Global Task Force on Cholera Control (GTFCC) Working Group on Case Management

Research update: recently published work and work in progress

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Acronyms and abbreviations

AWD	acute watery diarrhoea
CATI	case area targeted interventions
CCP	critical care pathway
CTC	cholera treatment centre
CTU	cholera treatment unit
DRC	Democratic Republic of Congo
FIH	first in-human
GTFCC	Global Task Force on Cholera Control
icddr,b	International Centre for Diarrhoeal Disease Research, Bangladesh
IV	intravenous
JHU	Johns Hopkins University
LSHTM	London School of Hygiene and Tropical Medicine
MSF	Médécins Sans Frontières
NCCP	national cholera control plan
NGO	non-governmental organization
OCV	oral cholera vaccine
ORS	oral rehydration salts
RRT	rapid response team
SAM	severe acute malnutrition
SOP	standard operating procedure
WASH	water, sanitation and hygiene
WHO	World Health Organization

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Introduction

The primary objective of the case management pillar of cholera prevention and control is rapid access to high quality treatment for patients. While current treatment protocols save lives, there is little evidence of best practice for certain specific groups, including children with severe acute malnutrition (SAM) and cholera.

Alongside treatment of patients with severe disease, the health sector is examining its role in preventive and curative activities in communities during outbreaks. What is the role and how can the sector best collaborate with other sectors to reduce the burden of cases and deaths?

During this session, colleagues presented recent work: an assessment of treatment of children with SAM and cholera; a literature review, retrospective case study and a planned field study of the health aspects of targeted community approaches during cholera outbreaks; and innovative work on the potential use of phages to prevent cholera as part of targeted community approaches.

The below are summaries of the presentations given and represent the point of view of the presenters. The presentations were chosen to provide information on a range of subjects being carried out by GTFCC partners, without being endorsed by the GTFCC. All presentations are available on the GTFCC website (www.gtfcc.org).

Randomised trial showing that rapid rehydration of severely malnourished children with dehydrating diarrhoea is as safe and effective as slow rehydration

Md. Nur Haque Alam, Emirates Scientist, NCSD, International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)

The WHO recommendation for correcting dehydration in severely malnourished children, especially those with severe acute malnutrition (SAM), includes oral rehydration and—where necessary—intravenous (IV) rehydration administered very slowly due to concerns about overhydration and/or heart failure. This recommendation is based on experience rather than evidence, and it was hypothesised that rapid rehydration might help achieve faster improvement in renal function and correction of acidosis, reduce vomiting, and subsequently reduce requirements for unscheduled IV. A 2009 uncontrolled study demonstrated that rapid IV rehydration (over four to six hours) of severely malnourished children with dehydrating cholera was safe and effective.

To confirm this finding, this open randomised controlled study compared rapid rehydration with slow rehydration in the management of dehydrating diarrhoea in severely malnourished children at the icddr,b hospital in Dhaka, Bangladesh. The study included children aged 6 months to 5 years with both severe acute and chronic malnutrition (weight for age < -3 Z score or weight for length/height <-3 z score or with bipedal edema.

The objectives were to evaluate the effectiveness and safety of rapid rehydration compared to slow rehydration in severely malnourished children with watery diarrhoea and severe dehydration, and to assess renal function at admission and again after 24 hours.

After enrolment, the children were randomized to receive either rapid rehydration 100 ml/kg over six hours , or slow rehydration following the WHO-recommended critical care pathway (CCP) over a period of 12 hours with 15 ml/kg over one hour, repeated if signs of improvement appear after the first hour followed by rice-ORS via nasogastric tube (5-10 ml/kg) In both groups ongoing stool losses were replaced with rice and ORS (oral rehydration salts) orally or through a naso-gastric tube @ 5-10 ml/kg after each watery stool according to the volume of stool. Other treatments—including supplementary food vitamins, minerals and antibiotic treatments—were similar in both groups.

The children's bodyweights were measured on admission and every six hours and their intakes and outputs were measured every six hours until discharge. After admission, blood samples were taken to determine haematocrit, total protein, serum albumin, glucose, and serum electrolytes and creatinine and were repeated after 24 hours of therapy. Stool samples were tested for microscopy and culture for *Shigella spp*, *Salmonella spp* and *Vibrio cholerae*.

Four outcomes were analysed: 1) unscheduled IV therapy or ORS failure if severe rehydration reappeared following initial IV therapy, 2) treatment failure was defined as not achieving complete rehydration after initial therapy, 3) Fluid overload and 4) heart failure.

There was no statistical difference between the two groups in the proportion of children requiring unscheduled IV therapy or achieving rehydration success. None of the children included in the study presented signs of fluid overload during the study.

The results of this study demonstrated that both rapid and slow rehydration of severely malnourished children, including those with SAM, who are suffering from severe dehydration due to acute diarrhoea are both effective and safe. Rapid rehydration is simple and saves time for rehydration.

Rapid rehydration may therefore be an option for children with severe dehydration due to cholera and severe malnutrition.

Case area targeted interventions (CATIs) for cholera outbreaks in humanitarian settings

***Paul Spiegel**, Johns Hopkins Center for Humanitarian Health*

Humanitarian settings and fragile states are especially vulnerable to major cholera outbreaks. Case area targeted interventions (CATIs) target households with cholera cases and their immediate neighbours to provide water, sanitation and hygiene (WASH) and/or health interventions via home visits. It is hypothesised that CATIs may be an important containment strategy in cholera outbreaks in resource-constrained environments, but their impact remains poorly characterized, as do the optimal protocols for timing and implementation.

This study set out to summarize available evidence on CATI effectiveness in cholera epidemics via a systematic review of peer-reviewed literature, with the aim of informing responses in future outbreaks; to characterize and define the composition, scope, activities and mechanisms of rapid response teams (RRT) and CATIs, distinguishing the two and conducting a landscape analysis through a grey literature review; and to document retrospective evidence of how CATI approaches in cholera outbreaks have been implemented using case studies in Democratic Republic of Congo (DRC), Haiti, Yemen and Zimbabwe, with a focus on health and surveillance components and their interaction with WASH.

The systematic search of peer-reviewed literature was done using PubMed and EMBASE. Grey literature included searches of google, ReliefWeb and publications of technical and coordinating bodies, implementing organizations and donor organizations. The retrospective information came from standardized questionnaires completed by and key informant interviews with government ministries responsible for WASH and health, UN bodies, and non-governmental organizations (NGOs).

Across the countries included in the review there was great variability in the composition, intervention components and activation mechanisms of both CATI and RRT activities, but all the interventions included WASH. Few details were available about health activities.

Between 2009-2019 11 peer-reviewed articles reported on CATIs in seven countries. Six of these included WASH interventions only, while five were integrated (i.e., included health and WASH interventions). No CATIs delivered health interventions alone. CATIs differed between countries in terms of the types of households targeted and both the scale and intensity of interventions and had moderate coverage (26-65%) such that not all outbreaks were responded to and targeted households may not all have been reached. Implementation barriers in several settings included coordination with alert and surveillance systems and coordination of timely reporting of confirmed cases.

If high levels of coverage cannot be attained, CATIs may be less effective than anticipated. Overall CATI effectiveness in cholera case reduction was reported in only two of the 11 studies. A randomized control trial in Bangladesh found a modest but statistically significant reduction of 5% in symptomatic infections among intervention recipients versus controls (George et al., 2016), while in Haiti integrated CATIs, which included the distribution of antibiotics, significantly reduced number of new cases and outbreak duration; but the overall evidence for effectiveness of CATI, as implemented in real-world

settings and assessed in terms of cholera case reduction is limited.

The retrospective study found striking variability in WASH, health and surveillance interventions among the four countries. Many protocols and standard operating procedures (SOPs) are not written down, and the choice of the number of surrounding households around a case in which to intervene is variable according to context—ultimately depending on the CATI team leader. Sharing of line-lists with WASH actors is problematic at the start of many responses but does tend to improve over time. Ultimately, the integration of WASH, health and surveillance is not uniform, and should be considered and acted on before outbreaks. Donors can play a key role in this.

In conclusion, there is high heterogeneity in reporting of information in all studies (peer-reviewed, grey literature and retrospective). Documentation is strongest on WASH components, with limited information on health and surveillance and even less on integration. Health interventions in CATIs are less well understood by governments, partners and donors than WASH interventions, and coordination mechanisms and systems for implementation among governments and partners need more clarity. Improved SOPs that provide options to adapt to context and field capacity (feasibility) are required as more data become available.

Modelling studies suggest that spatially targeted interventions such as CATIs may be more efficient mechanisms for reducing cholera transmission than mass interventions, but the review identified little compelling real-world evidence of their effectiveness. Delays in case confirmation, reporting, or CATI delivery could substantially decrease the effectiveness of the CATI approach, even if the interventions delivered by CATIs are themselves effective. Additional evidence of CATIs' delivery and effectiveness is critical to a more successful implementation of the GTFCC cholera reduction strategy.

Data in press from Ratnayake et al suggest that there is limited understanding of mechanisms by which CATI interventions work: antibiotics and single dose OCV have different impacts on reducing transmission rapidly and then sustaining it in addition to household WASH interventions. There is also unexplored potential for better use of enriched RDTs for targeting CATIs to true cases (versus acute watery diarrhoea/AWD). A spatio-temporal zone of 100 metres for seven days around primary case households is, however, justified by evidence. While CATIs with good detection capacity are justified in early and late phases of outbreaks or after mass vaccination campaigns, their capacity to contain transmission will be limited during large-scale epidemics.

Case-area targeted intervention for cholera outbreaks: protocol for an analytical observational study

***Ruwan Ratnayake**, London School of Hygiene and Tropical Medicine (LSHTM)*

This presentation outlined a study protocol developed to evaluate MSF's use of CATIs, defined as using OCV, antibiotics and household WASH delivered to a ring of 100-250 metres around the first identified case households in a new geographic area early in a cholera outbreak to contain or substantially slow transmission.

There have been no prospective evaluations of CATI. A retrospective analysis of data from 2015-17 in Haiti showed a reduction in the size and duration of small-scale outbreaks when CATI was used (with WASH and antibiotic chemoprophylaxis), and a randomized trial of culture-confirmed cases in Bangladesh in 2013 showed a reduction in intra-household transmission when household contacts were targeted with hygiene promotion and WASH versus standard messaging. Mathematical modelling also shows that CATIs can reduce epidemic duration when applied near the epidemic peak.

The aim of this protocol is to evaluate the effectiveness of CATI in rapid containment of case-clusters

at the start of a cholera outbreak by evaluating the effectiveness of CATI in reducing incidence of enriched RDT-positive cholera within targeted rings. The secondary objectives are to examine population-based coverage; spatiotemporal transmission patterns of the outbreak; effectiveness in the reduction of household transmission; antimicrobial resistance (AMR) related to chemoprophylaxis where used; and the resources and costs required. Guiding principles include the use of key transmission-reducing interventions: household WASH and antibiotic chemoprophylaxis for rapid impact and one-dose vaccination and household WASH for delayed but sustained protection. The study design is appropriate for an outbreak (e.g. with no explicit control group) and will use real-time data collection to evaluate a CATI strategy prospectively. Finally, understanding the pathway to impact requires assessing the coverage of CATI and its impact on household transmission and ring transmission.

The CATI intervention should be targeted only to enriched RDT-positive cases which are most likely to be true cases. In an analytical observational approach, immediately-implemented CATIs will be compared with naturally delayed CATIs on the incidence of enriched RDT-positive cholera, with the study units being the CATI rings (100-250 meters around the primary case-household(s) or—depending on context—entire rural settlements.

Regression analysis will be used to model the incidence of enriched RDT-positive cholera by the delay to intervention, with delay groups serving as an internal control. The primary outcomes will be the incidence of enriched RDT-positive cholera within the rings after the implementation of CATI and the reduction in spatiotemporal clustering of cases throughout the outbreak.

Data collection will be done at three levels: patient-level line-list data from cholera treatment facilities; geospatial data to link primary case households and households in the ring; and ring-level data to collect information on implementation within the ring.

Pathway to impact will be examined through sub-studies including a cohort study of household transmission reduction among household contacts; coverage surveys to measure coverage and reported uptake of CATI interventions at a time point after implementation in the ring; and systematic monitoring of antimicrobial resistance among *V. cholerae* isolates (with potential description of AMR at baseline and post-administration in commensal *E. coli* using rectal samples).

Implementation will be done by a number of Médécins Sans Frontières (MSF) teams in different operational centres and will include the use of oral cholera vaccine (OCV), preventive antibiotics, and household WASH, with evaluation using a research protocol developed by Epicentre and Dr Ratnayake with direct involvement from teams in the MSF centres. Potential sites have been identified in Cameroon, DRC and Zimbabwe, and the generic protocol will be adapted to local situations once the sites are chosen. The proposed timeline for this study is late 2020 through to 2021.

Johns Hopkins University (JHU) is planning a similar study with three implementing partners (Action Contre la Faim, Solidarités International, and Medair). The are incorporating flexibility into the research protocol to be able to adapt to partners' CATI implementation guidelines and country contexts, which are yet to be determined. JHU will not change partners' CATI interventions, but will provide technical and financial support related to the research. WASH, health, and surveillance interventions will be selected by partners and/or subject to national cholera outbreak response policy. JHU is collaborating with MSF/LSHTM to develop the protocol, ensure that results are complementary, and avoid overlaps between the study sites. The timeline is 2021-2022.

Phages for a Healthier World

***Minmin Yen**, PhagePro*

Phages are viruses that attack bacteria. Some of them have the potential to provide immediate protection against bacterial infection without contributing to antimicrobial resistance. PhagePro, a small, Boston-based biotech start-up, is seeking to take an intervention historically focussed on individual patients and develop it for use as part of a public health intervention.

Cholera phages may be most effective in the prevention of household transmission which may account for nearly 80% of secondary transmission in an outbreak. Phages may be an additional intervention to add to current approaches to protect household contacts of individuals with cholera.

The company has successfully isolated several cholera-specific phages. Three of these phages—ICP1, ICP2 and ICP3—have been combined to form a phage cocktail, PVC. PVC has been shown to be protective against cholera in rabbits, providing immediate protection specific for *V. cholerae*. The company is planning to develop PVC in pill form for ease of delivery.

PVC is still under development with further studies planned over the next 3 years. Studies to optimise the PVC, prove safety and to test efficacy are planned to be completed by the end of 2022. Manufacturing development will be carried out in parallel is set to run until 2023. It is hoped that a heat and humidity stable product will be ready for human trials in late 2023. In addition, clinical surveillance studies to generate a more up-to-date understanding of household transmission will run from late 2021 to the end of 2022.

It is envisaged that should this process be successful, WHO's future strategy for controlling cholera might incorporate phages alongside Surveillance, WASH, social mobilization, treatment and OCV. For PhagePro, success with cholera will be a platform to tackle more diseases with phage treatments, with Shigella and *E.coli* already targeted.

Closing comments

Philippe Barboza, *Leader of the GTFCC Secretariat*

There are still many challenges for the working group to tackle, including a range of practical questions that need to be answered about how to treat specific patients— children with SAM, for example. We need additional surveys, discussions, and research on whether and how to transform our treatment approaches. The research outlined here is hugely encouraging in that regard, especially as it is may contribute to producing concrete recommendations.

The work to clarify what we know of CATIs and how to improve that understanding illustrates what GTFCC can do best—multisectoral, multi-partner approaches in which different actors come together and produce combined solutions. It is extremely promising. The discussions about CATIs also clearly illustrate the need for more interaction between different working groups—laboratories, diagnostics, efficient surveillance and early detection are all needed outside research, and we have an obligation to improve and strengthen all of it. Links between WASH and OCV are another very interesting illustration of how we need to move forward collectively.

The phage presentation—while highlighting something that is clearly at a very early stage—shows how crucial it is not to stop thinking about alternative solutions that could provide answers, alternatives and solutions for, for example, biotherapy and issues around AMR. It is important in terms of research to consider what innovations we can bring to the wider picture, and not just for cholera. If cholera can blaze a path for other diseases, that would be a great achievement too.

We have a short-term priority to find the right solutions and protocols for the most efficient treatment, but we also have to learn to address outbreaks better and generate long term strategies for finding other solutions. This challenge clearly illustrates the wide scope of the field that still has to be covered by the case management working group.

Finally, on a procedural note: while webinars are not the same as face-to-face meetings, at the moment they remain necessary. We don't know what will happen next year, but we have to be prepared to continue like this. All working groups will need to reflect on this, and in the meantime carry on with regular, shorter discussions that continue to contribute to the life of the working group and push specific topics forward.