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Bachelor of Arts
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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

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Diarrhea causes 13% of deaths among children under 5 in India. A common household water treatment method to prevent diarrhea is water chlorination. A double-blind randomized controlled trial in Orissa, India saw no effect of a household water chlorination intervention on diarrhea among children under 5 during a 12 month period. However, adherence to the intervention was only observed by measurable residual free chlorine in the child's drinking water in less than one-third of the follow-up visits to intervention households. We conducted a reanalysis of the Orissa trial to identify demographic characteristics of households within the intervention arm associated with adherence and to demonstrate the effect of chlorination on under-5 diarrhea among adherent households. Adherence was classified as non-adherent, reported-only adherent for households who self-reported using the tablets but did not have measurable residual free chlorine, and confirmed adherent for households that did have measurable residual free chlorine. Education of the caregiver and living in the rural villages of Dhenkanal were associated with having confirmed adherence. Children in houses with confirmed adherence were 31% less likely to have diarrhea than children in non-adherent households (OR=0.69, 95% CI: 0.55–0.87). Our results agree with those of other open-label trials and contrast those of blinded published trials, which demonstrate no effect of treatment.

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Contents

Introduction

In 2000, government and community leaders worldwide adopted the new Millennium Development Goals for 2015 (1). One goal was to reduce childhood mortality from 9.9 million deaths among those under age 5 (2). Though progress has been made, with under-5 child mortality at 6.3 million in 2013, there is still much room for improvement (2). Interventions targeting pneumonia, diarrhea, and measles contributed to 50% of this mortality reduction, but these preventable diseases are still leading causes of death with a combined 2 million child deaths annually (2, 3). In India, diarrhea causes 13% of deaths among children under 5, approximately 300,000 deaths each year (4).

Further reducing childhood mortality linked to diarrhea is challenging because of the heterogeneity of risk factors for diarrhea. These include undernutrition, vitamin deficiencies, non-exclusive breastfeeding, poor maternal literacy, low socioeconomic conditions, and poor sanitation and hygiene conditions (4, 5). Cost-effective interventions recommended by the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) include household water treatment and safe storage (HWTS) methods (6). Water chlorination is a commonly used HWTS method because sodium dichloroisocyanurate (NaDCC) tablets and sodium hypochlorite solution are inexpensive to produce and distribute; tablets effectively inactivate bacteria, some viruses, and some protozoa (7, 8). The solution or tablets are added to water, which is agitated and then allowed to settle prior to consumption. Water chlorination interventions are often implemented in conjunction with education campaigns and safe storage interventions.

Though open-label trials have shown HWTS interventions to be effective, estimates of efficacy can vary across studies because of differences in cultural norms and conditions in the intervention setting (9). Acceptability and sustainability of HWTS interventions are tied to current sanitation practices and willingness to adopt new methods. These issues have often not been assessed as part of efficacy studies and could be unmeasured confounders in the analyses (10). Additionally, the prevalence of competing causes of diarrhea vary by setting and could differentially impact the results of studies (9). In response to limitations of these open-label studies, a randomized control trial was conducted in Orissa, India to evaluate the effect of household water chlorination on the incidence of diarrhea among children under 5 (11). In contrast to open-label trials that found an effect of household water treatment and safe storage interventions on diarrhea, this double-blind trial found no effect of water chlorination on diarrhea among children. These results are similar to those of other blinded trials that have been conducted (7, 12, 13).

The contrasting results from these blinded and open-label studies suggest the need for continued research into effects of water chlorination treatments on health (11). An important factor to consider in further analyses is that the lack of observed effects on diarrhea in blinded trials may have resulted from poor adherence to the intervention. In the Orissa trial, only half of the households randomized to the intervention arm reported that they had used the water chlorination tablets. Furthermore, only one-third of those intervention households had measurable levels of residual-free chlorine (RFC) — an objective measure of product adherence — in their children's drinking water throughout follow-up. Low adherence, evidenced by both reported and objective measures, complicates the interpretation of the Orissa trial with a standard intent-to-treat analysis (14). Quantifying the relationship between water chlorination and childhood diarrhea accounting for self-reported and confirmed product use within this blinded trial setting may strengthen the body of evidence about this HWTS method.

To address problems with inferring efficacy under conditions of low adherence, we conducted a reanalysis of the Orissa trial data to estimate chlorination tablet efficacy accounting for time-varying adherence patterns. Our primary research question was whether under-5 childhood diarrhea was lower among households with high tablet adherence, after accounting for confounding factors that might also be associated with both tablet use and diarrhea in this population. If found efficacious after controlling for non-adherence, our goal was to provide evidence for the modification of the HWTS intervention in a developing country setting to overcome adherence challenges.

Methods

Study Population

Data used in our analysis are a subset of those collected in the double-blind randomized placebo-controlled trial in Orissa, India between November 2010 and December 2011 (11). That trial included households in Bhubaneswar, the capital city of Orissa, and in rural villages of Dhenkanal. Participants who lived permanently in these areas were recruited at community meetings, and their households were eligible for the study if they included any children under the age of 5.

Figure 1 depicts the randomization of households by community after baseline assessment into the intervention and control arms. The intervention arm received free NaDCC disinfection tablets to add to their water storage containers. The control arm received placebo tablets that looked similar to the intervention tablets. Along with distributing tablets, researchers employed study staff to educate household members and engage the community through games, pictures, and posters.

In our analysis, only children living in houses in the intervention arm were considered. Though data were collected on adults, our analysis focuses on effect of the intervention on under-5 childhood diarrhea because this is of high public health importance. The households are subset by adherence, which is classified as “reported-only adherence,” “confirmed adherence,” or “non-adherence" based on both self-reports and RFC measurements. RFC was measured using the colorimetric method with the DPD1 reagent (11). Using a color comparator allowed for quantitative measurements of RFC instead of subjective observations (15). This method is considered an industry standard and better meets the American Water Works Association qualifications for disinfectant residual management than other methods (16, 17). We classified households as reported-only adherent for those follow-up visits when the household caregiver said that the drinking water was treated with the disinfection tablets and when there was no measurable presence of RFC. Households were classified as confirmed adherent for the follow-up visits when there was measurable presence of RFC, regardless of the self-reported adherence status. Households were classified as non-adherent when they neither reported tablet use nor had measurable RFC in the child's drinking water.

Outcome Assessment

In the first part of this analysis, we assessed which factors were associated with the adherence outcomes. Households were visited monthly over the course of a year from December 2010 through December 2011, with a maximum of 12 visits per household, not including the initial baseline assessment. The unit of analysis for adherence is days of observation. Because caregivers were asked to report diarrhea among children for the day of visit, the day prior to visit, and 2 days prior to visit, there were 3 possible days of observation per visit, per participant. With a total of 12 rounds of household visits during the study, this yields 36 possible days of observation per participant. The association between demographic characteristics at baseline assessments and adherence at each household visit were considered in this initial analysis.

For the primary analysis, our outcome was household diarrhea among children under 5. The WHO definition of 3 or more loose stools passed in one day was used as the case definition. At follow-up visits, caregivers were asked to recall if their children had diarrhea during the 3 days of observation. These reports of diarrhea were combined over the 3 day period, such that we classified that diarrhea had occurred if diarrhea was reported during any one of those 3 days.

Statistical Analysis

We used logistic regression models to estimate odds ratios for the association between demographic factors and adherence levels in the first analysis and between adherence and diarrhea incidence in the second analysis. In the first adherence analysis, repeated measures clustered within the same households over time were handled with generalized estimating equations (GEE) methods. Odds ratios and 95% confidence intervals based on robust standard errors were calculated to estimate the association between baseline household characteristics and either self-reported or confirmed adherence. Based on scientific judgment and *a priori* decisions, we included education of the head of household, education of the caregiver, gender of the head of household, treatment of water prior to the study, and study site as factors potentially associated with adherence. After assessing the association between each predictor and adherence separately, multivariable models were estimated by adding all predictors to 2 models with self-reported adherence and confirmed adherence as the outcomes.

In the second analysis of tablet efficacy accounting for adherence, clustering at the individual level across months of visitation was accounted for using GEEs with repeated measures for each individual. Clustering at the household level was accounted for by including predictors of household-based characteristics from our first analysis in the models. Follow-up observations of children only under the age of 5 were included in analysis. Odds ratios and 95% confidence intervals were calculated to estimate the association between adherence and having diarrhea during the observation period. As a sensitivity analysis, we built separate bivariate and multivariate models to estimate which measured confounders were influential in the primary efficacy association. All statistical analyses were conducted in SAS 9.2.

Results

Table 1 provides baseline characteristics of the intervention-arm households. The intervention group is comprised of 68.7% rural households. The heads of households are predominantly male. Though 17.4% of the heads of households are illiterate, over one-third have some secondary education. Over half of the caregivers have some secondary education. Less than half of the households treated water prior to the start of the study. Among those who did treat water, boiling was the primary method.

Each household had up to 12 follow-up visits throughout the study, with 3 days of observation per visit, including the day of follow-up, the previous day, and 2 days prior to follow-up (Figure 1). Throughout the 12 months of follow-up, there were 3,046 follow-up visits for a total of 9,138 days of observation for children with reported-only adherence, classified as children under 5 in the intervention group whose caregiver reported adherence but where RFC was not measured in the child's water. There were 4,392 follow-up visits for a total of 13,176 days of observation for children with confirmed adherence, classified as children under 5 in the intervention group who had measurable RFC in their drinking water, including observations where water chlorination tablet use was not self-reported. There were 6,898 follow-up visits for a total of 20,694 days of observation for children with no adherence, classified as children under 5 in the intervention group where the caregiver reported non-adherence and where RFC was not measured. Though both reported-only use and confirmed use increased from baseline to the end of the study period, there was a larger increase in the rate of confirmed use (Figure 2). During the last quarter from October through December, non-adherence and reported-only adherence decreased in parallel as confirmed adherence increased sharply.

Five hypothesized demographic confounders were evaluated for their association with reported-only and confirmed adherence (Table 2). For both heads of households and caregivers, primary education or higher was associated with lower odds of reported-only adherence (Head of Household: OR=0.86, 95% CI: 0.72–1.02; Caregiver: OR=0.74, 95% CI: 0.61–0.89) and with higher odds of confirmed adherence (Head of Household: OR=1.11, 95% CI: 0.95–1.31; Caregiver: OR=1.25, 95% CI: 1.05–1.48) compared to primary education or less. Households where water was treated prior to the study also had lower odds of reported-only adherence and higher odds of confirmed adherence compared to those that did not treat water prior to the study. Having a male head of household and living in Dhenkanal (the rural site) were associated with a higher odds of reported-only adherence and confirmed adherence than having a female head of household and living in Bhubaneswar (the urban site).

These measured confounders were included in the full exposure model estimating the association between adherence and incident diarrhea among children under 5 (Table 3). A model without the measured confounders was also developed. In both models, we found that any adherence, whether reported-only or confirmed, was protective against diarrhea, although we had lower standard errors and therefore less uncertainty about the confirmed adherence measure. The odds of diarrhea was lower among confirmed participants compared to non-adherent participants (OR=0.69, 95% CI: 0.55–0.87) than the odds among participants reporting only compared to non-adherent participants (OR=0.86, 95% CI: 0.66–1.12) (Figure 3).

Discussion

In this reanalysis to account for poor adherence patterns in a double-blind randomized placebo-controlled trial of water chlorination tablets to reduce the incidence of under-5 childhood diarrhea, we found that children in households with measurable quantities of RFC in their water were 31% less likely to have diarrhea than children in non-adherent households. In contrast to the intent-to-treat analysis presented in the primary report (11), we identified demographic characteristics associated with poor adherence to the chlorination intervention and adjusted for adherence measured in 2 ways to estimate the effect of chlorination on diarrhea in this population.

Though a lowered odds of diarrhea among children under 5 was observed both for children in households where adherence was only self-reported and for children in households where adherence was confirmed by measurable RFC in the drinking water, the association between confirmed adherence and diarrhea was stronger. The odds of diarrhea were 31% lower among children in households with measurable RFC in their drinking water compared to those in non-adherent households. Of the characteristics considered in association with adherence, households with some secondary education or more for the caregivers and households in the rural village of Dhenkanal had higher odds of confirmed adherence than households with less caregiver education and households in the capital city of Bhubaneswar.

Our results among the confirmed adherent population (OR=0.69, 95% CI: 0.55–0.87) differ from those in other blinded analyses (7, 12, 13) but are similar to those in open-label trials (18-26). In a meta-analysis of these open-label trials, a pooled effect estimate was calculated indicating that treating water with chlorine reduced childhood diarrhea by 29% (RR=0.71, 95% CI: 0.58–0.87) (9). The original study of our data indicating no reduction in diarrhea pointed to differences in study designs as an explanation for the differences in results between blinded and open-label trials (11). The similarity between our results and those from open-label trials suggests that blinded and open-label trial methodologies are not a sufficient explanation for observed differences in results between previous blinded and open-label trials. By stratifying intervention households by adherence, we observed a positive impact of water chlorination on reduction in childhood diarrhea in a blinded trial. For this reason, adherence should be considered as a possible explanation for the differences in results. Additionally, the original trial did not discourage households to continue using other methods of water quality improvement (11). Further analyses should consider if the reduction in childhood diarrhea is causally associated with water chlorination use or if it is confounded by other forms of water treatment.

We conducted this analysis to evaluate the role of low levels of adherence among the intervention arm on the results of the original chlorination trial (11). Though half of intervention households self-reported adherence at some time during the study, households only had measurable RFC in children's drinking water for less than one-third of days of observation. Associations between demographic characteristics like education, previous treatment of water, and location are similar to barriers identified in other HWTS research, including lack of demand for HWTS interventions and lack of information about HWTS interventions (27-30). For example, not using alternative water treatment methods prior to the study could indicate a lack of demand, which could be tied to a disbelief that diarrhea is a health problem or that unsafe drinking water is a cause of diarrhea. A potential barrier that was unmeasured in our analysis is that a dislike of the taste and odor caused by chlorination could reduce the acceptability of the intervention, as has been observed in other studies (31-33). Evaluations of other HWTS programs indicate the importance of strengthening social marketing campaigns, providing interventions free-of-charge, and creating strong partnerships between government bodies, community leaders, and the public sector as key factors to overcoming these barriers of successfully scaling an HWTS program (28, 29, 34). Though the original trial attempted to utilize these practices through an intensive education campaign, free tablets, and community engagement, a lack of efficacy and challenges to scaling up could have contributed to low levels of adherence among intervention participants (11). Though levels were low, the increase in confirmed adherence over time, specifically in conjunction with the decrease in non-confirmed adherence during the last quarter, indicates that the intervention was increasing in acceptability. This delay in uptake of the intervention, which has been observed in other trials, could be a result of the slow roll-out of the education campaign through the first quarter of the study (11, 23). Without data about the community's perception of the education campaign and community engagement, we are unable to discern which barriers to scaling up the intervention were most associated with adherence and what components of the campaign were successful in increasing adherence over time.

Limitations of this analysis included that the outcome of interest, diarrhea among children under 5, was reported by caregivers but not objectively confirmed. Though caregivers were only asked to recall episodes of diarrhea on the day of follow-up, the previous day, and 2 days prior to follow-up, there could be misclassification of the outcome as a result of recall bias or systematic misclassification if diarrhea regularly occurred outside of the days of observation. Similarly, misclassification of the exposure could occur due to self-reporting of tablet use. However, measuring the RFC in children's drinking water provides a more objective measurement of the association between confirmed adherence and self-reported diarrhea. By categorizing adherence into 3 levels, we were able to analyze diarrhea among confirmed participants, unlike in the original Orissa trial where all intervention participants were analyzed collectively (11). Another limitation with how adherence is classified is that adherence was measured at the household level, not the participant level. A child could be classified as having confirmed adherence for a follow-up visit because of measurable RFC in his drinking water, but that does not necessarily mean that he drank that water consistently. Additionally, it does not necessarily mean that the child did not drink untreated water from sources outside of the home (24). Similarly, a caregiver could self-report using the tablets, but this does not necessarily imply that the chlorinated water was consumed by the child. Though these limitations could cause misclassification of adherence and diarrhea, precautions were taken in the study design phase to limit such effects, including the short recall period and the measurement of RFC within a few hours of sample collection.

In conclusion, we found that water chlorination was associated with 31% lower odds of reported childhood diarrhea after accounting for adherence patterns of households within a double-blind randomized placebo-controlled trial testing water chlorination tablets in Orissa, India. Though both self-reported and confirmed adherence were considered, our primary outcome of interest was the confirmed adherent households who demonstrated measurable RFC in their drinking water. Overall, the association between education and adherence was concordant across both levels of adherence, where households with lower levels of education had higher odds of reported-only adherence and lower odds of confirmed adherence. Households in the rural villages of Dhenkanal were almost twice as likely to have confirmed adherence compared to urban households. In order to address both adherence and issues in scaling up interventions, the development of a comprehensive education campaign for the importance of HWST and water chlorination interventions should be prioritized and should target low education, urban settings. Our analysis also indicates that the odds of diarrhea among children under 5 were lower for participants with measurable RFC in their water compared to those who did not report adherence or have measurable RFC in their water. Thus our results support the WHO and UNICEF recommendation for using water chlorination interventions to reduce childhood diarrhea. However, our results point to the importance of understanding and addressing acceptability prior to implementing such programs. Even though our results and others demonstrate the intended outcome, increasing coverage of water chlorination tablets in populations that will have low adherence will not bring the reductions in intended health impacts necessary to meet objectives like the Millennium Development Goals (35). Our findings support that water chlorination is an effective HWTS intervention for reducing prevalence of diarrhea among children under 5 from an analytical perspective, but further research needs to be conducted to understand how successfully these interventions can be implemented.

Appendix

Table 1. Baseline characteristics of intervention households (n=1,080).

	Intervention Households	
	No.	**% intervention group**
Mean (SD) number of persons per household	5.7 (2.3)	
Education of head of household		
Illiterate	188	17.4
Literate no formal schooling	90	8.3
Some primary	160	14.8
Completed primary	146	13.5
Some secondary	400	37.0
Completed +2 y	48	4.4
Completed +3 y (university)	48	4.4
Education of caregiver		
Illiterate	136	12.6
Literate no formal schooling	68	6.3
Some primary	90	8.3
Completed primary	103	9.5
Some secondary	584	54.1
Completed +2 y	6	6.3
Completed +3 y (university)	31	2.9
Gender of head of household		
Male	1,016	94.2
Female	62	5.8
Treat water prior to study		
No	607	56.4
Yes	470	43.6
Treatment method		
Boil	331	70.3
Strain	106	22.5
Chlorine	9	1.9
Other	24	3.8
Site		
Urban	338	31.3
Rural	742	68.7

Table 2. Characteristics associated with adherence among the intervention group.

	Reported Adherence Only		Confirmed Adherence (including those who were both confirmed and reported)	
	Odds Ratio	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Education of head of household				
Primary or less	1.00	--	1.00	--
Some secondary or more	0.86	(0.72, 1.02)	1.11	(0.95, 1.31)
Education of caregiver				
Primary or less	1.00	--	1.00	--
Some secondary or more	0.74	(0.61, 0.89)	1.25	(1.05, 1.48)
Gender of head of household				
Female	1.00	--	1.00	--
Male	1.06	(0.76, 1.50)	1.10	(0.78, 1.56)
Treat water prior to study				
No	1.00	--	1.00	--
Yes	0.70	(0.59, 0.83)	1.10	(0.94, 1.30)
Site				
Urban	1.00	--	1.00	--
Rural	1.08	(0.90, 1.29)	1.90	(1.58, 2.28)

Table 3. Characteristics associated with diarrhoea among children under 5 in the intervention group.

	Reported Adherence Only		Confirmed Adherence (including those who were both confirmed and reported)	
	Odds Ratio	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Exposure Model:				
Adherence				
Non-adherent	1.00	--	1.00	--
Adherent	0.86	(0.66, 1.12)	0.69	(0.55, 0.87)
Exposure Model Controlling for Measured Confounders:				
Adherence				
Non-adherent	1.00	--	1.00	--
Adherent	0.89	(0.69, 1.16)	0.73	(0.58, 0.93)
Education of head of household				
Primary or less	1.00	--	1.00	--
Some secondary or more	0.70	(0.53, 0.93)	0.74	(0.57, 0.96)
Education of caregiver				
Primary or less	1.00	--	1.00	--
Some secondary or more	0.91	(0.70, 1.19)	0.88	(0.68, 1.15)
Gender of head of household				
Female	1.00	--	1.00	--
Male	0.97	(0.58, 1.61)	1.10	(0.66, 1.82)
Treat water prior to study		.		
No	1.00	--	1.00	--
Yes	0.94	(0.72, 1.22)	0.86	(0.67, 1.11)
Site				
Urban	1.00	--	1.00	--
Rural	0.58	(0.45, 0.75)	0.66	(0.51, 0.85)

Figure 1. Study profile for a double-blind randomized placebo-controlled trial in Orissa, India.

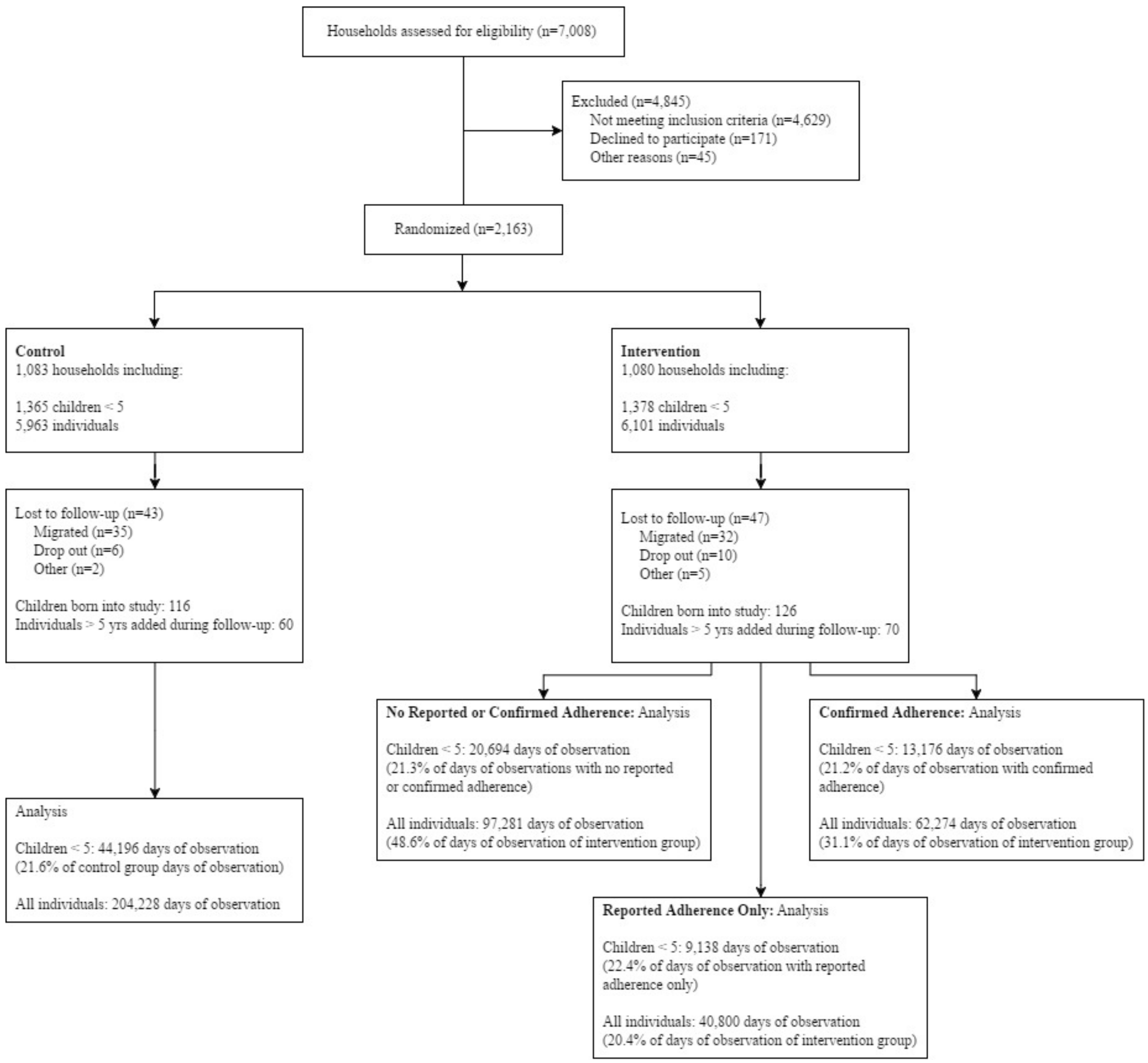
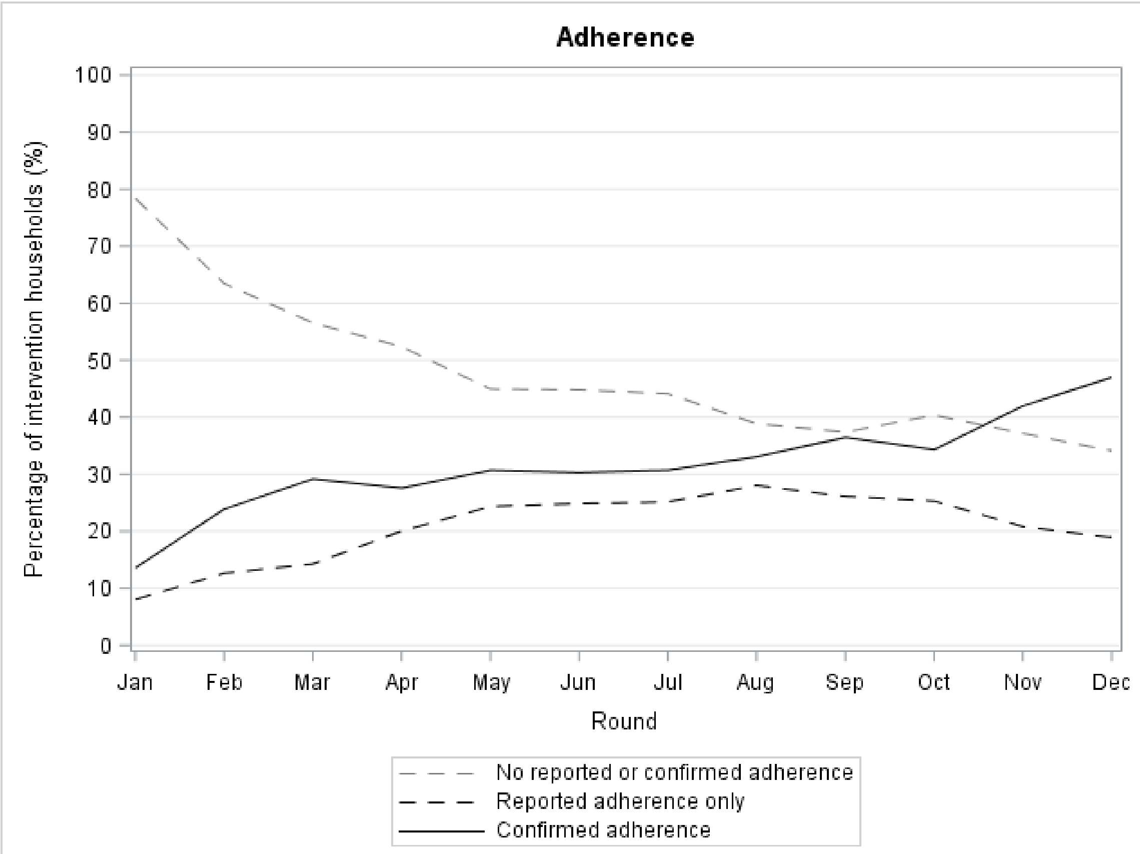


Figure 2. Adherence to water chlorination tablet use among intervention households assessed by self-reported use (reported only adherence) and presence of residual free chlorine in children's drinking water (confirmed adherence).



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