for 1-week, handwashing station) ▪ Safe storage ▪ POUWT (3m)	▪ OCV, 1-dose ▪ Hygiene kit including POUWT, soap, HP material ▪ HP	**Case-HH:** ▪ POUWT ▪ Storage ▪ HP **Community:** ▪ WCT ▪ HP (CHW)	**Case-HH:** ▪ POUWT ▪ Storage ▪ HHS ▪ HP ▪ ACP **Community:** ▪ Case-finding ▪ WCT ▪ HP ▪ Hygiene kit	**Case-HH:** ▪ POUWT ▪ Storage ▪ HHS ▪ HP **Community:** ▪ Case-finding ▪ WCT ▪ HP ▪ Hygiene kit	**Case-HH:** ▪ POUWT ▪ Storage ▪ HHS ▪ HP ▪ ACP **Community:** ▪ Case-finding ▪ Storage ▪ HP ▪ Hygiene kit ▪ Bladders
Team composition	Health promoter for HH visit	Health and WASH staff, logistician	Health promotor for HH visit	Health, WASH, vaccination staff	Epidemiologist/clinician, GIS staff, CHWs	Team lead, WASH staff, health promoter, nurse (for ACP)	Personnel from Water Ministry	Supervisor, health promoters, sprayers
Cost	Not reported	Not reported	45.50 USD (per household for 7 days) 227.50 USD (per case averted)	Not reported	Not reported	583,338 USD (monthly program cost) 10,234 USD (monthly team cost)	1.5-1.8 M USD (monthly program cost) 2,400-3,000 USD (monthly team cost)	Not reported

NR=not reported, HH=household, ACP=antibiotic chemoprophylaxis, POUWT=point of use water treatment, HHS=household spraying, HP=hygiene promotion using trained personnel, WCT=water collection treatment, OCV=oral cholera vaccination, "early" = first two weeks of onset.

Spatiotemporal windows

In Haiti, Kathmandu, and Yemen, radii of 50-100 meters were aimed for (estimated as 10-20 households in Haiti).[65-67] Directly-adjacent households in Douala and the neighborhoods of cases in Juba defined ring sizes.[61,63,64] The intended timing of initial household visit after case-presentation ranged from 24 hours (Douala, Haiti, Yemen) to 48 hours (Haiti, Kathmandu).[61-63,65,67] Most reports did not describe the duration CATI activities. In Kinshasa, a large 500-metre 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, coverage of alerts ranged from 54% of culture-confirmed cases in Kathmandu, 82% of RDT+ cases in Juba, health zones covering 78% of the caseload in Kinshasa, to >99% of suspected cases in Douala.[61,63,64,67,70] Among large epidemics, coverage of alerts varied (39% of small-scale outbreaks in Haiti; 83% of confirmed and 32% of suspected cases in Yemen).[65,66] In Kathmandu, a survey 6-8 months post-implementation estimated that 30% of catchment households received messaging.[67] In Juba, 51% (95% CI 42—60) of surveyed respondents reported vaccination through CATI.[64] OCV was not restricted to persons living in the neighborhood, and surveys may have biased toward lower coverage.

Mean delays from case-presentation to implementation of 3·9 days (range, 1—9) occurred in Kathmandu, with 2 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 organization of OCV.[64,91] Delays also reflected challenges in reaching communities. In Haiti, 75% of home visits were completed within the first 24 hours of case presentation and 85% within 48 hours in 2018.[65] Given extremely-restricted humanitarian access in Yemen, a relatively high proportion of home visits were made within 48 hours (46%) and 72 hours (69%).[65]

Costing

Costing was rarely reported. Yemen and Haiti documented costs of US$3000 USD and US$10234 per team per month.[65] In Dhaka, the cost per-household was US$45.50 and cost per-case averted was US$227.50.[60]

Table 4: Evaluations of CATI

With effect estimates						
Location, year, intervention	**Cases (or households) reached**	**Proportion responded to**	**Mean delay (detection to household visit)**	**Coverage (of ring)**	**Study design and limitations**	**Estimated impact**
Centre Department, Haiti, 2015-2017[62] HH: POUWT, storage, ACP, HHS, HP Community: CWT, HP	▪ 10,428 suspected cases ▪ 456 outbreaks	39% of outbreaks responded to	▪ >7 days (17%, 30/176) ▪ 3-7 days (14·2%, 25/176) ▪ 2 days (17·6%, 31/176) ▪ ≤1 day (51·1% 90/176)	NR	▪ Quasi-experimental study with groups stratified by response promptness ▪ Outcomes for 61% of the outbreaks not responded to not discussed ▪ Use of ACP could not be recorded and are unmeasured	▪ A first complete prompt CATI (≤1 day after outbreak onset) reduced accumulated cases by 74% (95% CI 58—84), and outbreak duration by 64% (95% CI 42—78), as compared to a first complete delayed CATI (>7 days after outbreak onset) ▪ The temporal response was consistent for smaller delays
Dhaka, Bangladesh, 2013 [59,60] HH-only: intensive HP, hand-washing station, POUWT, storage	Enrolled 84 culture-confirmed cases and 84 controls (RCT)	100% of enrolled 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%) though did not differ by arm	Among HH contacts in intervention arm: ▪ Reduction in symptomatic infections (OR=0, 95% CI 0—0·62) (no symptomatic infections were found among intervention contacts) ▪ Reduction in culture-confirmed cases (OR=0·5, 95% CI 0·21—1·18) ▪ No *Cholerae* in drinking water (OR=0, 95% CI 0—1·08) 6-12 months post-intervention: ▪ Increase in handwashing with soap at a key time during structured observation (OR 4·71, 95% CI 2·61—8·49) ▪ Reduction in households in the very high-risk category for stored drinking water (OR 0·38, 95% CI: 0·15—0·96)
Douala, Cameroon, 2004[61,63] HH: ACP, HHS; Community: ACP, WCT	▪ 5,020 suspected cases ▪ 161,725 contacts	99% of suspected cases	NR	NR	▪ Post-hoc analysis ▪ Observational study ▪ No comparison group	▪ Proportion of contacts in among all suspected cases decreased from 30% in first month to <1% in last month ▪ All stool samples remained susceptible to antimicrobials
Kinshasa, DRC, 2017-2018[70] HH: POUWT, storage, ACP, HHS, HP	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% and 83% 4 weeks and 8 weeks after the peak of the outbreak, respectively

Community: WCT, HP, storage, bladders						
Effects not measured						
Location, year, intervention	**Cases (or households) reached**	**Proportion responded to**	**Mean delay (detection to household visit)**	**Coverage (of ring)**	**Study design and limitations**	
Juba, South Sudan, 2015[64] Community: OCV, POUWT, soap, HP	14 RDT+ suspected cases (or 17 identified)	82% of RDT+ suspected cases	3·4 days (range 1-6 days)	51% (95% CI 41·7—60·3) vaccination coverage for sites	▪ Post-hoc analysis ▪ Denominator for coverage indicator unclear given CATI was delivered in community on a volunteer basis	
Kathmandu Valley, Nepal, 2016[67] HH: POUWT, safe storage, intensive HP; Community: WCT, HP	169 culture-confirmed cases	54% of RDT+ suspected cases	3·9 days (range 1-9 days); 1·7 days after culture result	30·2% (no CI reported increased knowledge of cholera among CATI-targeted communities	▪ Post-hoc analysis of delay between detection and implementation ▪ Coverage surveys conducted 1 year after CATI, increasing recall bias	
Yemen, 2017-[65] HH: POUWT, safe storage, ACP inconsistently, HHS, HP; Community: WCT, HP	NR	83% of confirmed cases; 32% of suspected cases	In 2018, 3% of suspected case responded to within 24h; 43% within 24-48h; 23% within 48-72h.	NR	▪ Post-hoc only analysis ▪ No impact measured ▪ Surveillance data used is difficult to interpret as it includes a high proportion of non-cholera diarrhea	
NR=not reported, HH=household, ACP=antibiotic chemoprophylaxis, POUWT=point of use water treatment, HHS=household spraying, HP=hygiene promotion using trained personnel, WCT=water collection treatment, OCV=oral cholera vaccination						

Impact on the reduction of transmission

The potential impact 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-metres 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% (IQR 7% to 35%), 2% (IQR −11% to 8%).[57]

Four evaluations with effect estimates were conducted in Douala, Kinshasa, Dhaka, and Haiti (2015-2017)[60-63,70]; two designs[60,62] were controlled (Table 4). In Douala, where ACP and well chlorination were used, a post-hoc analysis of surveillance data without a comparison group demonstrated a decrease in secondary attack rates among contacts of suspected cases from 30% during the first month to <1% in the last month of the epidemic.[61,63] This 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% and 83%, 4-weeks and 8-weeks after the outbreak peak.[70] While an uncontrolled study, the staggered implementation across sites over 4 weeks demonstrated similar reductions across outbreaks.

An RCT in Dhaka in which households of RDT+ and culture-confirmed cases were randomized to an intensive hygiene intervention, demonstrated a reduction in incidence of symptomatic infection [OR 0, 95% CI 0—0·62; no events in intervention arm] and a non-significant reduction in asymptomatic and symptomatic cases [OR 0·5, 95% CI 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, hand-washing 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 program would be realistic for outbreak response.

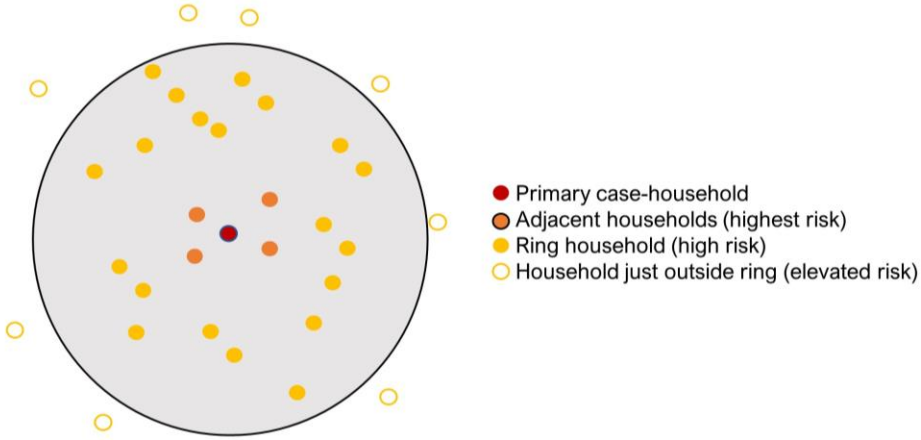
In Centre Department, Haiti, CATI's impact on epidemic duration and caseload was evaluated using a quasi-experimental design with groups stratified by the promptness of response.[62,66] 238 (53%) of 452 outbreaks (with ≥1 positive culture or severely-dehydrated case)

were prioritized for response based on severity (POUWT, hygiene promotion, hygiene kits, ACP [non-systematically], community water treatment). Compared to CATI ≥7 days after outbreak onset, CATI <7 days after outbreak onset reduced attack rates by 76% (95% CI 59—86), and outbreak duration by 61% (95% CI 41—75). A relationship with the timeliness of response suggested that CATI was effective. Reductions in attack rates (63% [95% CI 24—82] versus 39% [95% CI -38—73]) and duration (74% [95% CI 43-88] versus 58% [95% CI 11—80]) increased significantly if ACP was used, demonstrating the intervention-specific effect of ACP. However, the inconsistency in use of ACP and other interventions potentially reduced overall impact. The program may not have been operationally efficient; most CATI responses were triggered by syndromically-diagnosed cases, which resulted in 3,887 CATI responses, of which 16% were conducted during an outbreak.

Conceptual framework

Each intervention was placed along a timeline which starts with the identification of the primary case(s), and follows the spatiotemporal radius of 100-metres over 7 days (Figure 1). The highest risk of transmission occurs among household members, followed by adjacent households, and households in the ring. In red, fast-acting interventions within the case-household reduce transmission (e.g., ACP, POUWT facilitated with safe storage, soap, and hygiene promotion). ACP for adjacent households (in orange) promptly reduces risk, considering that case-households are small units wherein few persons are exposed to the primary case, and risk of exposure may be high in the community.[92] POUWT, storage, 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, while 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 1. Conceptual framework for CATI delivered within a 100-meter radius and 7 days (Figure modified from Roskosky et al, 2019)



Primary case-household	Adjacent households	Ring households
▪ ACP ▪ POUWT with safe storage and soap ▪ Intensive HP (1-day)	▪ ACP ▪ POUWT with safe storage and soap ▪ Community HP	▪ Single-dose OCV for ring households ▪ HP facilitated by CHW follow-up
Higher logistical burden and resources needed		
Intensive HP (2+ days)	Hygiene kit (POUWT, safe storage, soap) for adjacent households	Hygiene kit delivered with OCV (POUWT, safe storage, soap) and facilitated by CHW follow-up

HH=household, ACP=antibiotic chemoprophylaxis, POUWT=point of use water treatment, HP=hygiene promotion using community health workers (CHW), OCV=oral cholera vaccination (single-dose). Red pertains to the primary case-household, orange to the immediately-adjacent households, and yellow to the households in the 100-metre ring.

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 metres over 7 days in urban and rural contexts, likely related to intense household transmission and shared risk factors among households. This specifies an implementation radius which has been used in Haiti, Nepal, and Yemen. CATI's ability to address >80% of epidemic alerts suggests feasibility across settings.[61,63-65] While additional rigorous evaluation is needed, two controlled studies in Bangladesh and Haiti respectively showed a reduction in household transmission when targeting case-households, and in duration and size of case-clusters when targeting radii.[60,62] This reflects the findings of mathematical models where CATI[57] using OCV or similar OCV-targeting strategies[93] demonstrated reduced outbreak size and duration.

CATI's effectiveness in reducing local transmission depends on the ability of combined interventions to impact both transmission routes with a rapid onset of protection and an adequate radius of implementation. Rapidly-acting interventions like ACP and household WASH are a priority. ACP can protect uninfected and infected hosts, and was demonstrated to increase the impact of a WASH-focused CATI.[62] Hand-washing and hygienic behaviours underlie household transmission.[38,40] Single-dose OCV should be strongly considered for CATI, as it is the only intervention to incite extended protection, within a week, and is as effective as two doses over a two month to one year period.[24,27] On the horizon, a live attenuated OCV has demonstrated a 24-hour onset to protection in an infant rabbit model.[94] While the current evidence supports ring sizes of approximately 100-m, practical evaluation of the feasibility of implementation should be undertaken, particularly in urban contexts. The potential benefits of conducting 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 one-week period.

The rapid detection of case-clusters through sensitive surveillance and diagnostic specificity using enriched RDTs to select for cholera are an essential foundation for CATI which requires simultaneous field support.[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.[64,67] National preparedness and control plans should proactively integrate epidemiological scenarios for use of CATI to organize support for surveillance and interventions. Global preparedness policy requires consideration of CATI's particular use of interventions. The global OCV stockpile does not address provision for CATI, though vaccine supply is increasing and disbursing small batches to countries before the cholera season should be attainable.[29,72] The GTFCC 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 scale-up. 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$1M).[32,65] However, these costs reflect national, UNICEF-supported responses, which may exceed costs of smaller outbreaks and for national or non-governmental organizations. Maintaining implementation during a growing epidemic is challenging and resource-intensive. Few CATI experiences used CHW networks or oral rehydration points (ORP) whereas they provide existing infrastructure to engage communities and continue the delivery of CATI interventions, particularly where humanitarian access is poor.[67,96]

Limitations and future research

CATI strategies have focused on household WASH, with minimal integration of ACP and OCV. Prospective studies should evaluate the impact of packages of interventions which combine immediate impacts of interventions with longer-term protection by OCV. Given the logistical and ethical difficulties in conducting RCTs during epidemics, quasi-experimental designs with mathematical modelling and costing should be considered.[57,97] Low-level transmission during the dry season may be able to contained by CATI, 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 antibiotic resistance, similar to current investigations of ciprofloxacin use for ACP during meningococcal meningitis epidemics.[92,100] While increases in macrolide resistance occurred during a large trial of

azithromycin to reduce child mortality in Niger, the comparatively small volumes distributed for CATI may carry less resistance risk.[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, hygiene promotion) and extended-protection interventions in the ring (OCV); and resources to mount implementation in 50-100-metre 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.[34,80,84,103] 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 review. RR conducted the literature search, data extraction, and data synthesis, 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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