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By

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Abstract

Drinking Water Quality and Child Health in South Asia: The Role of Secondary Contamination

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Ensuring access to safe drinking water is a key strategy for reducing waterborne illness. The WHO/UNICEF Joint Monitoring Programme for Water Supply and Sanitation (JMP) differentiates between unimproved and improved sources to universally classify water access. This classification, however, is based on the type and location of the water source and does not take into account water quality; even sources classified as improved can have compromised water quality and pose a health risk from waterborne illness.

One type of improved water source in urban settings is piped drinking water on premises. However, the presence of a piped connection gives little information about the quality, quantity and frequency of water delivery. Even in settings with centralized water treatment, piped water distribution systems are vulnerable to performance deficiencies that can cause (re)contamination of treated water and plausibly lead to increased risk of gastrointestinal illness (GII) in consumers. It is well established that large system disruptions in piped water networks can cause GII outbreaks. We hypothesized that routine network problems can also contribute to background levels of waterborne illness and conducted a systematic review and meta-analysis to assess the impact of distribution system deficiencies on endemic GII. We reviewed published studies that compare direct tap water consumption to consumption of tap water re-treated at the point of use (POU) and studies of specific system deficiencies such as breach of physical or hydraulic pipe integrity and lack of disinfectant residual. In settings with network malfunction, consumers of tap versus POU-treated water had increased GII (IDR = 1.34, 1.00-1.79). The subset of non-blinded studies showed a marked association between GII and tap versus POU-treated water consumption (IDR = 1.52, 1.05-2.20); there was no association in studies that blinded participants to their POU water treatment status (IDR = 0.98, 0.90-1.08). Among studies focusing on specific network deficiencies, increased GII was associated with temporary water outages (RR = 3.26, 1.48-7.19) as well as chronic outages in intermittently operated distribution systems (OR = 1.61, 1.26-2.07). These findings suggest that tap water consumption is associated with GII in malfunctioning distribution networks. System deficiencies such as water outages increase the risk of GII, presenting a potential health risk for consumers served by piped water networks.

Additionally, intermittent delivery of piped water is a common form of water supply in low-income countries. Intermittent supply can lead to waterborne illness through contamination of water in pipelines or in household storage, use of unsafe water sources during intermittencies and limited water availability for hygiene. To assess the health impact of intermittent water delivery as a particular type of breach of hydraulic pipe integrity, we conducted a matched cohort study to assess the impact of switching from intermittent to continuous water supply in Hubli-Dharwad, India, on child diarrhea and mortality, and severe waterborne illness in tap water consumers. We used multivariate matching to match continuous supply areas to intermittent supply areas with comparable baseline characteristics in Hubli-Dharwad. We followed 3919 households with children under five over 15 months. In continuous supply areas, we observed 42% reduction in the percentage of households with at least one case of typhoid fever since the program was implemented (CIR = 0.58, 0.41-0.78) and potentially 49% reduction in the percentage of households with death of a child under the age of two (CIR = 0.51, 0.22-1.07). Consistently with these reductions, our findings also suggested reductions in seven-day prevalence of diarrhea (PR = 0.93, 0.83-1.04) blood or mucus in stool (PR = 0.78, 0.60-1.01) in children under five in continuous supply areas. These reductions were more pronounced in low-income households (diarrhea PR = 0.89, 0.76-1.04; blood/mucus PR = 0.63, 0.46-0.87). The effect of rainfall on the impact of continuous supply on child waterborne illness was inconclusive. Our findings indicate that switching from intermittent to continuous water supply reduced waterborne illness in Hubli-Dharwad.

Another type of improved water source, commonly used in rural settings, is tubewells that draw groundwater from shallow aquifers. Shallow tubewells are the primary drinking water source for the majority of rural Bangladeshis. While groundwater is often considered microbiologically safe, fecal contamination has been detected in tubewell water, typically at low concentrations at the source and at higher levels at the point of use. The magnitude of the waterborne disease burden associated with consumption of tubewell water is not well understood. We conducted a randomized controlled trial to assess whether improving the microbial quality of tubewell drinking water by household water treatment and safe storage would reduce diarrhea in children <2 y in rural Bangladesh. We randomly assigned 1800 households into one of three arms: chlorine plus safe storage, safe storage and control. We longitudinally followed households with monthly visits for one year to promote the products and collect health outcomes. Both interventions had high uptake in the study population. Safe storage, alone and in combination with chlorination, reduced heavy contamination of stored water. In the chlorine plus safe storage arm, 2% of stored water samples had *E. coli* concentrations exceeding 100 CFU/100 mL, compared to 7% in the safe storage arm and 21% in the control arm. Compared to controls, diarrhea prevalence in children <2 y was reduced by 36% in the chlorine plus safe storage arm (PR = 0.64, 0.55-0.73) and 31% in the safe storage arm (PR = 0.69, 0.60-0.80); there was no difference between the two intervention arms (PR = 0.92, 0.79-1.08). Our findings suggest that safe storage significantly improved drinking water quality and reduced child diarrhea in rural Bangladesh. There was no added benefit from combining safe storage with chlorination.

Taken together, this body of evidence confirms previous findings that, even for water sources categorized as improved by the JMP, there are water quality problems that can

pose a public health threat. Our findings highlight deteriorations in water quality associated with deficiencies in the distribution and handling of drinking water from the point of source to the point of consumption, rather than contamination at the water source. These findings suggest that efforts to improve drinking water quality should place emphasis on preventing contamination at each step of the chain leading from the water source to the point of consumption, including the distribution system and household storage containers, to maximize the protection against waterborne illness.

Dedication

To Inci Ercumen and Nejat Ercumen, my parents whose unfaltering support crossed oceans and continents through patchy Skype connections and found its way to all the corners of the world that I was fortunate to call home while conducting this work.

To Emily Kumpel and Zachary Burt, my close collaborators, dear friends and wonderful human beings who set the bar incredibly high for future collaborations.

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Chapter 1. Introduction

Ensuring access to safe drinking water is a key strategy for reducing waterborne illness. The definition of water access is widely variable both within and between world regions. The WHO/UNICEF Joint Monitoring Programme for Water Supply and Sanitation (JMP) defines access to water according to the drinking water ladder, which classifies drinking water sources as improved and unimproved based on the type and location of the source [WHO-UNICEF 2013]. Unimproved sources include unprotected dug wells and springs, carts with small tanks or drums, surface water and bottled water while improved sources include public taps or standpipes, tubewells or boreholes, protected dug wells and springs, and rainwater collection; piped water on the premises is considered the highest rank on the ladder [WHO-UNICEF 2013]. While providing an objective metric for categorizing drinking water access, the JMP classification does not take water quality into account, and previous research has shown that even sources classified as improved can have compromised water quality [Onda et al. 2012].

Here we focus on the health impact associated with two different types of improved water sources; piped water supply in an urban setting and tubewell water in a rural setting. We investigate in particular the role of secondary contamination of these water sources, such as (re)contamination of piped water within the distribution system and point-of-use contamination of tubewell water in households during collection, handling and storage, as these mechanisms can pose a health risk from drinking water even when source water quality (i.e., prior to distribution system entry or prior to household storage) is good.

I discuss diarrheal illness outcomes associated with urban piped water supplies in Chapters 2 and 3. Chapter 2 describes the meta-analysis and systematic review we conducted to assess the relationship between waterborne illness and deficiencies in water distribution systems in urban settings that can lead to contamination of water in the pipes and pose a health risk for tap water consumers. A variety of mechanisms can deteriorate drinking water quality in the distribution system, including breaches of physical integrity (e.g., cross-connections, cracks and leaks), breaches of hydraulic integrity (e.g., pressure loss in pipes) and breaches of water quality integrity (e.g., decay of chlorine residual) [LeChevallier et al. 2003, NRC 2006]. It has been well documented that distribution system deficiencies can lead to outbreaks of waterborne illness [Craun and Calderon 2001; Craun et al. 2010; Lee and Schwab 2005]. However, evidence regarding the association between background, endemic levels of waterborne illness and routine distribution system problems has been inconclusive. We searched the published literature for studies that compare health outcomes between users that directly consume tap water and users that treat their tap at the point of use before consumption; we focused on settings that deliver centrally treated water that meets water quality regulations to isolate the role of the distribution system in causing contamination. In addition, we reviewed studies that focus on specific distribution network problems (i.e., breach of physical or hydraulic pipe integrity and lack of disinfectant residual). We used meta-analysis methods to combine the quantitative evidence on the association between distribution systems and waterborne disease when appropriate, and explored factors that might lead to heterogeneous findings among the studies included in our review.

In Chapter 3, I focus on intermittent delivery of piped water, a particular form of distribution system deficiency that is the norm of water delivery in many low-income countries. Intermittent water supply, where sub-segments of a distribution system receive water service on a rotating basis, can lead to deterioration of water quality in pipelines by intrusion of pathogen through leaks and cracks during periods of no pressure between supply cycles. Intermittent availability of water also forces households to store drinking water, where it can become further contaminated, in addition to potentially leading households to obtain drinking water from unsafe sources during intermittencies as well as limiting the water quantity available for maintaining hygiene practices. As a result, intermittent water delivery can lead to increased levels of waterborne illness. Short-term intermittencies in water service have been associated with diarrhea [Huang et al. 2011; Hunter et al. 2005; Nygard et al. 2007; Özkan et al. 2007]. Few studies have focused on the health impact of lack of continuous water service; these have suggested increased waterborne illness associated with intermittent water supply. However, the previous studies have relied on cross-sectional designs, necessitating a rigorous evaluation to verify these findings. In Chapter 3, I discuss a matched cohort study in urban India, where we assessed the impact of switching from intermittent to continuous delivery of piped water waterborne illness. The study was conducted in 2010-2012 in Hubli-Dharwad in the state of Karnataka, one of the first cities in India that implemented continuous water delivery on a pilot basis. 10% of Hubli-Dharwad receives water continuously since 2007-2008 while the rest of the city continues to receive intermittent service. We used multivariate matching to select areas with intermittent supply that are comparable in their key characteristics to areas with continuous water supply. We enrolled 2000 households with children under the age of five in each study group and conducted longitudinal follow-up through four household visits over 15 months to measure the impact of intermittent vs. continuous water delivery on diarrheal illness in children under the age of five, all-cause mortality in children under the age of two and the occurrence of severe waterborne illness, including typhoid fever, cholera and hepatitis.

In Chapter 4, I focus on tubewell water in the rural Bangladeshi setting, where tubewells serve as the primary drinking water sources for the majority of the population. The widespread installation of tubewells was led in the 1970s by UNICEF in an effort to reduce waterborne illness resulting from the use of highly contaminated surface water sources for drinking in rural Bangladesh. However, while groundwater is traditionally considered microbiologically safe, studies conducted at the time of the tubewell installation campaign showed no difference in diarrheal disease outcomes between tubewell users and non-users [Briscoe 1978; Khan et al. 1981; Levine et al. 1976; Sommer and Woodward 1972]. One reason for this lack of reduction in diarrhea might be that tubewell water contains enough pathogens to pose risk of waterborne illness. An alternative reason might be that water collected from tubewells is further contaminated with pathogens during storage in households and becomes microbiologically unsafe by the time it is consumed by household members. Chapter 4 describes a randomized control trial in rural Bangladesh, where I led a study in 2011-2012 assessing the individual and combined impact of treating and safely storing tubewell drinking water in households on diarrhea in children under the age of two. We enrolled 1800 households with a child under the age of two and randomly assigned them into one of three groups: (1) chlorine plus safe storage arm that received sodiumdichloroisocyanurate (NaDCC) tablets for household water treatment, coupled with a safe storage container with a narrow mouth, tightly fitting lid and tap for safe water retrieval, (2) safe storage arm that received only the safe storage container and (3) control arm that did not receive an intervention and continued their usual water handling practices. We followed households longitudinally with 10 visits over one year and measured intervention uptake, water quality and health outcomes in children.

In Chapter 5, I summarize the principal conclusions of my work and discuss the implications of these findings in terms of provision of safe drinking water.

Chapter 2. Water Distribution System Deficiencies and Gastrointestinal Illness: A Systematic Review and Meta-Analysis

Diarrheal diseases are responsible for a large health burden worldwide, with an estimated two billion cases and 1.5 million deaths per year, mostly in children in the developing world [WHO 2009]. Diarrhea is also common in developed countries [Herikstad et al. 2002; Roy et al. 2006] and can have large economic implications in terms of medical expenditures and loss of workdays [Payment and Hunter 2001]. One of the risk factors leading to this global disease burden is unsafe drinking water, both in developing and developed country settings [Black et al. 2003; Colford et al. 2006; Messner et al. 2006; Reynolds et al. 2008].

The focus of this review is drinking water-related diarrheal disease risk in settings where water is centrally distributed via a piped network. In such settings, diarrheal disease due to drinking water can be caused by contamination at the source, at the treatment plant (if any), in the distribution system, or at user end-points [Craun et al. 2010]. Here, we focus on (re)contamination of water in the distribution network before it reaches consumer taps, which can put consumers at risk of diarrheal illness even when treatment plant effluent is in compliance with all drinking water quality regulations. Such contamination events are caused by deficiencies in the distribution system, including breach of physical pipe integrity (i.e., pipes can no longer provide adequate physical barrier against external contamination due to factors such as cross-connections with non-potable lines, fractures, leaky joints, corrosion associated with aging), breach of hydraulic pipe integrity (i.e., pipes can no longer provide a reliable water supply in terms of volume or pressure due to factors such as main breaks, pump outages or sudden changes in demand) and breach of water quality integrity (i.e., water quality deteriorates in pipes through factors such as decay of disinfectant residual) [NRC 2006]. Both physical and hydraulic breaches are necessary for contamination to occur; lack of water pressure during hydraulic breaches allows external contamination to enter pipelines through the portals created by physical breaches. Entry of pathogens can be in the form of backflow from cross-connections or intrusion through leaks and cracks [Besner et al. 2011; LeChevallier et al. 2003]. Aging water infrastructure in the U.S. and other developed countries makes water distribution systems particularly vulnerable to pathogen intrusion through increasingly frequent pipe breaks and other types of aging-related deterioration as pipelines approach the end of their service lives [USEPA 2011], and breaks, cracks and leaks in pipelines are also very common in the inadequately maintained and often overburdened water distribution systems of developing countries [Lee and Schwab 2005]. The WHO recommends maintaining a chlorine residual of 0.2 to 0.5 mg/L in the distribution network to provide protection against pathogen intrusion in the event of breaches of physical and/or hydraulic pipe integrity [WHO 2011]. However, not all networks maintain the recommended level of residual, and even in adequately chlorinated networks it is debated whether the disinfectant residual can effectively inactivate intruding pathogens and preserve the water quality integrity [Gadgil 1998; Payment 1999].

Links between waterborne disease outbreaks and distribution system deficiencies have been well documented in the U.S. and in developing countries [Craun and Calderon 2001; Craun et al. 2010; Lee and Schwab 2005]. In contrast, the contribution of distribution systems to waterborne illness under non-outbreak conditions is not well understood. Risk assessment models have suggested distribution system problems as a potential risk factor for sporadic gastrointestinal illness (GII) [Lambertini et al. 2012; McInnis 2004; Teunis et al. 2010]. Such models, however, typically rely on several assumptions. Findings from epidemiologic studies on the association between distribution systems and endemic GII have been mixed and, while previous reviews of limited scope on the subject exist [Colford et al. 2006; NRC 2006], the body of epidemiologic evidence on endemic levels of GII due to distribution system deficiencies, to our knowledge, has not been systematically reviewed previously.

We conducted a systematic review and meta-analysis to investigate whether distribution system deficiencies lead to increased risk of endemic waterborne illness in consumers of tap water. Our first research question was whether consumption of centrally treated and distributed tap water increases the risk of GII compared to consumption of tap water re-treated at the point of use (POU). By focusing on water that has been treated at a centralized facility and is safe to drink as it exits the treatment plant, we aimed to isolate the role of the distribution network from other potential causes of contamination at the source or treatment plant. Our second research question was whether reported distribution system problems such as breach of physical, hydraulic or water quality integrity in pipelines increase the risk of GII in tap water consumers served by piped networks.

METHODS

Literature Search

We searched the Cochrane Library, Medline, EMBASE and Web of Science for relevant published articles using combinations of the keywords “tap water, drinking water, distribution system(s), public water supply, municipal water supply” with “diarrh(o)ea, diarrh(o)eal, gastrointestinal, gastroenteritis, gastritis.” The titles and abstracts of articles were screened for eligibility, and full texts of relevant articles were reviewed. The bibliographies of eligible articles were screened to identify additional studies.

Selection Criteria

The primary inclusion criterion was that the measured exposure was consumption of tap water, as obtained from the tap without further treatment. For studies comparing direct consumption of tap water to consumption of tap water re-treated at the POU, an additional criterion was that study participants received their tap water from centralized water treatment systems that did not report treatment failures at the time of the study and/or were reported to be in compliance with microbial water quality regulations. The second inclusion criterion was that the reported outcome was endemic GII, under non-outbreak conditions as reported by the authors. Multiple GII definitions were accepted including diarrhea, gastroenteritis, acute gastrointestinal illness (AGI, defined as a combination of diarrhea and vomiting), highly credible gastrointestinal illness (HCGI, defined as different combinations of diarrhea, vomiting, nausea and abdominal pain), highly credible gastroenteritis (HCG, defined similarly to HCGI) and infections with specific diarrheagenic pathogens (e.g., *Campylobacter*); however, infections with protozoan pathogens such as *Cryptosporidium* and *Giardia* were excluded as these organisms can be resistant to water treatment [Steiner et al. 1997] , making it difficult to isolate contamination occurring in the distribution system from treatment failure at the plant. The third inclusion criterion was the use of epidemiological methods to link exposures to health outcomes; studies using a risk assessment approach to infer GII outcomes from water quality data were excluded as these use theoretical transmission models that rely on several assumptions [Soller 2006] to estimate disease risk in contrast to epidemiological methods that measure disease outcomes directly. Finally, because the objective of our review is to characterize the risk of endemic GII among general populations that are exposed to distribution system deficiencies, we excluded studies on specific sub-populations that are particularly vulnerable to GII from waterborne pathogens, such as the elderly and immuno-compromised [Colford Jr et al. 2005a, 2009; Gerba et al. 1996] or individuals that are not representative of a resident population, such as travelers [Ericsson 1998]. The review was limited to studies in English, German or Spanish (the languages spoken by the authors), with no limitations on study location or quality.

Data Extraction and Meta-Analysis

Data were extracted independently by two unblinded authors (AE and JSG), and discrepancies were resolved by discussion. Estimates of relative risk (RR), such as incidence density ratios (IDR) and odds ratios (OR) along with 95% confidence intervals were extracted from the selected studies when available, and otherwise calculated from the reported data using standard methods [Rothman et al. 2008]. All relative measures were expressed such that a value larger than 1.0 indicates increased risk in the exposed group. If a study reported both unadjusted and adjusted estimates controlling for covariates, the adjusted estimates were used. If effect estimates for multiple age groups were reported, the estimates for all ages combined were extracted.

To address our research questions, the studies were grouped as follows: (1) studies comparing consumption of tap water obtained directly from the tap to consumption of tap water re-treated at the POU, and (2) studies assessing the risk of GII associated with specific distribution system deficiencies. The second group was further sub-classified as per previously defined categories of distribution system problems [NRC 2006] into studies that focus on: (1) breach of physical pipe integrity such as cross-connections, cracks and aging-related pipe deterioration, (2) breach of hydraulic pipe integrity such as pressure loss in the network, and (3) breach of water quality integrity such as lack of adequate disinfection residual. We conducted a separate meta-analysis for each subgroup of studies (Figure 1) as we anticipated different types of distribution system deficiencies to have different health impacts as well as different policy implications.

The meta-analysis was conducted using STATA (version 12, STATA Corp., College Station, TX). Fixed and random effects models with inverse variance weighting were used to pool the risk estimates, when appropriate. Heterogeneity was assessed using the Mantel-Haenszel χ^2 statistic, and random effects models were used when heterogeneity was detected, defined as a p-value less than 0.20 on the χ^2 statistic. Fixed effects models were used when there was no evidence of heterogeneity. Several factors were specified *a priori* as potential sources of heterogeneity, including location (developed vs. developing country as per the International Monetary Fund's definition of "advanced economies vs. "emerging and developing economies" [IMF 2013], characteristics of the study design (randomized vs. observational, blinded vs. non-blinded) and distribution system performance during study period (continuously vs. intermittently operated, malfunctioning vs. non-malfunctioning (Figure 1)). For the purposes of our analysis, a malfunctioning system was defined *a priori* as one that had reported breaches of physical integrity (e.g., pipe breaks), breaches of hydraulic integrity (e.g., service intermittencies, low or negative pressure events) or breaches of water quality integrity (e.g., inadequate disinfectant residual in the network despite chlorination prior to distribution system entry). Subgroup analyses were performed to explore the impact of these factors on summary estimates. Sensitivity analyses were conducted to determine if pooled estimates were disproportionately affected by any one study. Publication bias was assessed using the Begg's test, with a p-value less than 0.20 interpreted as evidence for bias [Egger et al. 2001].

RESULTS

The titles and/or abstracts of 6,245 studies were screened and the full texts of 62 articles were reviewed (Figure 2). Of these, 20 studies were identified for inclusion in the systematic review and 14 of these with combinable data were included in the meta-analysis. Of the articles reviewed in full text, studies were excluded because they were reviews or general articles with no health outcomes (n=18), contamination occurred prior to distribution system entry (at the water source or treatment plant) or there was not sufficient information to differentiate contamination in the distribution system from contamination at the source or plant (n=17), exposure was either not tap water or a mix of tap water and other sources (n=6) or study authors did not report data on the association between the tap water exposures and GII outcomes (n=1).

Studies of Tap Water vs. POU-Treated Water

Six studies investigated the effects of consuming tap water versus POU-treated tap water (Tables 1 and 2) [Colford Jr et al. 2002, 2005b; Hellard et al. 2001; Payment et al. 1991, 1997; Semenza et al. 1998].

Study Characteristics. Five of the studies were cluster-randomized trials (CRT), and one study was an observational analysis within a CRT (Table 1). In all studies, the exposed group consumed tap water directly from the tap without further treatment. In five studies, control group tap water was re-treated at the POU; one study provided households with bottles of treated plant water re-filtered by reverse osmosis or bottles of spring water, both of which were ozonated prior to bottling. Three studies achieved blinding by employing water treatment devices in the POU-treatment group that did not alter the taste of water and providing households in the tap water group with a sham device that looked identical to the active water treatment device. The remaining three studies were non-blinded. All six studies ascertained GII status through self-report.

Water System Characteristics. Five of the studies were conducted in developed countries and one in a developing country (Table 2). The water system characteristics varied between the studies. The source water ranged from well-protected forest catchments to rivers heavily contaminated with sewage and run-off. Five studies provided source water quality data, and all five reported that pathogens or fecal indicator organisms were detected in the source water. The water treatment plants employed conventional treatment with chlorination or chloramination in four studies, and only chlorination in two studies. Four studies reported the finished plant effluent to be in compliance with microbial water quality regulations, and none of the studies reported treatment plant failures during the study period. Four studies had a malfunctioning distribution system as reported by study authors and by independent investigators [Besner et al. 2010; LeChevallier et al. 2002], while one study was conducted in a system with no evidence of malfunctioning and one study did not provide information on distribution system operation.

Summary of Study Findings. Four of the studies showed elevated risk of GII from tap water consumption, but in two of these studies chance could not be ruled out as an explanation of the results. The remaining two studies found no increased risk (Table 1). The Begg's test suggested evidence of publication bias ($p = 0.056$). Significant heterogeneity was observed across the six studies ($p < 0.0005$); an overall pooled estimate was therefore not calculated.

Sources of heterogeneity were explored by performing subgroup analyses with respect to study location (developed vs. developing country), study type (CRT vs. observational), blinding status (blinded vs. non-blinded) and distribution system performance during the study period (malfunctioning vs. non-malfunctioning based on reported data on network hydraulics and chlorine residual) (Table 3). The one observational study conducted in a developing country (IDR = 2.61, 1.71-4.00) showed a stronger association compared to the randomized controlled trials in developed countries (random effects pooled IDR = 1.09, 0.95-1.25). Non-blinded studies where participants in the intervention group were aware that they were consuming POU-treated water showed a marked increase in GII associated with direct tap water consumption (random effects pooled IDR = 1.52, 1.05-2.20); significant heterogeneity remained among these studies ($p = 0.003$). In contrast, this association disappeared in blinded studies (fixed effects pooled IDR = 0.98, 0.90-1.08) and there was no evidence of heterogeneity ($p = 0.534$). In the subset of studies with a malfunctioning distribution system, tap water was associated with a 34% increase in the rate of GII (random effects pooled IDR = 1.34, 1.00-1.79) (Figure 3) but significant heterogeneity remained ($p < 0.0005$). Excluding the developing country study that had more severe distribution system deficiencies (approximately half of users reporting discernible pressure loss as opposed to transient low pressures detected by loggers in the other studies) resulted in a diminished relative risk associated with tap water consumption (random effects pooled IDR = 1.14, 0.95-1.37) and reduced but did not eliminate the heterogeneity (p = 0.056). Two of the studies in malfunctioning systems showed dose-response relationships where increasing risk of GII was observed with increasing water consumption in the tap water group but not in the treatment group [Payment et al. 1991, 1997]. The studies that did not provide information on distribution system operation or were conducted in a properly operating system did not show a significant association.

Studies on Loss of Physical Pipe Integrity

Six studies focused on loss of physical pipe integrity (Tables 4 and 5) [Abu Amr and Yassin 2008; D'Argenio et al. 1995; Mohanty et al. 2002; Nygard et al. 2004; Tinker et al. 2009; Yassin et al. 2006].

Study Characteristics. One study focused on the impact of cross-connections with sewer lines, one used pipe material as a proxy for physical integrity, two focused on pipe age as a proxy for aging-related deterioration and two focused on pipe length and hydraulic residence time as an aggregate measure (longer pipelines are more likely to have a larger number of leaks and fractures and there are more opportunities for intrusion of pathogens through these when the water spends more time in pipes) (Table 4). Data on pipe characteristics were obtained from water utilities or reported by participants. With the exception of one study, where there was media awareness about fecal contamination in the network caused by the cross-connections [D'Argenio et al. 1995], participants were effectively blind to their exposure status as knowledge of the physical state of water pipes as a risk factor for GII was presumably limited in study populations. GII outcomes were assessed by surveillance records or from self-reported symptoms.

Water System Characteristics. Three of the studies were conducted in developed countries and three in developing countries (Table 5). The developed country studies presumably had continuously operated distribution systems while in all three developing country studies distribution system operation was reported to be intermittent, with water delivered for a limited number of hours per day. One study did not provide data on disinfectant residual in the network; the rest were conducted in chlorinated systems with varying levels of residual.

Summary of Study Findings. All studies showed increased GII associated with loss of physical pipe integrity but only three studies had sufficient statistical power (Table 4). Due to the differences in the exposure definitions among the studies, a meta-analysis on health outcomes was not conducted; instead we summarize the general findings of the individual studies. Presence of cross-connections between water and sewer lines was associated with the occurrence of self-reported GII symptoms [D'Argenio et al. 1995]. Percent of cast-iron water pipes, as opposed to more leak-prone materials, in a given service area appeared protective against self-reported GII outcomes aggregated at the service area level [Mohanty et al. 2002]. In two studies, increased illness was observed in consumers served by networks older than a year, but without sufficient statistical power [Abu Amr and Yassin 2008; Yassin et al. 2006]. Two studies demonstrated increasing risk of GII with increasing water residence time in the distribution system. One found increased incidence of *Campylobacter* infections for every meter increase in water pipe length per person in a given service area (defined as the total length of the distribution network in the municipality divided by the number of people served) [Nygard et al. 2004]. The other study reported that service zones with the longest water residence time (typically located furthest away from the treatment facility) were more likely to have medical visits related to GII in comparison to zones with moderate water residence time [Tinker et al. 2009]. Additionally, two of the previously discussed CRTs [Payment et al. 1991, 1997] had mixed findings on the impact of distance from the treatment plant on GII. Secondary analysis of the data from the 1991 study showed increasing GII with increasing residence time in the distribution system [Payment et al. 1993] while no such association was found in the 1997 study.

Studies on Loss of Hydraulic Pipe Integrity

Nine studies investigated the effects of loss of hydraulic pipe integrity (Tables 6 and 7) [Abu Amr and Yassin 2008; Cifuentes et al. 2002; Fewtrell et al. 1997; Huang et al. 2011; Hunter et al. 2005; Abu Mourad 2004; Nygard et al. 2007; Özkan et al. 2007; Yassin et al. 2006].

Study Characteristics. The exposure in five studies was temporary pressure loss at the tap (i.e., water outage) typically caused by main breaks or repair work in otherwise continuously operated distribution networks, and in four studies the exposure was chronic outages in intermittent systems (Table 6). The studies obtained water outage data from water utilities or through self-report by participants. By the nature of the exposure, participants were non-blinded to their exposure status as loss of pressure at the tap was evident to study participants; however, knowledge of pressure loss as a risk factor for GII was presumably limited. GII symptoms were ascertained from surveillance or hospital data or from self-reported symptoms.

Water System Characteristics. Of the five studies in continuous distribution systems, all but one were conducted in developed countries while the four studies of intermittent systems were all conducted in developing countries. None of the studies of continuous systems provided additional information on water system characteristics, with the exception of one study reporting that the water utility was compliant with drinking water regulations (Table 7). Among the studies of intermittent systems, one did not specify whether the source water was chlorinated before distribution. The other three were conducted in chlorinated networks and, of these, only two reported the level of residual.

Summary of Study Findings. All nine studies suggested increased risk of GII associated with water outages, both in continuously and intermittently operated systems (Table 6). Because of inherent operational differences between intermittent and continuous distribution networks, studies in these categories were analyzed separately. Among the five studies in continuous systems, one study was excluded from the pooled analysis because it only reported a correlation coefficient. For the remaining four studies, the Begg's test suggested evidence of publication bias ($p = 0.042$). The pooled analysis showed a marked increase in GII associated with water outages (random effects pooled RR = 3.26, 1.48-7.19) (Figure 4) with significant heterogeneity among studies (p<0.0005). Limiting the analysis to studies in developed countries somewhat reduced the pooled estimate (random effects pooled RR = 2.34, 1.13-4.86) but did not reduce the heterogeneity (p<0.0005). One of the studies reported increased GII when the outages lasted longer than six hours (OR = 1.90, 1.00-3.40) as well as increased GII with increasing water consumption in the study group that experienced outages but not in the unexposed group [Nygard et al. 2007].

For studies in intermittently operated systems, publication bias could not be assessed due to the small number of studies. The pooled analysis of the two studies on chronic intermittencies in water delivery showed increased odds of GII (fixed effects pooled OR = 1.61, 1.26-2.07) with no evidence of heterogeneity (p = 0.432). The pooled analysis of the two studies on the duration of intermittencies showed a marked increase in GII with intermittencies lasting longer than a day (fixed effects pooled RR = 1.42, 1.11-1.82) with no evidence of heterogeneity (p = 0.666).

Studies on Loss of Water Quality Integrity

Three studies assessed the effects of low or non-detectable residual in the distribution system despite centralized chlorination prior to distribution (Table 8) [Egorov et al. 2002; Mohanty et al. 2002; Semenza et al. 1998].

<u>Study Characteristics</u>. The exposure definitions varied between the studies (Table 8). One study focused on lack of detectable chlorine residual at the tap. One study investigated the effect of interquartile decrease in free chlorine residual in the network (relative to the residual in the plant effluent). One study focused on the percentage of distribution system samples without detectable residual within a given service area. Exposure was assessed by measurement of chlorine residual by the utility or study investigators, and GII outcomes were ascertained through self-report in all studies.

<u>Water System Characteristics</u>. Two studies were conducted in previously described distribution systems with intermittencies in delivery [Mohanty et al. 2002; Semenza et al. 1998] (Tables 2 and 5) and one was conducted in a system serving conventionally treated and chlorinated groundwater via a network with variable water pressure in different parts but no reported pressure loss events [Egorov et al. 2002] .

<u>Summary of Study Findings</u>. All three studies suggested an increase in GII illness with decreasing chlorine residual but only one study had sufficient statistical power (Table 8). One of the studies noted a correlation between decreasing chlorine residual and increasing distance from the plant, suggesting residence time in the network as a potential causal factor behind the association between the decrease in chlorine residual and increase in GII [Egorov et al. 2002]. Due to the differences in study designs and exposure definitions among the studies, a meta-analysis was not performed.

DISCUSSION

Our review of studies that compare tap to POU-treated water consumption suggests that directly consuming tap water is associated with GII outcomes in settings where distribution systems are documented to have deficiencies such as low-pressure events or inadequate disinfectant residual (IDR = 1.34, 1.00-1.79) (Table 3). No significant association was observed in studies done in properly functioning distribution systems. The subset of non-blinded studies showed a marked association between GII and tap versus POU-treated water consumption (IDR = 1.52, 1.05-2.20); however, there was no association in blinded studies (IDR = 0.98, 0.90-1.08) (Table 3). In our review, we also identified articles that focused on specific system deficiencies. We found that increases in GII are significantly associated with water outages in continuously operated distribution systems (RR = 3.26, 1.48-7.19) as well as chronic outages in intermittent systems (OR = 1.61, 1.26-2.07). In both types of systems, longer outages lead to increased risk of GII. Other network deficiencies such as breach of physical pipe integrity and lack of chlorine residual were also associated with GII outcomes. Taken together, these findings suggest that (re)contamination of drinking water in distribution systems can present a health risk for consumers served by piped water networks.

It is important to note that our findings indicate evidence of publication bias, suggesting that studies with positive findings may have been preferentially published over those with null or inconclusive findings. It is therefore possible that our pooled effect estimates are higher than the true health risk associated with distribution systems. Moreover, our review indicates that there are relatively few studies to date that focus on this critical topic, suggesting the need for further research.

Heterogeneity between Study Settings and Designs

There was significant heterogeneity among study settings and water system characteristics. We used meta-analysis as a tool to explore the impact of these heterogeneities on study findings. Studies conducted in similar settings were combined, and pooled estimates were contrasted between such subgroups to highlight important differences (e.g., between continuous and intermittent systems or malfunctioning and non-malfunctioning networks). However, significant heterogeneity often remained even within subgroups.

One potential source of remaining heterogeneity, even after classifying studies as those conducted in malfunctioning vs. non-malfunctioning systems, is that myriad factors can influence the health risk associated with distribution systems, such as the number and size of leaks and cracks in pipes, the levels of fecal contamination present in the vicinity of pipelines, the magnitude and frequency of pressure loss events and levels of disinfectant residual in the affected pipe segments [LeChevallier et al. 2003]. While broadly classifying networks as malfunctioning vs. non-malfunctioning based on system-wide performance data provides a basic tool for comparison, given the expected temporal and spatial variability in these factors, it is not surprising that our classifications did not fully capture the heterogeneity across studies. Moreover, most distribution systems have cracks and leaks as evidenced by water losses, which can be as high as 32% in US utilities [LeChevallier et al. 2003] and over 40% in developing countries [Lee and Schwab 2005], suggesting that no distribution system is truly non-malfunctioning. However, the presence of cracks and leaks alone is not sufficient for pathogen intrusion, given that the network maintains adequate pressure and disinfectant residual [Besner et al. 2011]. This suggests that our classification of networks with adequate levels of residual and no documented pressure loss during the study as "non-malfunctioning" is consistent with the principles of pathogen intrusion into pipes and that our findings are relevant to the contexts under which most systems operate. Nonetheless, collection of more fine-grained data on these system parameters could improve the interpretation of future studies.

Study designs also varied widely between articles identified in our review. While the studies comparing tap versus POU-treated water consumption almost exclusively employed randomized designs, studies of specific distribution system characteristics used observational methods including cohort, cross-sectional and ecological designs. Observational studies varied in their attempts to control for confounding; some reported unadjusted estimates while others controlled for confounding. Factors that investigators controlled for were also not consistent across studies. The most common observational design was cross-sectional studies. One potential flaw of this design is the inability to establish temporality [Rothman et al. 2008]. Ecological studies were also commonly used to study network characteristics at service area levels, and this design is vulnerable to the "ecological fallacy" where associations observed between aggregate exposures and outcomes may not reflect true causal relationships at the individual level [Rothman et al. 2008]. Regardless, in our review we found that results were generally consistent (effect measures >1 associated with distribution system deficiencies), despite the differences in study designs.

Potential Limitations of Studies

Recall Bias. In studies with self-reported outcomes (e.g., diarrhea symptoms), there is evidence from the literature that exposure status can influence symptom recall and consequently effect measures [Colford Jr et al. 2009; Hunter 2009; Schmidt and Cairncross 2009]. Consistent with this evidence, the subset of non-blinded studies in our review showed a significant association between tap versus POU-treated water consumption and self-reported GII, yet there was no evidence of an association in blinded studies. We could not explore the role of lack of blinding separately from malfunctioning systems due to overlap between studies, and therefore cannot rule out recall bias. Studies in our review that focused on specific network deficiencies such as water outages were non-blinded by the nature of the exposures studied. One of these studies assessed the impact of participants' knowledge of their exposure status on the findings [Nygard et al. 2007]. In this study, investigators selected participants who experienced an outage based on water utility data. They then asked participants whether they thought there was a main break or repair in the pipes supplying their homes; 75% of exposed participants replied "yes" compared to 25% of unexposed participants ($p < 0.001$) indicating awareness of exposure. However, stratified analyses among participants who believed they were exposed versus unexposed showed similar associations between water outage and GII, suggesting that any bias in reporting of outcomes due to lack of blinding had a negligible impact on their findings. Another study assessing the impact of cross-connections reported increased recall of GII symptoms in the exposed group during the period when there was media awareness about fecal contamination in the pipe [D'Argenio et al. 1995]. The authors showed elevated relative risk associated with the cross-connections during this period compared to when the presence of contamination was not yet publicly known. However, the exposed group with cross-connections had higher risk of GII than the unexposed group during both periods, again suggesting that the findings are robust to recall bias. Nonetheless, objective measures of waterborne illness, such as pathogen-specific antigen responses, could improve future reporting of non-blinded studies evaluating the impact of water distribution systems on the health of consumers. Falsification outcomes (i.e., outcomes that are not expected to be affected by tap water exposure) can be used to assess the magnitude of recall bias when measuring objective outcomes is not feasible (Lipsitch et al. 2010).

Water Contamination prior to Distribution System Entry. In studies comparing tap versus POU-treated water, there is the possibility that water contamination prior to rather than within the distribution system is responsible for the increase in GII in tap water consumers. In the studies in our review, plant effluent was in compliance with regulations and no treatment failures were reported. However, regulatory standards are often based on indicator organisms for fecal contamination, whose ability to predict disease is controversial [Gundry et al. 2004]. Only three studies performed additional tests for selected human enteric viruses and parasites in the finished plant water, and no such organisms were detected. For the remaining studies, one cannot exclude the possibility that the plant effluent may contain disinfection-resistant pathogens such as *Cryptosporidium*, whose absence cannot be confirmed by the absence of indicator organisms [Gadgil 1998]. Short-term imperfections in plant performance, such as transient breakthrough of turbidity from filters, and low-level or sporadic breakthrough of pathogens have also been suggested as mechanisms for contamination that would not be detected by routine plant performance monitoring [Payment and Hunter 2001]. One of the studies in our review did have an additional study arm consuming finished plant water that had been bottled before distribution system entry. GII in this group was similar to the group consuming POU-treated water and significantly lower than the tap water group [Payment et al. 1997]. While we cannot rule out the role of water contamination prior to distribution for the other studies in our review, this study was able to isolate the distribution system as the source of contamination. Similar methods could improve the interpretation of future studies.

Water Contamination at User Endpoints. One limitation of the studies investigating the effects of water outages is their failure to account for water handling and hygiene practices during the outages. In these studies, it is possible that the observed increase in illness may be mediated by altered practices in the household during the intermittencies in service, as opposed to pathogen intrusion into pipelines during pressure loss in the system. Such practices could include reverting to alternate sources of water that are of poor quality, secondary contamination of stored water in the household [Mintz et al. 1995] or poor hygiene due to reduced quantities of available water [Esrey et al. 1991]. One of the studies in our review reported no deterioration in tap water quality following water outages, suggesting that an alternative pathway was the primary risk factor for the observed increase in GII symptoms [Huang et al. 2011]. This would not change the general conclusion that service disruptions increase the risk of GII, but would have different policy implications with emphasis on preventing water outages as opposed to measures to minimize pathogen intrusion during an outage. However, another study in our review reported that the odds of GII were reduced when the pipe segment affected by the main break or repair work was flushed or re-chlorinated, suggesting that pathogen intrusion into pipelines during periods of pressure loss is at least partly responsible for increased illness [Nygard et al. 2007].

Dose-Response Relationships

Findings from several studies in our review suggested a dose-response relationship between GII and the volume of tap water consumed [Nygard et al. 2007; Payment et al. 1991, 1997], the duration of a water outage [Abu Amr and Yassin 2008; Nygard et al. 2007; Yassin et al. 2006] and the residence time of water in the distribution system (i.e., pipe length) [Nygard et al. 2004; Payment et al. 1993; Tinker et al. 2009]. Volume of contaminated tap water intake would be expected to predict consumers' ingested pathogen load. Importantly, a dose-response with water consumption was only reported in tap water consumers in malfunctioning systems; participants with POU-treated water [Payment et al. 1991, 1997] or those not exposed to water outages [Nygard et al. 2007] did not show evidence of increasing GII with increasing water consumption. Along similar lines, increasing duration of water outages would make pipes vulnerable to backflow and intrusion for longer periods while longer pipelines would have a larger number of cracks and leaks, increasing the number of potential portals for pathogen intrusion. Both factors would be expected to increase opportunities for recontamination of water in distribution pipes and elevate the risk of GII, which is consistent with the findings of this review. A dose response is an important piece of evidence regarding the presence of a causal link between an exposure and outcome [Hill 1965] and, taken together, these dose-response relationships support the evidence from this review of a causal relationship between distribution system deficiencies and increased GII.

CONCLUSIONS

Although it is well established that large disruptions in water distribution systems can cause outbreaks of waterborne illness [Craun and Calderon 2001; Craun et al. 2010; Lee and Schwab 2005], we believe this to be the first systematic review of the available published evidence of the impact of routine distribution system problems on low-level, background gastrointestinal illness. The evidence we present suggests that tap water consumption is associated with endemic GII in malfunctioning distribution networks. Specific system deficiencies such as loss of pipe integrity, water outages and inadequate residual are also associated with increased risk of GII. Although the available evidence does not allow us to rule out recall bias as a partial explanation for this association, the magnitude of our findings justify further research on this critical topic.

Randomized controlled trials comparing tap water consumption to consumption of water treated at the point of use remain a strong study design for characterizing health risk from overall distribution system deficiencies. Prospective cohort studies that use utility data to identify system failures and follow up with affected and unaffected tap water consumers are a suitable study design to investigate the health impact of specific distribution system problems that allows establishing temporality between exposures and outcomes. Future studies should, ideally, include blinding or objective outcomes to minimize recall bias, collect more detailed water system measurements relevant to the homes of participants to better characterize individual exposure to distribution system problems and measure microbiological water quality at key points between the water treatment plant and the point of consumption to differentiate contamination occurring in the distribution system from treatment plant failures or point-of-use contamination.

TABLES

TABLE 1. Study Characteristics in Studies of Tap Water vs. Water Treated at Point of Use

Reference	Design	Comparison Group	Effect Estimate
Payment et al. 1991	CRT Non-blinded	RO treatment	IDR = 1.36 (1.10, 1.69) [a]
Payment et al. 1997	CRT Non-blinded	Ozonated bottles of RO-treated plant water or spring water	IDR = 1.14 (0.91, 1.42) [a]
Semenza et al. 1998	Cohort [b] Non-blinded	Chlorination	IDR = 2.61 (1.71, 4.00) [a]
Hellard et al. 2001	CRT Blinded	Microfiltration + UV	IDR = 1.00 (0.86, 1.15)
Colford et al. 2002	CRT Blinded	Microfiltration + UV	IDR = 1.32 (0.75, 2.33)
Colford et al. 2005	CRT Blinded	Microfiltration + UV	IDR = 0.96 (0.85, 1.08)

CRT: cluster-randomized trial; RO: reverse osmosis; UV: ultraviolet, IDR: incidence density ratio

[a] Calculated from data reported in study.

[b] Observational arm within cluster-randomized trial.

TABLE 2. Water System Characteristics in Studies of Tap Water vs. Water Treated at Point of Use

Reference	Location	Source Water	Treatment Plant	Distribution System
Payment et al. 1991	Canada	River receiving sewage; coliforms and viruses detected	Conventional treatment with chlorination; no coliforms or viruses in effluent	▪ Negative pressures ▪ Inadequate residual
Payment et al. 1997	Canada	Same river as 1991; coliforms, parasites and viruses detected	Conventional treatment with ozonation and chlorination; no coliforms, parasites or viruses in effluent	▪ Same system as 1991 ▪ No fecal coliforms ▪ Coliforms detected in 0.6% of samples
Semenza et al. 1998	Uzbekistan	Not reported	Two-stage chlorination	▪ Pressure loss events ▪ Inadequate residual
Hellard et al. 2001	Australia	Protected forest catchments; fecal coliforms detected	Chlorination; no coliforms in effluent	▪ Inadequate residual ▪ No fecal coliforms ▪ Coliforms detected in 19% of samples
Colford et al. 2002	USA	River receiving agriculture and industry run-off; pathogens detected	Conventional treatment with chloramination; effluent in compliance with regulations	▪ Not reported
Colford et al. 2005	USA	River receiving sewage; parasites and viruses detected	Conventional treatment with chlorination; no coliforms, parasites, viruses in effluent	▪ No negative pressures ▪ Adequate residual ▪ No coliforms

TABLE 3. Meta-Analysis of Studies of Tap Water vs. Water Treated at Point of Use

Subgroup (n = Number of Studies)	**IDR**	**Heterogeneity** [a]
Study Type/Location		
CRT/Developed Country (n = 5)	1.09 (0.95, 1.25)	χ^2 = 9.48, p = 0.050
Cohort/Developing Country (n = 1)	2.61 (1.71, 4.00)	N/A
Blinding		
Non-Blinded (n = 3)	1.52 (1.05, 2.20)	χ^2 = 11.40, p = 0.003
Blinded (n = 3)	0.98 (0.90, 1.08)	c^2 = 1.25, p = 0.534
Distribution System		
Malfunctioning System (n = 4)	1.34 (1.00, 1.79)	χ^2 = 20.28, p < 0.0005
Non-Malfunctioning System (n = 1)	0.96 (0.85, 1.08)	N/A
No Data on System (n = 1)	1.32 (0.75, 2.33)	N/A

IDR: incidence density ratio; CRT: cluster-randomized trial

[a] χ^2 Statistic with a p-value less than 0.20 defined as evidence of heterogeneity.

TABLE 4. Study Characteristics in Studies of Physical Pipe Integrity [a]

Reference	**Design**	**Exposure**	**Outcome**	**Effect Estimate**
D'Argenio et al. 1995	Cohort	Cross-connections	Self-report	RR = 2.67 (1.16, 6.11) [b]
Mohanty et al. 2002	Ecological	% of cast iron pipes	Self-report	Regression Coefficient -0.42 (p = 0.10)
Yassin et al. 2006	Cross-sectional	Network >1 yr old	Self-report	RR = 1.51 (0.80, 2.83) [b]
Abu Amr et al. 2008	Cross-sectional	Network >1 yr old	Self-report	RR = 1.03 (0.68, 1.56) [b]
Nygard et al. 2004	Ecological	Pipe length/person	Surveillance records	IDR = 1.12 (1.08, 1.16)
Tinker et al. 2009	Ecological	Hydraulic residence time	Emergency dept records	OR = 1.06 (1.04, 1.08)

RR: relative risk; IDR: incidence density ratio; OR: odds ratio

[a] Results not pooled

[b] Calculated from data reported in the study

TABLE 5. Water System Characteristics in Studies of Physical Pipe Integrity

Reference	**Location**	**Source Water**	**Water Treatment**	**Distribution System**
D'Argenio et al. 1995	Italy	Not reported	Not reported	▪ Not reported
Mohanty et al. 2002	India	Surface water	Conventional treatment with chlorination	▪ Intermittently operated ▪ Inadequate residual
Yassin et al. 2006	Palestine	Groundwater	Chlorination	▪ Intermittently operated ▪ Inadequate residual ▪ Fecal contamination detected more often than at the source
Abu Amr et al. 2008	Palestine	Groundwater	Chlorination	▪ Intermittently operated ▪ Inadequate residual ▪ Fecal contamination detected more often than at the source
Nygard et al. 2004	Sweden	Surface- and groundwater	Chlorination (for surface water only)	▪ Continuously operated ▪ Low level residual
Tinker et al. 2009	USA	Not reported	Not reported	▪ Continuously operated ▪ Adequate residual

TABLE 6. Study Characteristics in Studies of Hydraulic Pipe Integrity

Reference	Design	Exposure	Outcome	Effect Estimate
Continuously Operated Distribution Systems				
Fewtrell et al. 1997	Ecological	Water outage	Surveillance records	Correlation coefficient Shigella 0.42 (p = 0.07) [a, b] Hep A 0.67 (p = 0.001) [a, b]
Hunter et al. 2005	Cross-sectional [c]	Water outage	Self-report	OR = 12.50 (3.49, 44.71)
Nygard et al. 2007	Cohort Cross-sectional [d]	Water outage Outage duration	Self-report Self-report	OR = 2.00 (1.30, 3.20) OR = 1.90 (1.00, 3.40) [b]
Ozkan et al. 2007	Cross-sectional	Water outage	Self-report	OR = 10.28 (2.95, 35.48)
Huang et al. 2011	Ecological	Water outage	Hospital records	IDR = 1.31 (1.26, 1.37)
Intermittently Operated Distribution Systems				
Cifuentes et al. 2002	Cross- sectional	Intermittent supply	Self-report	OR = 2.00 (1.16, 3.70)
Abu Mourad 2004	Cross-sectional	Intermittent supply	Self-report	OR = 1.53 (1.15, 2.03) [e]
Yassin et al. 2006	Cross-sectional	Intermittency duration	Self-report	RR = 1.33 (0.92, 1.91) [e]
Abu Amr et al. 2008	Cross-sectional	Intermittency duration	Self-report	RR = 1.49 (1.06, 2.09) [e]

OR: odds ratio; IDR: incidence density ratio; RR: relative risk

[a] Results from 1991; no summary result reported by authors for all years in study.

[b] Not included in pooled analyses.

[c] Cross-sectional analysis within control group of case-control study.

[d] Cross-sectional analysis within exposed group of same cohort study.

[e] Calculated from data reported in study.

TABLE 7. Water System Characteristics in Studies of Hydraulic Pipe Integrity

Reference	Location	Source Water	Water Treatment	Distribution System
Continuously Operated Distribution Systems				
Fewtrell et al. 1997	UK	Not reported	Not reported	Not reported
Hunter et al. 2005	UK	Not reported	Effluent in compliance with regulations	Not reported
Nygard et al. 2007	Norway	Not reported	Not reported	Not reported
Ozkan et al. 2007	Turkey	Not reported	Not reported	Not reported
Huang et al. 2011	Taiwan	Not reported	Not reported	Not reported
Intermittently Operated Distribution Systems				
Cifuentes et al. 2002	Mexico	Groundwater	Chlorination	Not reported
Abu Mourad 2004	Palestine	Groundwater	Not reported	Not reported
Yassin et al. 2006	Palestine	Groundwater	Chlorination	Inadequate residual
Abu Amr et al. 2008	Palestine	Groundwater	Chlorination	Inadequate residual

TABLE 8. Study Characteristics in Studies of Water Quality Integrity [a]

Reference	Design	Exposure	Outcome	Effect Estimate
Semenza et al. 1998	Cross-sectional [b]	Non-detect chlorine	Self-report	IDR = 1.60 (0.70, 3.70)
Egorov et al. 2002	Cross-sectional	Interquartile range decrease in chlorine	Self-report	IDR = 1.42 (1.05, 1.91)
Mohanty et al. 2002	Ecological	% of samples with non-detect chlorine	Self-report	Regression Coefficient 0.46 (p = 0.64)

IDR: incidence density ratio

[a] Results not pooled.

[b] Cross-sectional analysis within exposed group of cluster-randomized trial.

FIGURES

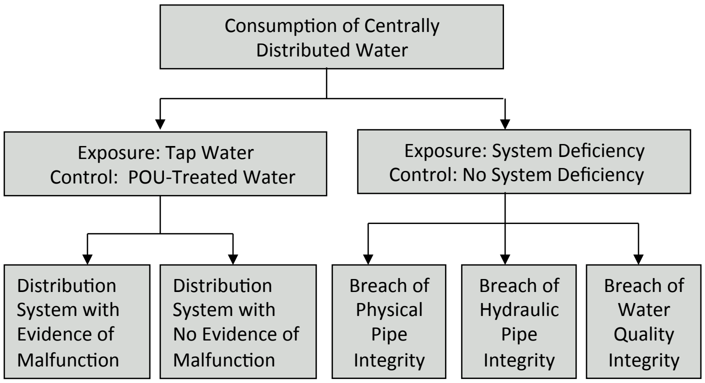


FIGURE 1. Categorization of Studies for Meta-Analysis

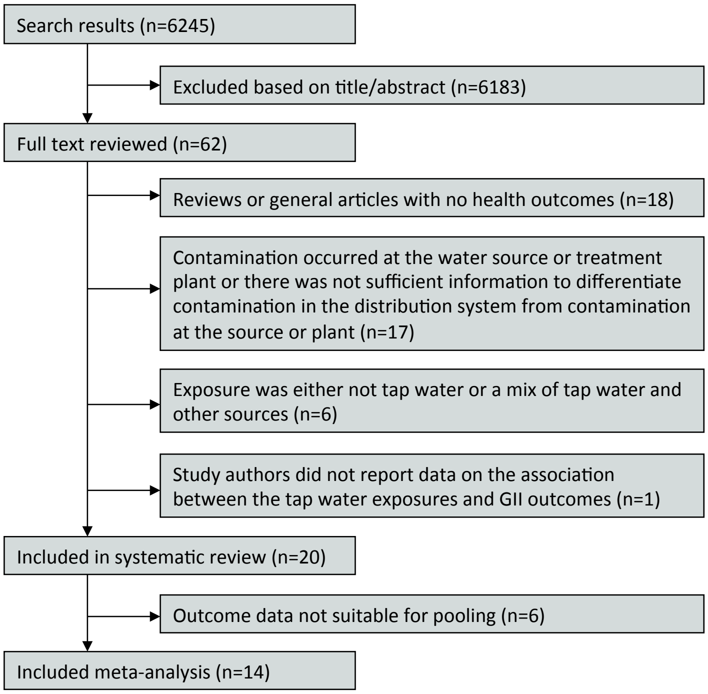


FIGURE 2. Flowchart for Inclusion and Exclusion of Articles

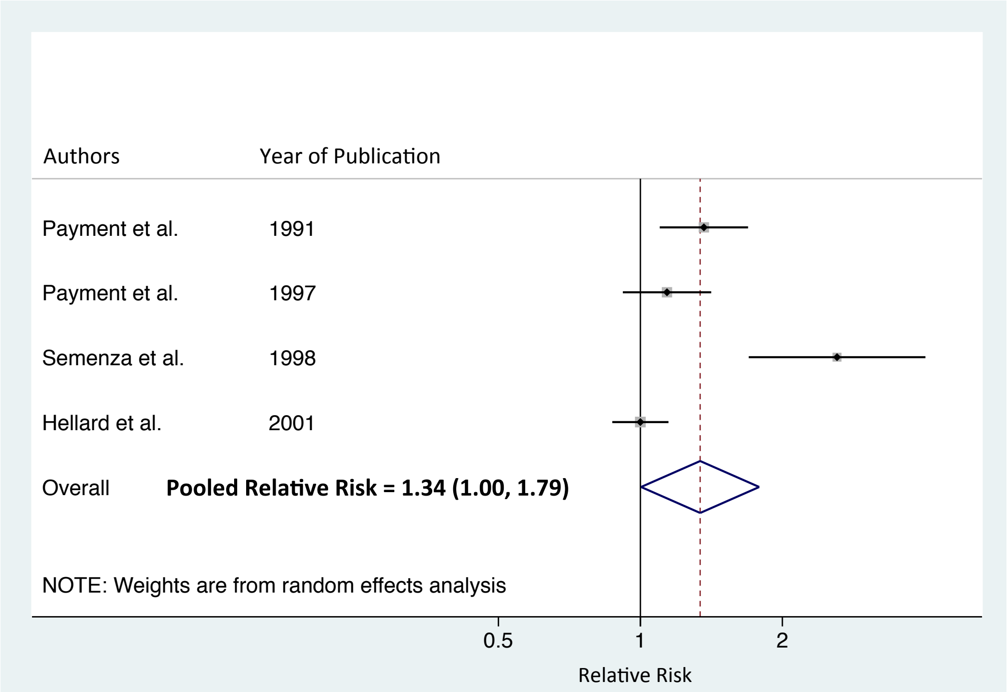


FIGURE 3. Random Effects Meta-Analysis of GII and Tap Water vs. Water Treated at POU

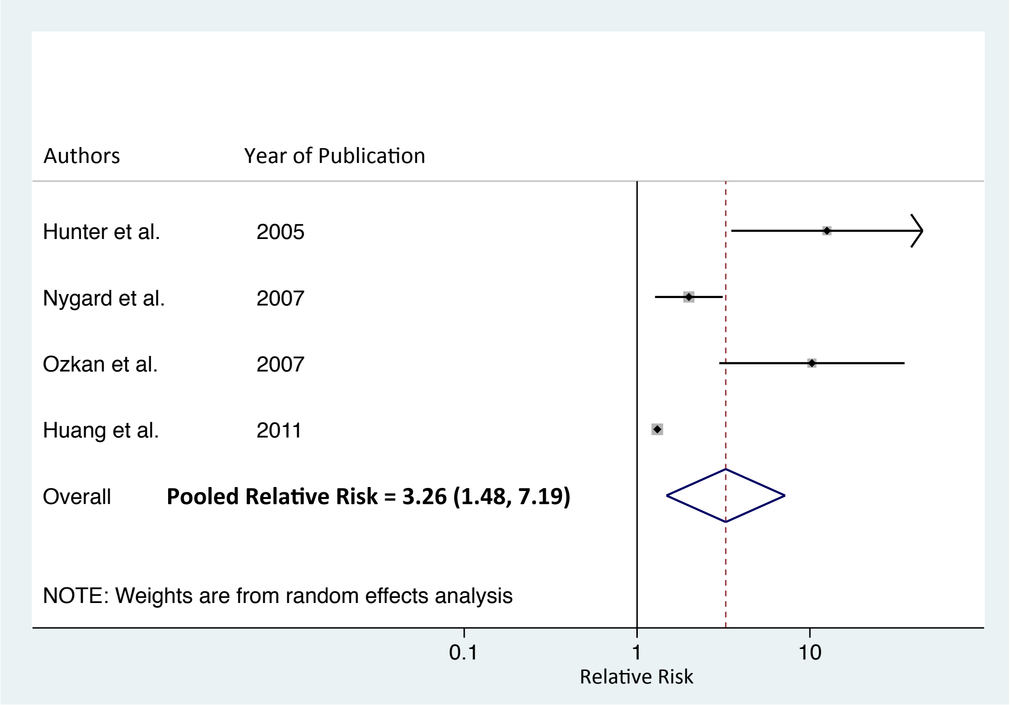


FIGURE 4. Random Effects Meta-Analysis of GII and Water Outage in Continuous Systems

Chapter 3. Impact of Continuous vs. Intermittent Piped Water Delivery on Waterborne Illness in Urban India

Access to safe drinking water is a key strategy to reduce morbidity from waterborne diarrheal diseases. How access is defined varies between and within world regions. To objectively characterize water access across the globe, the WHO/UNICEF Joint Monitoring Programme for Water Supply and Sanitation (JMP) has defined a drinking-water ladder that ascends from unimproved water sources to improved water sources based on the type and location of the source, with "piped water on premises with a piped household water connection inside the user's dwelling, plot or yard" considered the highest category [WHO-UNICEF 2013]. As of 2011, 80% of the world's urban population and 74% of the urban population in low-income countries have access to piped water on their premises [WHO-UNICEF 2013]. However, the presence of a piped connection gives little information about the quality, quantity and frequency of water delivery; piped water is often supplied intermittently in low-income countries [Lee and Schwab 2005].

Intermittent provision of water through piped distribution networks can pose a waterborne health risk through various mechanisms. Lack of continuous pressure in pipelines leaves them vulnerable to contamination [Kumpel and Nelson 2013; LeChevallier et al. 2003]. Intermittency in supply forces users to store drinking water in the home between supply cycles, where it is at risk of further contamination during collection, handling and storage [Wright et al. 2004], or to obtain drinking water from potentially unsafe alternative sources. Intermittent supply can also limit the quantity of water available for personal and domestic hygiene and thus lead to increased levels of water-washed diseases [Cairncross and Feachem 1999]. There are scarce data on the health impact of having intermittent vs. continuous water supply. Short-term intermittencies in otherwise continuously operated distribution systems have been documented to lead to increased gastrointestinal illness in both higher income and lower income settings [Huang et al. 2011; Hunter et al. 2005; Nygard et al. 2007; Özkan et al. 2007]. Lack of continuous water supply in low-income countries has also been shown to be associated with waterborne illness [Cifuentes et al. 2002; Abu Mourad 2004], with longer intermittencies between supply cycles leading to higher risk of illness [Abu Amr and Yassin 2008; Yassin et al. 2006]. The majority of this evidence, however, comes from cross-sectional studies and has not been verified using more rigorous study designs.

Regulating the water delivery frequency in a distribution system (e.g., switching from intermittent to continuous supply) requires heavy infrastructure requirements that can typically only be implemented at large scale. This puts the health impact assessment of intermittent vs. continuous delivery of piped water beyond the reach of most experimental study designs in epidemiology because random treatment assignment is not realistically feasible. Quasi-experimental methods such as matched cohort studies provide a rigorous tool to study non-randomized interventions [Arnold et al. 2010].

We conducted a matched cohort study in Hubli-Dharwad, Karnataka, India (one of the first cities in South Asia to implement a conversion from intermittent to continuous water delivery on a pilot scale) to provide the first rigorous large-scale assessment of the health benefits from continuous water supply. Our study hypothesis was that children in households with continuous supply would have reduced levels of waterborne illness compared to children in households with intermittent supply; we further hypothesized *a priori* that the impact of continuous supply on diarrheal illness would be greater among households of low socioeconomic status and after recent rainfall.

METHODS

Study Setting

Currently, 10% of Hubli-Dharwad receives continuous water supply through a World Bank-funded pilot project, while the rest of the city receives water approximately once per week. Hubli-Dharwad has 67 administrative units called wards. Continuous supply was implemented in eight wards selected by the Karnataka Urban Infrastructure Development and Finance Corporation (KUIDFC). The criteria for selection were: (1) being able to hydraulically isolate the section of the distribution network serving the ward, (2) customer connections in all selected wards constituting approximately 10% of the total connections in the city, and (3) ward residents being representative of the socio-economic spread of Hubli-Dharwad [Sangameswaran et al. 2008]. Delivery of continuous supply in the selected wards started in 2007 in Hubli and 2008 in Dharwad, and was accompanied by an upgrading of the distribution network and customer connections, and removal of public standpipes [Sangameswaran et al. 2008].

Ward Selection

As the selection of continuous supply wards was non-random, we used a genetic matching algorithm [Diamond and Sekhon 2012; Sekhon 2011] to identify wards from among the pool of intermittent supply wards in Hubli-Dharwad that were comparable to the selected continuous supply wards based on key characteristics anticipated to affect waterborne illness. Using a pre-intervention dataset collected from a systematic subset of 15,400 Hubli-Dharwad residents [CMDR 2006], wards were matched on socioeconomic indicators (percent of pukka, low-income, one-room and slum households and percent of illiterate females), water and sanitation conditions (percent of households with own tap, receiving water less often than every five days, with own latrine, with garbage collection service) and monthly household health expenditures. Selected wards were visited by study investigators to qualitatively evaluate the appropriateness of the match based on visible ward characteristics such as population density, and socioeconomic and sanitary conditions.

Participant Selection

Each selected ward was divided by the study investigators into socioeconomically homogeneous sampling segments separated by barriers such as train tracks, main roads or open fields, based on maps of the city augmented by field observations. Participants were recruited from each segment in proportion to the segment's geographical size and observed population density to have a representative sample from each ward. In each segment, study investigators selected an easily identifiable landmark (such as a temple or bus stop). Field staff started recruitment from the street closest to the landmark and systematically approached every household for enrollment until the desired number of participants in the segment was reached. Households with at least one child under the age of five were eligible to participate and were enrolled if the primary caregiver of the children provided informed consent.

Outcome Definition and Measurement

Households were visited longitudinally over 15 months between November 2010 and February 2012 for a total of four visits per household to capture seasonal trends. A structured questionnaire was administered at each visit to collect caregiver-reported illness over the previous seven days in children under the age of five. Recorded symptoms included diarrhea (defined as three or more loose stools in any 24-hour period), highly credible gastrointestinal illness (HCGI, defined as the occurrence of at least one of the following: liquid diarrhea, soft diarrhea with abdominal cramps, vomiting, or nausea with abdominal cramps) [Colford Jr et al. 2002; Payment et al. 1991], and blood or mucus in the stool. Interviewers also collected symptom information for coughs or cold and scrapes or bruises to serve as negative control outcomes [Lipsitch et al. 2010]; these symptoms should plausibly not be impacted by water supply frequency and served as a robustness check for differential bias in symptom reporting. During the final follow-up visit, data were collected on caregiver-reported all-cause mortality in children under the age of two and episodes of cholera, typhoid fever or hepatitis in any household member as reported by the respondent since the implementation of continuous supply in 2007/2008.

Data were also collected on intermediate outcomes on the causal path between water supply frequency and waterborne illness (Figure 1). Structured questionnaires and spot check observations were conducted on households' water infrastructure and services, and participants' water collection, handling and storage practices to track objective outputs from the implementation of continuous supply and document any changes in water-related household practices in response to the infrastructure improvements. Water samples were collected from consumer taps and storage containers and analyzed for microbiological contamination to assess drinking water quality (details for the water quality sampling component have been described elsewhere) [Kumpel and Nelson 2013].

Statistical Methods

The primary outcome in this study was the caregiver-reported seven-day prevalence of diarrhea in children under the age of five. With an assumed diarrhea prevalence of 10% in the intermittent supply group the study was sized to detect a 30% (three percentage-point) reduction in diarrhea prevalence in the continuous supply group. We assumed an intracluster correlation coefficient (ICC) of 0.02 for households in the same ward [Katz et al. 1993], 0.1 for children in the same household and 0.1 for repeated observations within the same child. Assuming 1.4 children under five per household and 10% dropout, we calculated that 125 households per ward would give us 80% power to detect a three percentage-point difference between study arms with a one-sided alpha of 0.05. Pre-specified secondary outcomes included HCGI and blood or mucus in stool in children under five, all-cause mortality in children under two and the occurrence of typhoid fever, hepatitis and cholera in households. We specified household socioeconomic status and rainfall *a priori* as potential effect modifiers; we enrolled 250 households per ward (2000 households per arm) to allow us to conduct subgroup analyses for high- vs. low-income households and wet vs. dry weather conditions.

We calculated prevalence ratios between study arms for diarrhea and related outcomes using generalized linear models with a log link and a binomial error distribution. We estimated confidence intervals with bootstrapping stratified by ward and clustered by household to account for correlated outcomes, defining the target population as a fixed population determined by the selection of study wards. We calculated crude PRs and adjusted PRs controlling for potential confounders including child age, child sex, daily rainfall, household socioeconomics, religion, handwashing infrastructure, latrine ownership, sewerage and garbage disposal; we only included variables in the adjusted models that could not plausibly be impacted by the continuous supply intervention. We also conducted permutation tests to non-parametrically test for differences in outcomes between study groups using ward level means and a Wilcoxon rank-sum test statistic [Feng et al. 2001; Rosenbaum 2002]. As a robustness check for any spillover effects due to potential water sharing and/or waterborne illness transmission between participants in different study groups, we recalculated effect estimates with households on the immediate intermittent vs. continuous supply boundary excluded from analysis. The immediate boundary was defined as continuous supply areas that were not separated from neighboring intermittent supply areas by a major barrier such as a main road or railway tracks and vice versa.

We investigated effect modification by socioeconomic status and rainfall by including interaction terms in the regression models. We defined socioeconomic status based on an asset index calculated with principal components analysis from reported asset ownership and observed housing materials in participating households [Vyas and Kumaranayake 2006]. The 50th percentile of the index was used to classify study households as above median wealth vs. below median wealth. We defined wet vs. dry weather conditions based on daily rainfall data from a local weather station; households interviewed within 10 days after a rain event were categorized under wet weather. This time window was selected to allow for the typical incubation period of up to three days for most bacterial and viral diarrheagenic pathogens prior to our seven-day recall period.

We calculated cumulative incidence ratios for the severe health outcomes (under two child death, and typhoid, cholera and hepatitis in any household member) with generalized linear models. Confidence intervals were estimated through bootstrapping stratified by ward. We calculated crude CIRs as well as CIRs adjusted for household socioeconomics, religion, handwashing infrastructure, latrine ownership, sewerage and garbage disposal, and we conducted permutation tests to test for differences between study groups in ward-level means of the outcomes as described above.

RESULTS

Pre-Intervention Characteristics of Study Wards

The eight continuous supply wards (four each in Hubli and Dharwad) were matched with eight intermittent supply wards (five in Hubli and three in Dharwad) (Figure 2). Genetic matching produced study groups that were balanced on numerous key pre-intervention characteristics (Table 1). Compared to the pool of 59 wards with intermittent supply, the eight chosen for the study had improved comparability to the eight continuous supply wards in terms of demographic, socioeconomic and sanitation and hygiene conditions as measured in ward-level means and standardized differences (SD, defined as difference between ward-level means in the two study arms divided by ward-level standard deviation in the continuous supply arm) (Table 1). Overall, matching improved the balance in 26 out of 44 pre-intervention variables (Table S1 in Supplemental Materials).

Post-Intervention Characteristics of Study Participants

We enrolled 3919 households with 5420 children under five. Households in the two study arms were well balanced across a wide range of relevant covariates; the balance was assessed for household characteristics that were not anticipated to be affected by continuous water delivery (Table 2). Of the enrolled households, 3305 (84%) completed the study. The rate of loss to follow-up was similar in the two study groups over the study period (Figure 3), and households that completed the study remained well balanced in terms of possible confounding characteristics (Table 2). Households that were lost to follow-up were similar to those that remained in the study, except that they were less likely to be homeowners (Table S2 in Supplemental Materials).

Water Infrastructure and Household Water-Handling Practices

There were marked improvements in water infrastructure and services due continuous water supply and the associated distribution network and customer connection upgrades. Compared to intermittent supply wards, a higher percentage of households in continuous supply wards collected water from their own tap (67% vs. 58%), had their tap indoors (35% vs. 18%) and had the mouth of the tap elevated from the ground (86% vs. 70%) (Table 3). Customer satisfaction also improved, with a higher percentage of respondents in continuous supply wards reporting being content with the quality, quantity and pressure of their water supply (Table 3). Both tap and stored water quality was significantly improved in households with continuous supply [Kumpel and Nelson 2013]; however, the majority of participants with continuous supply continued to store drinking water in their homes (Table 3) and contamination during storage was common in both intermittent and continuous supply households [Kumpel and Nelson 2013]. A similar percentage of intermittent and continuous supply households practiced drinking water treatment (Table 3). There was a marked reduction in the use of water from other sources such as borewells in continuous supply wards (Table 3). The total quantity of water consumed per capita increased in households with continuous water supply [Kumpel 2013, unpublished data] but there was no difference in the percentage of households with water available at their handwashing facility between the two groups (Table 3).

Waterborne Illness

Diarrhea prevalence in children under five in the study population was 8% over the study period. HCGI prevalence was 11% and the prevalence of blood or mucus in stool was 2%. All symptoms were more prevalent in children living in below median wealth households compared to above median wealth households (Table 4). Rainfall did not have an impact on the prevalence of child waterborne illness (Table 4). In the three years since the implementation of continuous supply, approximately 5% of households experienced at least one case of typhoid fever, 0.3% had cholera, 3% had hepatitis, and 1% lost a child under the age of two.

Children in continuous supply wards had 7% lower diarrhea prevalence (adj. PR = 0.93, 0.83-1.04) and 22% lower prevalence of blood or mucus in stool (adj. PR = 0.78, 0.60-1.01), with differences that were borderline significant at the 95% confidence level (Table 4). HCGI prevalence in children did not differ between the two groups (adj. PR = 1.01, 0.92-1.11) (Table 4). The negative control outcomes also did not differ between groups. Continuous supply wards had 42% reduction in the percentage of households that had experienced at least one case of typhoid fever since the implementation of continuous water supply (adj. PR = 0.58, 0.41-0.78) (Table 5). We did not have sufficient statistical power to discern the impact of continuous supply on cholera, hepatitis and child mortality; our findings suggested a 49% reduction in the percentage of households where a child death had occurred (adj. PR = 0.51, 0.22-1.07) in continuous supply wards but it was not possible to rule out chance as a possible explanation of this difference due to the small number of deaths in the study (n=32) (Table 5). The crude and adjusted effect estimates were similar for all health outcomes (Tables 4 and 5). Excluding households located in the boundary areas between continuous vs. intermittent supply from the analysis to protect against possible spillover effects between groups did not change the results (Tables S3 and S4 in Supplemental Materials).

The provision of continuous water supply led to larger health improvements among children living in low-income households; children in below median wealth households in continuous supply wards had 11% reduction in diarrhea prevalence (PR = 0.89, 0.76-1.04) while there was no impact in above median health households (PR = 0.98, 0.84-1.16). The interaction, however, was not significant (p = 0.35) (Table 4). Prevalence of blood or mucus in stool showed significant effect modification with socioeconomic status (p = 0.03), with below median wealth households experiencing 37% reduction due to continuous water supply (PR = 0.63, 0.46-0.87) and above median wealth households experiencing no impact (PR = 1.08, 0.73-1.63) (Table 4). Socioeconomic status had no effect on the impact of continuous supply on child HCGI. The impact of rainfall events on effect estimates was inconclusive for all waterborne symptoms in children. Continuous supply led to 13% reduction in diarrhea prevalence in the rainy periods (PR = 0.87, 0.75-1.00) and had no impact during the dry periods (PR = 1.01, 0.86-1.18) (p=0.14) while there was a reduction in blood or mucus in stool during both weather conditions but the reduction appeared to be larger in the dry periods (PR = 0.69, 0.49-0.97) than in the wet periods (PR = 0.87, 0.62-1.22) (p=0.30) (Table 4). Rainfall did not affect the impact on continuous supply on child HCGI (Table 4).

DISCUSSION

Summary of Findings

This large-scale, matched cohort study is the first effort to measure the health effects of continuous water supply compared to intermittent water supply in urban populations in low-income countries. In Hubli-Dharwad, India, the provision of continuous supply led to improvements in water infrastructure and services (Table 3), and drinking water quality [Kumpel and Nelson 2013]. Some household behaviors changed in response to having access to a continuous water supply, including a reduced reliance on alternative water sources, while some others remained unchanged, most notably the common practice of storing water in the home for drinking purposes. Children in households with continuous supply had 7% reduction in the prevalence of diarrhea (adj. PR = 0.93, 0.83-1.04) and a 22% reduction in the prevalence of blood or mucus in stool (adj. PR = 0.78, 0.60-1.01) (Table 4). The reductions in waterborne illness symptoms in children were more pronounced in below median wealth households compared to above median wealth households (Table 4). In continuous supply wards, there was 42% reduction in the percentage of households with at least one case of typhoid fever since the implementation of continuous water supply (adj. CIR = 0.58, 0.41-0.78) and potentially 49% reduction in the percentage of households with death of a child under the age of two (CIR = 0.51, 0.22-1.07) (Table 5).

Our findings suggest larger reductions due to continuous water supply in severe waterborne illness compared to the more general symptoms we measured. We observed more pronounced reductions in infections that lead to blood or mucus in stool, which is typically caused by shigellosis and amoebic dysentery that are both transmitted through waterborne and water-washed pathways [Cairncross and Feachem 1999]. We also observed a significant reduction in households with typhoid cases in continuous supply areas; this is consistent with previous evidence linking typhoid fever to the municipal water supply and, more specifically, to contamination in the water distribution system [Mermin et al. 1999; Ram et al. 2007]. In contrast, we observed no reduction in HCGI (a broad category including various gastrointestinal symptoms) and only a modest reduction in diarrhea. This attenuated effect in more generalized measures of gastrointestinal illness could be due to the continued presence of non-waterborne pathogens leading to general symptoms of enteric infection despite reduced pathogen transmission through the water supply under a continuous supply scheme.

Implications for Water Service Delivery

It is notable that the practice of storing drinking water was maintained in the continuous supply households despite the availability of water directly from the tap. Reasons for this behavior might include habit as well as convenience since households often have their tap connections located at the entrance to the compound, making it inconvenient to directly use tap water for drinking and cooking needs. Stored water can become contaminated with pathogens during collection, handling and storage in the home [Wright et al. 2004]. Our findings are consistent with this phenomenon; while continuous supply improved both tap and stored water quality in our study population, both study groups experienced deterioration in water quality between the tap and the point of consumption [Kumpel and Nelson 2013]. The difference in stored water quality between the two groups was less pronounced than the difference in tap water quality [Kumpel and Nelson 2013], potentially preventing consumers from achieving the full potential of health benefits from continuous water supply. These findings imply that additional measures such as provision of indoor plumbing to extend tap connections into the kitchen area to eliminate the need for storage, promotion of direct use of tap water or, at a minimum, use of safe storage vessels for storing drinking water have the potential to enhance the health benefits from continuous water supply.

We also observed larger reductions in child waterborne illness symptoms in below median wealth households in response to continuous water supply than in above median wealth households. There are several possible explanations for this observation. Low-income areas typically have poor sanitation infrastructure; open sewers and pooling of wastewater on the streets is common and water lines are often surrounded by or submerged in sewage-contaminated water. The rate of pathogen intrusion into pipelines is a function of the degree of fecal contamination in the vicinity of water lines [LeChevallier et al. 2003]. The unsanitary conditions in low-income areas would be expected to increase the opportunities for pathogen intrusion into the water distribution system during non-pressurized periods between supply cycles. Having continuous supply (i.e., continuous pressure in pipes) would therefore be expected to have a more marked impact on drinking water quality and waterborne illness in low-income areas compared to high-income areas with better sanitation infrastructure. Household water treatment in intermittent supply wards was also more prevalent among high-income households in our study population than among low-income households, providing additional protection against the water quality deterioration under intermittent supply in high-income households. In addition, high-income households have access to several coping mechanisms to alleviate the strain on water availability imposed by intermittent supply. Most have high-capacity underground and rooftop storage tanks that are connected to indoor plumbing, allowing them to effectively simulate a continuous water supply in their homes. In contrast, low-income households rely on storage containers of limited volume to secure water for all households needs until the following supply cycle and are likely to experience a bigger strain on water availability under intermittent supply, and consequently benefit more from a conversion to continuous supply. These findings warrant prioritizing vulnerable, low-income populations in the provision of continuous supply to achieve the greatest health benefits.

Study Limitations

One limitation of this study is that we could not randomly allocate the continuous water supply intervention to city wards. Given the engineering constraints and extremely high cost imposed by water supply infrastructure, we expect that it would be nearly impossible to randomize continuous and intermittent water supply interventions in urban settings. In the absence of randomization, the matched cohort design is a strong alternative to construct well-balanced groups, but the design can only ensure balance on observable characteristics; as with all non-randomized designs, there remains the possibility that study groups have underlying differences in unobservable characteristics that could bias the study findings [Arnold et al. 2010]. While it is possible that residual confounding remains due to unobservable differences between the continuous and intermittent supply groups in our study, we expect that matching in the design removed the major sources of confounding given the high quality of the data used to match wards and the exceptionally good balance between intervention and control groups as measured by observable characteristics (Table 2). Furthermore, adjusted effect estimates coincided with unadjusted estimates (Tables 4 and 5), which demonstrates that matching in the design lessened the need to rely on statistical adjustment for unbiased inference (similar to a randomized trial) [Ho et al. 2007].

Another limitation of our study is that the intervention we evaluated was non-blinded by its nature, and we relied on caregiver-reported health outcomes. Non-blinded studies with subjectively reported outcomes are potentially vulnerable to reporting bias in the group receiving the intervention [Wood et al. 2008]. However, the outcomes that showed the most pronounced impact in our study (blood or mucus in children's stool and typhoid fever in household members) were of relatively non-subjective nature, and we would expect participants to accurately remember and report these severe symptoms with minimal bias. In addition, the lack of reductions in the negative control outcomes provides an additional robustness check, suggesting minimal reporting bias.

Finally, the conversion to continuous water supply in Hubli-Dharwad was accompanied by an upgrading of the distribution system, including complete pipe replacement for improved leak management. As such, our study cannot discern the individual impact of water delivery frequency from the impact of replacing leaky pipes; further studies are needed to assess whether the water quality improvements and health benefits observed in this study can be achieved without complete replacement of water pipelines.

CONCLUSIONS

Our findings indicate that switching from intermittent to continuous water supply along with replacing leaky pipes is associated with a reduction in the prevalence of diarrhea and dysentery in children under the age of five and the incidence of typhoid fever among tap water consumers. The reductions in child waterborne illness are more pronounced in low-income households, suggesting that these vulnerable populations would benefit from receiving priority in the provision of continuous water supply. Continued storage of drinking water was common in our study population despite continuous water supply, and point-of-use contamination of water during storage may have attenuated the health benefits from continuous supply in this setting. Complementary measures to eliminate household storage or minimize point-of-use contamination could potentially increase the protection against waterborne illness from continuous supply.

TABLES

TABLE 1. Comparison of Pre-Intervention Characteristics by Study Group before and after Matching in Hubli-Dharwad (source: CMDR, 2006)

	Full Set of Intermittent Supply Wards (N=59)		Matched Set of Intermittent Supply Wards (N=8)		Continuous Supply Wards (N=8)
	Mean	SD [a]	Mean	SD [a]	Mean
Demographics and socioeconomics					
Mean number of persons per household	5.1	-68	5.0	-30	4.8
Mean number of children <5 yrs per household	1.4	-115	1.4	-85	1.3
% of illiterate females	17.7	-13	16.4	15	17.1
% of individuals working as agricultural labourer	12.0	6	12.3	2	12.4
% of non-Hindu households	26.0	-83	22.2	-40	18.7
% of scheduled caste or tribe households	14.6	-94	10.4	4	10.5
% of slum households (self-report)	22.8	10	23.7	6	25.0
% of migrant households	14.5	-63	13.1	-47	8.6
% of BPL card holder households [b]	25.9	-8	26.7	-14	24.8
% of households with income <$350/year	12.2	-47	11.6	-37	9.5
% of households that own their home	65.9	92	72.5	16	73.9
% of pukka homes [c]	71.5	15	75.6	-11	73.9
% of one-room homes	6.3	-213	5.2	-141	2.9
% of housholds that have:					
Electricity	94.4	49	95.4	11	95.8
Fridge	16.0	-10	17.0	-17	14.6
Bicycle	26.9	41	30.4	15	32.4
Motorcycle	29.7	7	35.6	-33	30.6
Phone	38.4	1	40.4	-8	38.7
Radio	39.4	51	42.5	30	46.7
Water, sanitation and hygiene conditions					
% of household with own tap	79.5	136	88.9	25	91.1
% of households receiving water every 5 or more days	7.7	-313	2.8	-72	1.3
% of households with own latrine	74.5	32	79.1	5	80.0
% of household served by open drain	8.4	65	12.0	55	31.3
% of househols with designated garbage bin or collection at door	47.1	9	45.6	16	49.0
% of households with garbage cleared regularly by municipality	37.5	-9	37.9	-11	35.5
% of household with health expenditures >$2/month	24.5	46	21.1	64	33.3

SD: Standardized difference, BPL: Below poverty level

[a] SD is the difference between ward-level means in two study arms divided by the ward-level standard deviation in continuous supply arm.

[b] BPL card is issued by the government based on household income.

[c] Pukka refers to concrete or reinforced cement concrete.

TABLE 2. Comparison of Post-Intervention Characteristics by Study Group (at enrollment and at end of study)

	At Enrollment				At End of Study			
	Continuous Supply		Intermittent Supply		Continuous Supply		Intermittent Supply	
	N	%	N	%	N	%	N	%
Demographics and socioeconomics								
Mean number of persons per household	1968	6.5	1951	6.5	1668	6.7	1634	6.7
Mean number of children <5 yrs per household	1968	1.4	1951	1.4	1668	1.4	1634	1.4
Mean age of primary caregiver of children <5 yrs	1956	26.9	1945	27.0	1656	27.0	1629	27.2
Mean monthly household income (USD)	1562	195.9	1466	202.9	1321	198.2	1233	206.6
Mean number of rooms in household	1967	2.4	1951	2.3	1667	2.5	1634	2.4
% of households with:								
Pukka roof [a]	1967	44.0	1951	45.2	1667	44.5	1634	45.3
Pukka walls [a]	1814	56.4	1781	63.4	1637	56.7	1600	63.1
Pukka floor [a]	1814	95.1	1781	96.5	1637	94.9	1600	96.6
Fridge	1968	25.5	1951	30.2	1668	25.3	1634	31.1
Motorcycle	1968	47.4	1951	48.9	1668	48.3	1634	50.4
Mobile phone	1968	90.5	1951	89.9	1668	90.9	1634	90.1
% of household owning at least one home	1966	66.9	1951	64.4	1666	71.5	1634	69.8
% of self-employed father	1962	32.7	1945	35.3	1662	32.9	1628	36.6
% of illiterate mother	1962	8.5	1948	10.1	1662	8.0	1632	10.4
% Hindu	1967	73.1	1951	66.0	1667	72.5	1634	66.8
Water, sanitation and hygiene indicators								
% of households with handwashing facility:								
Inside the household	1968	73.6	1951	73.5	1668	73.7	1634	73.6
In yard	1968	24.8	1951	25.1	1668	24.9	1634	25.3
No specific place	1968	1.6	1951	1.4	1668	1.4	1634	1.1
% of households with sanitation access:								
Private latrine	1815	91.2	1782	91.6	1638	91.0	1600	91.8
Public latrine	1815	6.0	1782	3.6	1638	6.1	1600	3.7
No latrine	1815	2.9	1782	4.7	1638	2.9	1600	4.6
% of households where children <5 yrs defecate:								
In latrine or potty	1811	64.9	1781	65.0	1634	65.5	1599	65.3
In area within household compound	1811	19.5	1781	16.5	1634	19.5	1599	16.6
In area outside household compound	1811	16.9	1781	19.5	1634	16.7	1599	19.1
% of households with sewarage in vicinity:								
Underground piped sewer	1813	78.3	1777	74.4	1636	78.4	1596	74.1
Open drain or nala	1813	71.6	1777	75.1	1636	71.9	1596	75.3
% of household with garbage disposal:								
In open heap	1814	34.5	1781	25.9	1637	34.3	1600	25.2
Designed bin	1814	43.9	1781	45.8	1637	44.0	1600	46.5
Collected at the door	1814	18.6	1781	24.5	1637	18.6	1600	24.6

USD: US dollars.

[a] Pukka refers to concrete or reinforced cement concrete.

TABLE 3. Water Infrastructure and Water-Related Household Behaviors

	Continuous Supply		Intermittent Supply	
	N	%	N	%
Water infrastructure and services				
Collects municipal water from:				
Own connection	1968	67.3	1951	58.3
Landlord's or neighbor's connection	1968	32.5	1951	35.4
Public connection	1968	0.2	1951	6.3
Location of tap:				
Indoors within household	1964	35.1	1907	17.9
Outdoors within premises	1964	61.0	1907	69.3
Not on premises	1964	3.3	1907	10.9
Location of mouth of tap:				
Elevated from the ground	1966	85.9	1881	69.9
On the ground	1966	13.5	1881	17.3
Inside a tank	1966	0.4	1881	12.2
Customer satisfaction: [a]				
Tap water does not smell or look dirty	7090	72.5	7006	59.8
Happy with tap water quality	7166	77.4	7066	54.4
Happy with tap water quantity	7166	93.8	7066	67.9
Happy with tap water presssure	7166	90.1	7066	53.6
Water-related household behaviors				
Retrieves drinking water from: [a]				
Tap connected directly to waterline	7008	9.5	6896	1.6
Tap connected to overhead tank	7008	0.7	6896	0.2
Storage container	7008	76.5	6896	83.4
Commercial water treatment device	7008	11.8	6896	13.3
Bottled water	7008	1.4	6896	1.5
Collects water from other sources: [a]				
Borewell (public or private)	7167	5.4	7067	37.8
Water truck	7167	0.0	7067	2.1
Washes vegetables:				
Outside	1815	27.5	1783	15.4
In kitchen	1815	57.3	1783	76.8
In bathroom	1815	14.9	1783	7.6
Washes utensils:				
Outside	1815	71.3	1783	78.7
In kitchen	1815	12.8	1783	10.7
In bathroom	1815	15.5	1783	9.9
Has handwashing facility with water	1962	95.9	1949	93.4

[a] The N for these variables is higher because these questions were asked at each round.

TABLE 4. Seven-Day Prevalence of Waterborne Illness Outcomes in Children < 5 Yrs

	Intermittent Supply		Continuous Supply						
	N	Prev %	N	Prev %	PR	(95% CI [a])	Adj. PR	(95% CI [a])	p-value
Main analysis									Perm Test [c]
Diarrhea	10019	8.4	10054	7.9	0.94	(0.84 , 1.05)	0.93	(0.83 , 1.04)	0.94
HCGI	10000	11.3	10035	11.5	1.02	(0.93 , 1.11)	1.01	(0.92 , 1.11)	0.78
Blood or mucus in stool	10016	1.9	10052	1.5	0.81	(0.65 , 1.02)	0.78	(0.60 , 1.01)	0.25
Subgroup analysis by wealth									Interaction [d]
Above median wealth									
Diarrhea	5043	7.0	5037	6.9	0.98	(0.83 , 1.16)	0.98	(0.84 , 1.16)	0.35
HCGI	5034	10.1	5026	10.4	1.03	(0.90 , 1.18)	1.04	(0.91 , 1.20)	0.59
Blood or mucus in stool	5041	1.2	5036	1.4	1.11	(0.77 , 1.63)	1.08	(0.73 , 1.63)	0.03
Below median wealth									
Diarrhea	4970	9.8	4991	8.8	0.90	(0.78 , 1.03)	0.89	(0.76 , 1.04)	--
HCGI	4960	12.6	4983	12.6	1.00	(0.88 , 1.13)	0.99	(0.87 , 1.13)	--
Blood or mucus in stool	4969	2.5	4990	1.6	0.64	(0.47 , 0.85)	0.63	(0.46 , 0.87)	--
Subgroup analysis by rainfall									Interaction [d]
Dry Period (>10 days after rain)									
Diarrhea	4284	8.3	4343	8.4	1.01	(0.87 , 1.17)	1.01	(0.86 , 1.18)	0.14
HCGI	4276	10.7	4337	11.3	1.05	(0.93 , 1.20)	1.05	(0.92 , 1.22)	0.42
Blood or mucus in stool	4282	2.2	4342	1.5	0.70	(0.50 , 0.95)	0.69	(0.49 , 0.97)	0.30
Wet Period (<10 days after rain)									
Diarrhea	5735	8.5	5711	7.6	0.89	(0.77 , 1.02)	0.87	(0.75 , 1.00)	--
HCGI	5724	11.8	5698	11.7	0.99	(0.89 , 1.11)	0.99	(0.88 , 1.11)	--
Blood or mucus in stool	5734	1.6	5710	1.5	0.93	(0.68 , 1.26)	0.87	(0.62 , 1.22)	--

PR: Prevalence ratio, CI: Confidence interval, HCGI: Highly credible gastrointestinal illness

[a] Confidence intervals obtained by bootstrapping within strata of wards with clustering at household level.

[b] Adjusted for child age, child sex, season, household SES, religion, handwashing infrastructure, latrine ownership, sewerage and garbage disposal.

[c] p-value from permutation test.

[d] p-value for interaction.

TABLE 5. Severe Health Outcomes since Implementation of Continuous Supply

	Intermittent Supply			Continuous Supply							
	N	# HHs	I [a]	N	# HHs	I [a]	CIR	(95% CI [b])	Adj.CIR	(95% CI [b])	p [d]
Typhoid	1690	103	60.9	1711	58	33.9	0.56	(0.40 , 0.76)	0.58	(0.41 , 0.78)	0.43
Cholera	1691	4	2.4	1711	6	3.5	1.48	(0.37 , 6.92)	-- [e]	(-- , --)	0.69
Hepatitis	1690	46	27.2	1711	59	34.5	1.27	(0.87 , 1.87)	1.13	(0.76 , 1.73)	0.67
Under 2-yr child death	1695	20	11.8	1713	12	7.0	0.59	(0.26 , 1.19)	0.51	(0.22 , 1.07)	0.16

HH: Household, I: Incidence, CIR: Cumulative incidence ratio, CI: Confidence interval

[a] Households with at least one case (per 1000 households) since implementation of 24x7.

[b] Confidence intervals obtained by bootstrapping within strata of wards.

[c] Adjusted for household SES, religion, handwashing infrastructure, latrine ownersip, sewerage and garbage disposal.

[d] p-value from permutation test.

[e] Adjusted CIR not calculated due to sparse data.

SUPPLEMENTARY TABLES

TABLE S1. Comparison of Pre-Intervention Characteristics by Study Group before and after Matching in Hubli-Dharwad (source: CMDR, 2006)

	Full Set of Intermittent Supply Wards (N=59)		Matched Set of Intermittent Supply Wards (N=8)		Continuous Supply Wards (N=8)
	Mean	SD [a]	Mean	SD [a]	Mean
Demographics and socioeconomics					
Mean number of persons per household	5.1	-68	5.0	-30	4.8
Mean number of children <5 yrs per household	1.4	-115	1.4	-85	1.3
% of < 5 yrs childen	7.7	-60	6.9	-14	6.7
% of males	51.8	17	52.5	-26	52.0
% of married individuals	47.4	100	48.6	57	50.2
% of illiterate females	17.7	-13	16.4	15	17.1
% of individuals working as agricultural labourer	12.0	6	12.3	2	12.4
% of non-Hindu households	26.0	-83	22.2	-40	18.7
% of scheduled caste or tribe households	14.6	-94	10.4	4	10.5
% of slum households (self-report)	22.8	10	23.7	6	25.0
% of migrant households	14.5	-63	13.1	-47	8.6
% of BPL card holder households [b]	25.9	-8	26.7	-14	24.8
% of households with income <$350/year	12.2	-47	11.6	-37	9.5
% of households that borrow money	12.6	-117	11.4	-94	6.2
% of households that save money	6.9	-16	7.9	-30	5.8
% of households that report having sufficient income	85.1	177	89.6	103	95.8
% iof households that own agricultural land	8.0	-75	7.0	-55	4.1
% of households that own their home	65.9	92	72.5	16	73.9
% of pukka homes [c]	71.5	15	75.6	-11	73.9
% of one-room homes	6.3	-213	5.2	-141	2.9
% of housholds that have:					
Electricity	94.4	49	95.4	11	95.8
TV	77.6	2	78.5	-3	78.0
Phone	38.4	1	40.4	-8	38.7
Fridge	16.0	-10	17.0	-17	14.6
Grinder	53.7	13	55.5	1	55.6
Radio	39.4	51	42.5	30	46.7
LPG cylnder	66.7	32	70.8	7	71.9
Bicycle	26.9	41	30.4	15	32.4
Motorcycle	29.7	7	35.6	-33	30.6
Car	3.5	-6	4.6	-39	3.3
Computer	3.1	-8	3.2	-11	2.9
Agricultural assets	2.3	-119	1.7	-72	0.8
Livestock	1.9	-1	1.3	17	1.9
Number of households in ward	2313.6	-39	2433.0	-67	2148.9
Ward infrastructure index [d]	0.2	-66	0.2	-69	0.1
Water, sanitation and hygiene conditions					
% of household with own tap	79.5	136	88.9	25	91.1
% of households receiving water every 5 or more days	7.7	-313	2.8	-72	1.3
% of households paying >$2/month for water	3.5	-51	4.1	-77	2.4
% of households with own latrine	74.5	32	79.1	5	80.0
% of household served by open drain	8.4	65	12.0	55	31.3
% of househols with designated garbage bin or collection at door	47.1	9	45.6	16	49.0
% of households with garbage cleared regularly by municipality	37.5	-9	37.9	-11	35.5
% of household with health expenditures >$2/month	24.5	46	21.1	64	33.3
% of households receiving healthcare at private hospital or clinic	68.1	-70	69.0	-74	53.5

SD: Standardized difference, BPL: Below poverty level, LPG: Liquid propane gas.

[a] SD is the difference between ward-level means in two study arms divided by the ward-level standard deviation in continuous supply arm.

[b] BPL card is issued by the government based on household income.

[c] Pukka refers to concrete or reinforced cement concrete.

[d] Ward infrastrucutre index is a combined metric based on the number of schools, hospitals and other amenities in the ward.

TABLE S2. Comparison of Post-Intervention Characteristics by Loss to Follow-Up Status

	HHs that completed study (N=3305)		HHs lost to follow-up (N=617)	
	N	%	N	%
Demographics and socioeconomics				
Mean number of persons per household	3302	6.7	617	5.4
Mean number of children <5 yrs per household	3302	1.4	617	1.4
Mean age of primary caregiver of children <5 yrs	3285	27.1	616	26.5
Mean monthly household income (USD)	2554	202.2	474	183.4
Mean number of rooms in household	3301	2.4	617	2.0
% of households with:				
Pukka roof [a]	3301	44.9	617	43.1
Pukka walls [a]	3240	59.8	358	60.3
Pukka floor [a]	3240	95.8	358	96.1
Fridge	3305	28.1	617	26.1
Motorcycle	3305	49.3	617	41.7
Mobile phone	3305	90.4	617	88.7
% of household owning at least one home	3300	70.7	617	38.7
% of self-employed father	3290	34.7	617	30.1
% of illiterate mother	3294	9.2	616	9.9
% Hindu	3301	69.7	617	69.0
Water, sanitation and hygiene indicators				
% of households with handwashing facility:				
Inside the household	3302	73.7	617	72.9
In yard	3302	25.1	617	24.1
No specific place	3302	1.2	617	2.9
% of households with sanitation access:				
Private latrine	3241	91.4	359	91.9
Public latrine	3241	4.9	359	3.9
No latrine	3241	3.7	359	4.2
% of households where children <5 yrs defecate:				
In latrine or potty	3236	65.4	359	61.3
In area within household compound	3236	18.0	359	18.1
In area outside household compound	3236	17.9	359	21.2
% of households with sewarage in vicinity:				
Underground piped sewer	3235	76.3	358	77.1
Open drain or nala	3235	73.6	358	70.9
% of household with garbage disposal:				
In open heap	3240	29.8	358	33.8
Designed bin	3240	45.3	358	41.6
Collected at the door	3240	21.6	358	21.2

HH: Household, USD: US dollars.

[a] Pukka refers to concrete or reinforced cement concrete.

TABLE S3. Seven-Day Prevalence of Health Outcomes in Children <5 Yrs (excluding boundary households)

	Intermittent Supply		Continuous Supply						
	N	Prev %	N	Prev %	PR	(95% CI [a])	Adj. PR	(95% CI [a])	Perm. Test [c]
Diarrhea	10019	8.4	7679	7.9	0.94	(0.83 , 1.06)	0.93	(0.82 , 1.05)	0.96
HCGI	10000	11.3	7664	11.8	1.04	(0.94 , 1.14)	1.03	(0.93 , 1.14)	0.67
Blood or mucus in stool	10016	1.9	7677	1.6	0.84	(0.65 , 1.06)	0.83	(0.62 , 1.10)	0.35

PR: Prevalence ratio, CI: Confidence interval, HCGI: Highly credible gastrointestinal illness

[a] Confidence intervals obtained by bootstrapping within strata of wards with clustering at household level.

[b] Adjusted for child age, child sex, season, household SES, religion, handwashing infrastructure, latrine ownership, sewerage and garbage disposal.

[c] p-value from permutation test.

TABLE S4. Severe Health Outcomes since Implementation of Continuous Supply (excluding boundary households)

	Intermittent Supply			Continuous Supply							
	N	# HHs	cidence [a]	N	# HHs	cidence	PR	(95% CI [b])	Adj. PR	(95% CI [b])	p [d]
Typhoid	1690	103	60.9	1377	49	35.6	0.58	(0.42 , 0.81)	0.61	(0.42 , 0.87)	0.35
Cholera	1691	4	2.4	1378	5	3.6	1.53	(0.37 , 7.36)	-- [e]	(-- , --)	1.00
Hepatitis	1690	46	27.2	1377	50	36.3	1.33	(0.91 , 1.98)	1.22	(0.81 , 1.88)	0.35
Under 2-yr child death	1695	20	11.8	1378	9	6.5	0.55	(0.22 , 1.15)	0.48	(0.17 , 1.04)	0.13

HH: Household, CIR: Cumulative incidence ratio, CI: Confidence interval

[a] HHs with at least one case (per 1000 HHs) since implementation of 24x7.

[b] Confidence intervals obtained by bootstrapping within strata of wards.

[c] Adjusted for household SES, religion, handwashing infrastructure, latrine ownersip, sewerage and garbage disposal.

[d] p-value from permutation test.

[e] Adjusted CIR not calculated due to sparse data.

FIGURES

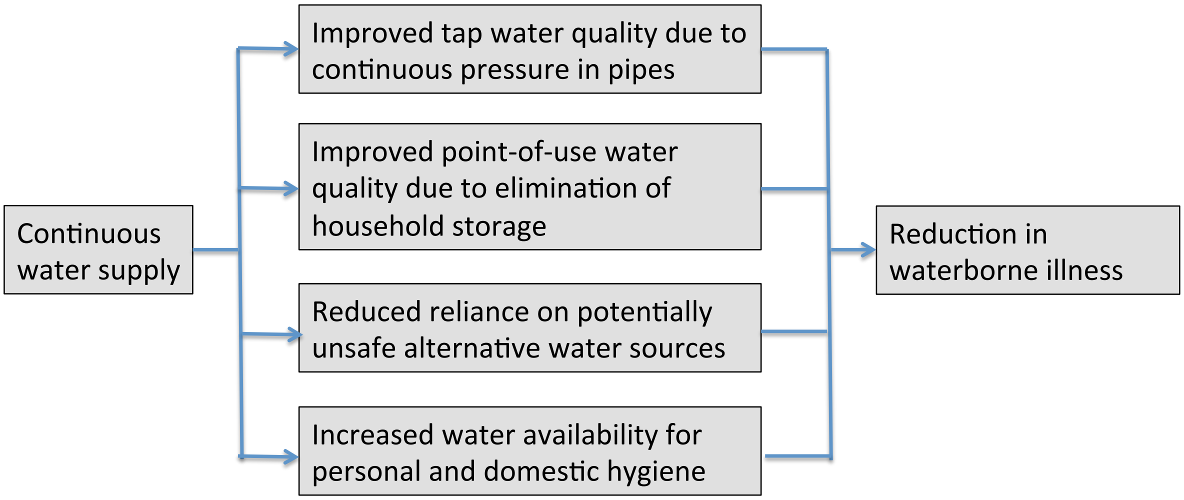


FIGURE 1. Causal Chain between Continuous Water Supply and Reduction in Waterborne Illness

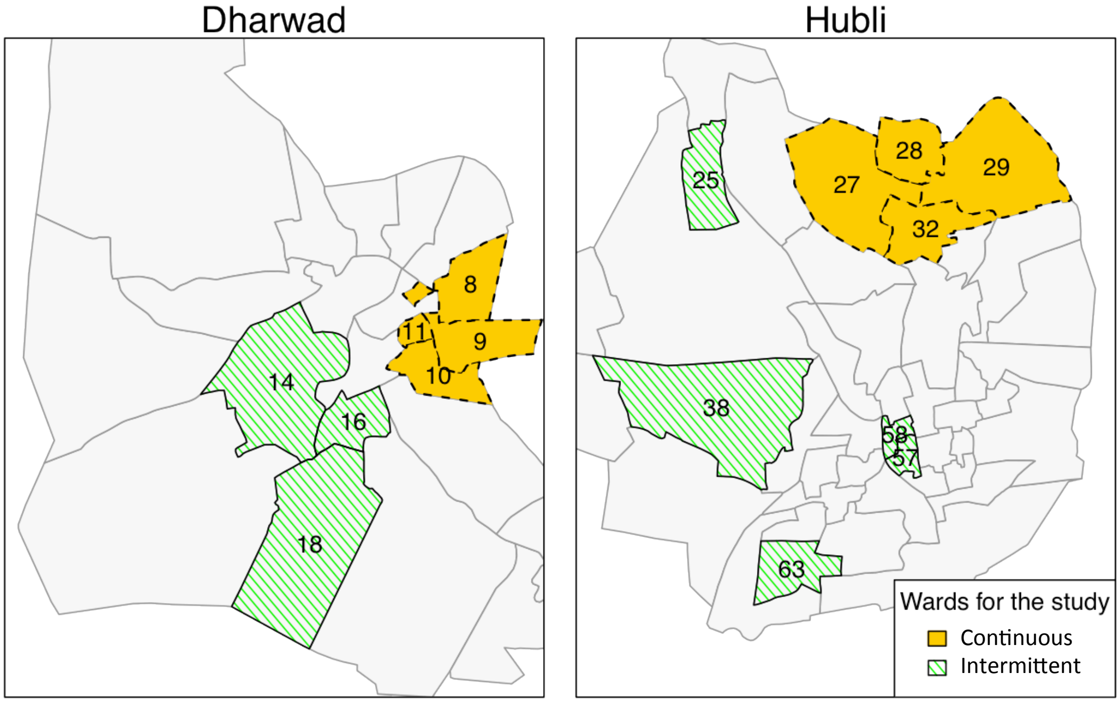


FIGURE 2. Study Wards with Intermittent and Continuous Supply in Hubli-Dharwad

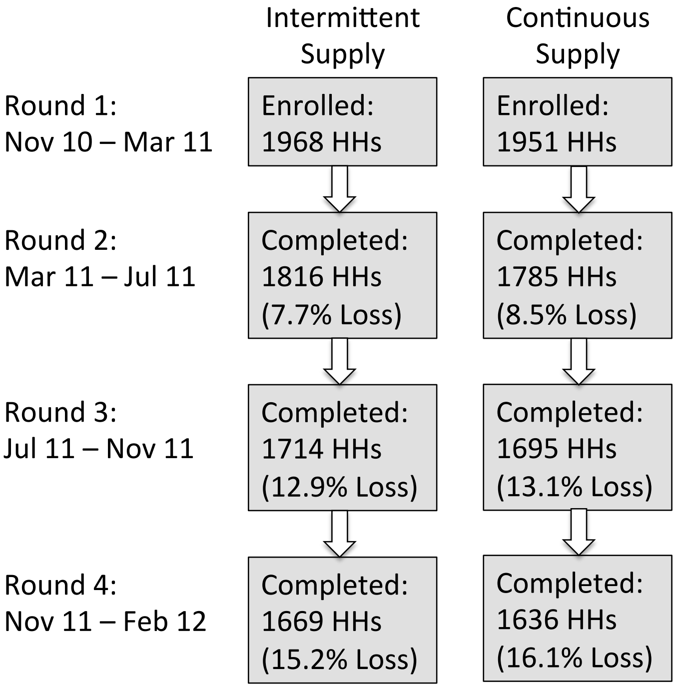


FIGURE 3. Loss to Follow-Up across Study Arms and Data Collection Rounds

Chapter 4. Randomized Controlled Trial Evaluating Health Impact of Treating and Safely Storing Shallow Tubewell Drinking Water in Rural Bangladesh

The majority of rural Bangladeshis obtain drinking water from groundwater aquifers using shallow tubewells [NIPORT 2009, BBS-UNICEF 2010]. Tubewells have been in use in Bangladesh since the 1940s but their ubiquitous adoption was motivated by a UNICEF campaign in the 1970s that replaced fecally contaminated drinking water sources such as ponds and other surface waters with tubewells [Smith et al. 2000]. Groundwater is typically considered microbiologically safer due to natural pathogen removal and inactivation by percolation through soil [Gadgil 1998]. However, studies conducted during the period of widespread tubewell installation in Bangladesh in the 1970s failed to detect reductions in rates of cholera and other diarrheal diseases in tubewell users vs. non-users [Briscoe 1978; Khan et al. 1981; Levine et al. 1976; Sommer and Woodward 1972].

One possible explanation for the failure of tubewells to prevent diarrhea could be that tubewell water remains sufficiently contaminated with pathogens to pose a health risk. Fecal contamination has been detected in groundwater sources from various settings in developed as well as developing countries [Lloyd and Bartram 1991; Raina et al. 1999; Strauss et al. 2001]. Recent studies in Bangladesh have demonstrated that up to 65% of tubewells can contain indicators of fecal contamination such as fecal/thermotolerant coliforms and *Escherichia coli*; the level of contamination, however, is typically low [Ferguson et al. 2012; van Geen et al. 2011; Hoque et al. 2006; Islam et al. 2001; Knappett et al. 2012; Leber et al. 2011; Luby et al. 2006, 2008]. Fecal pathogens including rotavirus, adenovirus, *Shigella*, *Vibrio cholerae* and enterotoxigenic *E. coli* have also been detected in tubewell water [Ferguson et al. 2012; Knappett et al. 2012]. Tubewells in rural Bangladesh are often located in close proximity to latrines and ponds. Possible mechanisms for tubewell contamination with fecal pathogens include infiltration into the groundwater aquifers from nearby latrines, septic tanks and ponds [Knappett et al. 2011a, 2011b], short-circuiting of contaminated surface water into the wells through leaky seals of various tubewell components [Knappett et al. 2012] or harboring of bacteria in contaminated handpumps [Ferguson et al. 2011].

An alternative explanation for the lack of a reduction in diarrhea after tubewell installation could be that, although tubewell water may be relatively safe at the source, it becomes contaminated during collection, handling and storage in households. On average, 55% of Bangladeshis store water for drinking and cooking purposes, depending on season and the proximity of the tubewell to the kitchen [Hoque et al. 2006]. The most commonly used storage container is the *kolshi*; a lidless aluminum vessel with a wide brim, which leaves it vulnerable to contamination by contact with hands [Clasen et al. 2007]. There is evidence from various settings on contamination of drinking water during household storage, and the extent of point-of-use contamination is typically more pronounced in settings where the source water quality is relatively good, such as in the case of tubewell water in Bangladesh [Trevett et al. 2005; Wright et al. 2004]. In rural Bangladesh, deterioration in the microbiological quality of stored water is common [Hoque et al. 2006], and the presence of fecal indicators in stored water (as opposed to in source water) has been associated with increased diarrhea risk among children [Bhargava et al. 2003].

An estimated 16,600 to 27,700 children die each year in Bangladesh from diarrheal disease [Tanaka et al. 2007]. As a large majority of Bangladeshis rely on tubewells for drinking water, the issue of whether and to what extent contamination of tubewell water at the source or at the point of use contributes to this disease burden is a critically important question. In addition to microbial contamination, groundwater in many regions of Bangladesh is also contaminated with high levels of naturally occurring arsenic [BGS& DPHE 2001]. There is high spatial variation in the distribution of groundwater arsenic, and therefore a common mitigation method for reducing exposure is for a family with a contaminated tubewell to switch to a nearby, arsenic-free tubewell [Ahmed et al. 2006]. However, recent research indicates that arsenic concentration in shallow tubewells is inversely related to microbiological contamination [van Geen et al. 2011; Leber et al. 2011]. This makes the provision of safe drinking water in Bangladesh particularly difficult. As families switch to low-arsenic wells and inadvertently put themselves at risk of increased pathogen exposure [Wu et al. 2011], assessing whether taking additional steps such as treating and safely storing tubewell drinking water can effectively reduce diarrhea in this setting is of particular importance in ensuring access to drinking water in Bangladesh that is safe both from a microbiological and chemical perspective.

We conducted a randomized controlled trial to evaluate the individual and combined impact of safely storing and chlorinating tubewell water on household water quality and diarrhea among children under two years of age in rural Bangladesh. Point-of-use water treatment with chlorine and safe storage have been shown to effectively improve water quality and reduce childhood diarrhea in various settings [Arnold and Colford 2007; Roberts et al. 2001]. We hypothesized that children under two who drink treated and safely stored tubewell water would have less diarrhea than those who drink untreated tubewell water stored with the standard water handling practices of rural Bangladesh. We also hypothesized that, while safe storage would be beneficial compared to standard practice, it would lead to larger reductions in diarrhea when combined with chlorination (compared to safe storage alone).

METHODS

Participant Selection and Enrollment

We selected the study location based on local groundwater chemistry. Groundwater in parts of Bangladesh is rich in iron, exerting chlorine demand and limiting the amount of free chlorine residual available for pathogen inactivation. We therefore conducted the study in Mymensingh district in central Bangladesh where iron concentrations in groundwater are low (Figure S1 under Supplemental Materials) [BGS & DPHE 2001]. A pilot study in the area confirmed low iron presence in tubewell water, allowing the achievement of consistent free chlorine residual to maximize the efficacy of the chlorination intervention.

We screened 87 randomly selected villages in the Fulbaria sub-district of Mymensingh for households that consistently relied on a shallow tubewell (<250 ft) as their primary source of drinking water, had no complaints of iron presence in their tubewell, had a child between the ages of six and 18 months living in the household, and did not plan to move within the study period. Families with iron complaints were excluded as an initial chlorine dosing exercise in the study area indicated self-reported iron to be a sensitive predictor of whether a household's tubewell water would fall short of acceptable chlorine residual (Tables S1 and S2 under Supplemental Materials). The lower age limit of six months was chosen because of the national Bangladeshi policy that requires infants under six months to be exclusively breastfed and not given any water. The upper age limit of 18 months was chosen to ensure that the majority of the children would be under the age of two during the follow-up period, and would represent the age group that is most vulnerable to waterborne illness and its longterm sequalae [Walker et al. 2012].

We selected a random subset of 1800 households from those that met our eligibility criteria. Households in Bangladesh are clustered into compounds called baris consisting of extended families. If there were multiple eligible households in a compound, only one household was randomly selected to avoid correlated diarrhea outcomes among households in the same compound. In households with more than one child in the eligible age range, all eligible children were enrolled. Field staff approached selected households to obtain informed consent from the primary caregiver of children under the age of two in the household and administer a baseline questionnaire that assessed the pre-intervention child health status, water and sanitation practices, demographics and socioeconomic status.

Randomization Assignment and Allocation Concealment

The lead investigators (AE and AMN) generated the randomization sequence using the random allocation function of STATA software (version 10.1, STATA Corp., College Station, TX). The study area was divided into 15 distinct geographical regions; in each region eligible households were listed in the order they were identified during screening, and block randomization with a block size of three was applied to assign 1800 households to one of three study arms: (1) chlorine plus safe storage: sodium dichloroisocyanurate (NaDCC) tablets and a narrow-mouth vessel with a lid and tap; (2) safe storage: a narrow-mouth vessel with a lid and tap; and (3) control: no intervention. Field teams delivering the interventions and collecting follow-up data were informed about the randomization assignment after the completion of participant enrollment and baseline data collection.

Intervention Delivery and Promotion

NaDCC tablets have been proven effective in improving water quality in other settings [Clasen et al. 2007; Jain et al. 2010] and a previous study has found them acceptable to users in a low-income urban community in Dhaka, Bangladesh [Clasen et al. 2007]. The tablets are easier to store, handle and correctly dose than liquid forms of chlorine [Clasen and Edmondson 2006]. A dosing exercise was conducted in the study area to identify the ideal dose that meets the target criteria of having a minimum free chlorine residual of 0.2 mg/L to ensure adequate disinfection and a maximum residual of 2 mg/L to minimize taste and odor concerns, as recommended by the Centers for Disease Control and Prevention (CDC). It should be noted that the 2 mg/L taste and odor threshold is well under the WHO health limit of 5 mg/L [WHO 2011]. One 33 mg NaDCC tablet in 10 liters of water, corresponding to an initial free chlorine dose of 2 mg/L, was identified as adequate to meet these targets (Table S3 under Supplemental Materials). We identified a commercial storage jar with a tightly fitting lid, a narrow mouth (10.5 cm diameter) and a durable tap as a suitable safe storage container (Figure S2 under Supplemental Materials).

Field staff distributed the intervention products to study households following the baseline interview and demonstrated their use, including how to clean the safe storage containers with the provided brush and detergent. They left an illustrated instruction sheet at a visible spot in the household to serve as a reminder. They instructed participants in both intervention arms to discard any remaining water after 24 hours and collect a fresh 10-liter batch and to exclusively give treated and/or safely stored water to all children under the age of two as well as any other children under five that live in the household. The field team continued to visit households approximately once a month for one year to promote correct and consistent use of the products and replenish the supply of tablets. In order to prevent potential differential Hawthorne effects between study arms, where Hawthorne effect is defined as subjects perceiving or reporting spurious health benefits as a consequence of "being watched and unusual attention being paid" [Adair 1984; Loevinsohn 1990], the control group was visited with the same frequency as the intervention groups. The promotion activities in this group provided no information on water treatment or safe storage but focused on general information on diarrhea and oral rehydration therapy, not expected to affect diarrhea prevalence in the control group.

Outcome Definition and Measurement

A separate field team conducted unannounced monthly follow-up visits to record caregiver-reported two-day and seven-day prevalence of diarrhea (defined as three or more loose stools within a 24-hour period) in children under two years as well as any children under five that live in the same household. We specified *a priori* to use seven-day prevalence in our analysis unless we detect evidence of differential recall bias (i.e., difference in the magnitude of effect estimates obtained using two- vs. seven-day recall) [Arnold et al. 2013]. In addition to diarrhea, the field team recorded caregiver-reported prevalence of skin rashes and ear infections to serve as negative control outcomes [Lipsitch et al. 2010]; these were symptoms that could not plausibly be affected by the drinking water interventions and were used to detect potential differential reporting bias associated with subjective, self-reported outcomes in response to non-blinded interventions.

During each follow-up visit, the team monitored intervention uptake by recording self-reported use, conducting spot checks on the presence and status of the intervention products and collecting stored water samples in all households in the chlorine arm to test for free chlorine residual. In a rotating systematic subsample of 10% of households in all study arms, the field team also collected tubewell and stored water samples for microbiological testing. Samples were transported on ice to the field laboratory. Laboratory staff measured free chlorine residual with the n,n-diethyl-p-phenylenediamine (DPD) colorimetric method using a digital colorimeter (Hach, Loveland, CO, USA; lower estimated detection limit: 0.02 mg/L; precision ± 0.05 mg/L). *E. coli* was enumerated with membrane filtration using U.S. EPA Method 1604 within eight hours of sample collection [USEPA

2002]. Quality control measures including 10% blanks and 10% duplicates were followed. *E. coli* concentration was measured in colony forming units (CFU) per 100 mL, and samples were classified according to the WHO thresholds of no risk (0 CFU/100 mL), low risk (1-10 CFU/100 mL), moderate risk (11-100 CFU/100 mL), high risk (101-1000 CFU/100 ml) and very high risk (>1000 CFU/100 mL) [WHO 1997].

Statistical Methods

Our primary outcome was the seven-day period prevalence of caregiver-reported diarrhea in children <2 y. We conservatively sized the study to detect a difference in the two-day prevalence of diarrhea due to safe storage plus chlorination over safe storage alone. We assumed 14% two-day diarrhea prevalence in the control group based on data from a large-scale study in rural Bangladesh (SHEWA-B) [Huda et al. 2012], 11.6 % prevalence in the safe storage group based on 30% diarrhea reduction due to safe storage [Roberts et al. 2001] and 55% of participants storing water in the home [Hoque et al. 2006], and 9.1% prevalence in the combined intervention group based on 35% diarrhea reduction due to safe storage plus chlorination [Arnold and Colford 2007]. Assuming one child of eligible age per household, an intra-cluster correlation coefficient of 0.13 for repeated observations within a child based on the SHEWA-B study, 5% drop-out and a one-sided α of 0.05, we calculated that 575 participants visited five times would provide 84% power to detect the difference between 11.6% and 9.1% diarrhea prevalence. We enrolled 600 households in each study arm. We anticipated seasonal trends in intervention effectiveness; we conducted five visits during the dry season (October 2011 through May 2012) and five additional visits during the monsoon season (June 2012 through November 2012) to ensure sufficient power to individually detect a health difference in either season. We calculated disease prevalence ratios (PR) between pairs of study arms using generalized linear models with a log link, a binomial error distribution, and robust standard errors to account for clustering due to longitudinal sampling and multiple children per household when there was more than one eligible child [McNutt et al. 2003]. We investigated effect modification by two pre-specified characteristics through the inclusion of interaction terms in the regression models: season (dry vs. monsoon) and child age (6-12 mo, 13-18 mo and > 18 mo at enrollment).

Our secondary outcome was fecal contamination of stored water, defined as the proportion of samples with an *E. coli* count exceeding the WHO thresholds of no risk, low risk and moderate risk. We compared stored as well as source water quality across study arms using chi square tests for the proportion of samples in these risk categories and conducted subgroup analyses with season. The complete data management process and statistical analyses for the primary and secondary outcomes were independently replicated by both lead investigators (AE and AMN) to ensure identical, replicable results.

Ethical and Other Considerations

All study participants provided informed consent prior to enrollment. The study protocol was reviewed and approved by institutional review boards at the University of California, Berkeley and at icddr,b. The study was registered at ClinicalTrials.gov (NCT01350063). Medentech provided the NaDCC tablets used in the study free of charge but did not have a role in the study design, implementation, analysis or interpretation of results. CONSORT guidelines were followed (Table S4 under Supplemental Materials) [Campbell 2012].

RESULTS

Baseline Characteristics

Baseline data collection was conducted between July and September 2011. Households in the three study arms had similar distributions of demographics, socioeconomic status and water, sanitation and hygiene-related practices at baseline (Table 1). Water treatment was rarely practiced among study participants at baseline, with 1-2% of households reporting treating their drinking water (Table 1). In 40-43% of households, respondents retrieved water directly from the tubewell when asked to provide a glass of water as if giving it to their young children; the remainder obtained water from storage containers (Table 1). The most frequently observed water storage containers were traditional *kolshis* and jugs.

Longitudinal Follow-Up

Of the 1800 households enrolled and randomly assigned into study arms, 1786 received the interventions; 14 households were lost due to relocation (n=10), refusal to participate (n=3) and death of enrolled child (n=1) before intervention implementation. A total of 10 follow-up visits per household were conducted between October 2011 and November 2012; 1649 households completed the study while a cumulative 151 households were lost to follow-up due to relocation (n=120), refusal to participate (n=26), and death of enrolled child (n=5) (Figure 1). Households that left the study were similar in their characteristics to households that completed the study, and the balance of baseline variables between the three study arms was maintained among the households that remained in the study (Tables S5 and S6 under Supplemental Materials).

Intervention Uptake

The safe storage and chlorination interventions achieved high uptake during the one-year study period. The delivered storage container was observed to contain water in 91% of spot check observations in the safe storage arm and 87% of observations in the chlorine arm over all follow-up visits (Table 2). Of the households that had water in the intervention container at the time of the visit, 83% had free chlorine residual over the minimum CDC-recommended value of 0.2 mg/L (Table 2); the percentage of households in compliance with this target was stable over the study period (Figure S3 under Supplemental Materials). When asked to provide a glass of water for their children under two, 84-89% of caregivers in the intervention arms retrieved water from the provided container (Table 2).

Water Quality

The field team collected 1726 source water samples and 1676 coupled stored water samples over the study period; only one type of sample was collected if the other type was not available (e.g., storage vessel empty at time of interview) in the household selected for systematic sampling. Among tubewell samples, 41% were positive for *E. coli*. In 14% of samples, *E. coli* counts were over the low-risk limit of 10 CFU/100 mL and 3% exceeded the moderate-risk limit of 100 CFU/100 mL (Figure 2); there were no differences in the percentage of samples falling in these risk categories between any pairs of study arms (p>0.05), indicating similar source water quality across study arms (Table S7 under Supplemental Materials). Contamination of tubewell water seemed more common and *E. coli* concentrations higher during the monsoon season than in the dry season (Table S7).

Stored water quality showed marked differences between the three arms. In the control arm, 89% of samples were positive for *E. coli*, suggesting widespread contamination during household storage, compared to 70% in the safe storage arm and 26% in the combined safe storage and chlorination arm (Figure 3). The percentage of samples with *E. coli* >10 CFU/100 mL was 61% in the control arm, 27% in the safe storage arm and 9% in the chlorine arm, and the percentage of samples with *E. coli* >100 CFU/100 mL was 21% in the control arm, 7% in the safe storage arm and 2% in the chlorine arm (Figure 3). All differences were significant between each pair of study arms (p<0.05) (Table S7). Stored water contamination appeared to be more pronounced during the monsoon season compared to the dry season across all three study arms (Figures 4 and 5).

Child Diarrhea

Diarrhea prevalence in children <2 years in the control arm was 10.6% over the study period; in all three arms prevalence decreased with increasing study duration but showed a peak at the onset of the monsoon (Figure 6). The youngest age group had the highest diarrhea prevalence (Table 3). The intra-class correlation coefficient for repeated diarrhea measures within children was 0.06.

Compared to the control arm, caregiver reported diarrhea in children <2 years was significantly reduced in both the chlorine plus safe storage arm (PR = 0.64, 0.55-0.73) and the safe storage arm (PR = 0.69, 0.60-0.80); there was no difference in the chlorine plus safe storage versus safe storage arm (PR = 0.92, 0.79-1.08) (Table 3). Prevalence ratio estimates using two-day prevalence were similar, suggesting no differential recall by study group (Table S8 under Supplemental Materials). There was no significant difference in the seven-day prevalence of the negative control outcomes in the chlorine plus safe storage arm (skin rash PR = 0.86, 0.66-1.10, ear infection PR = 0.94, 0.61-1.45) or the safe storage arm (skin rash PR = 0.88, 0.68-1.14, ear infection PR = 1.26, 0.84-1.91) compared to control (Table S9 under Supplemental Materials). There appeared to be increased protection from safe storage and chlorination combined in the monsoon season compared to the dry season but the interaction was not significant (Table 3). There was no evidence of differential intervention impact by child age for either intervention (Table 3).

DISCUSSION

Summary of Findings

The interventions achieved high uptake in the study population. We found significant improvements in stored water quality due to safe storage with and without chlorination, with 7% of stored water samples in the safe storage arm and 2% of stored water samples in the chlorine arm exceeding moderate-risk contamination levels compared to 21% in controls (Figure 3). There was 31% reduction in diarrhea prevalence in children <2 in the safe storage arm (PR = 0.69, 0.60-0.80) and 36% reduction in the combined safe storage and chlorination arm (PR = 0.64, 0.55-0.73) compared to control, with no difference between the two intervention arms (PR = 0.92, 0.79-1.08) (Table 3).

Effectiveness of Safe Storage vs. Safe Storage and Chlorination

Our findings indicate that safe storage, alone or combined with chlorination, was effective in reducing child diarrhea in rural Bangladesh compared to standard practice, and, given safe storage, there was no additional benefit from chlorination. There are several possible explanations for this. It is possible that, if drinking water is safely stored and handled, there truly is no added benefit from adding chlorine in this particular setting. Our water quality testing results support this explanation; the source water quality was relatively good in the study area, and contamination of water stored in households was common, as evidenced by the high percentage of *E. coli* positive stored water samples in the control group (Figures 2 and 3). Safe storage combined with chlorination was more effective at preventing low-level contamination of stored water than safe storage alone but both achieved comparable protection against moderate and high levels of point-of-use contamination (Figures 4 and 5). There is evidence from the literature of a threshold effect for disease risk from ingestion of pathogens in source water, where a critical concentration of fecal indicator bacteria is necessary to pose a health risk [Moe et al. 1991]. A threshold effect has been suggested for stored water quality as well [Brown et al. 2008]. Our findings are consistent with the presence of such a threshold; safe storage was sufficient to prevent heavy contamination during storage, which might have constituted the main health risk in this setting.

It is also possible that the lack of additional diarrhea reduction from chlorination in addition to safe storage may be due to the presence of chlorine-resistant organisms in traditionally stored groundwater in the study setting. While chlorine is very efficacious in inactivating bacterial pathogens, its efficacy is only moderate against viruses and poor against protozoan cysts [Gadgil 1998; Steiner et al. 1997]. If groundwater stored with standard practice in rural Bangladesh becomes predominantly contaminated with chlorine-resistant diarrheagenic pathogens due to contact from infected household members, safe storage would be expected to reduce diarrhea by reducing contact but chlorination would not provide additional protection against the pathogens that enter the safe storage container. This type of resistant fecal contamination in chlorinated stored water would not be detected by our *E. coli* measurements as *E. coli* is effectively inactivated by chlorine and is not a good indicator for more resistant organisms such as *Giardia* or *Cryptosporidium* [Gadgil 1998; Steiner et al. 1997]. However, bacterial pathogens including enterotoxigenic *E. coli*, *Shigella*, *Campylobacter jejuni* and *Vibrio cholerae* are frequently isolated in stool samples from children with diarrhea in Bangladesh [Albert et al. 1999; Black et al. 1981; Kotloff et al. 2012]. It is therefore unlikely that the dominance of chlorine-resistant pathogens in stored drinking water can explain the lack of additional diarrhea reduction from safe storage plus chlorination compared to safe storage alone.

Limitations

One limitation of our study is that it employs a non-blinded design with self-reported outcomes. An alternative explanation for the similar health impact in the two intervention groups may therefore be that the reported reductions in diarrhea in both groups may be a result of courtesy bias and/or a placebo effect due to provision of intervention products to participants. It has been suggested that exaggerated reporting of health improvements in non-blinded studies with self-reported outcomes can partially or fully explain health benefits documented in previous water treatment trials [Hunter 2009; Schmidt and Cairncross 2009]; indeed, such effects would not be additive for combined interventions. However, this is unlikely in our case given the several measures we implemented to minimize biased reporting. The interventions were distributed and promoted by different field staff than those who collected the health data to minimize courtesy bias. We collected data on negative control outcomes such as skin diseases and ear infections that would not be expected to be affected by the interventions; we found no impact of either intervention on these caregiver-reported symptoms, suggesting no evidence of a placebo effect. Finally, our stored water quality measurements present an objective intermediate outcome on the causal chain between the interventions and child health, and provide support for a diarrhea reduction of similar magnitude in both intervention arms.

Finally, it is important to note that this study was an efficacy trial where our objective was to find out whether consistently treating and safely storing tubewell water would improve water quality and reduce diarrhea in rural Bangladesh. We identified easy-to-use, aspirational products, provided them to participants for free and promoted their use through regular household visits. While both products achieved high uptake among study participants and reduced diarrhea, their uptake and consequently their health impact is likely to be lower in the absence of free materials and intensive promotion efforts.

CONCLUSIONS

Safe storage, used alone or in combination with chlorination, markedly improved the microbiological quality of stored water in the study setting. Both interventions significantly reduced diarrhea prevalence in children <2 years. Chlorination, however, did not provide an additional reduction beyond that seen with safe storage. This is plausible because the level of contamination was low at the water source, and both safe storage alone and safe storage combined with chlorination reduced high-level contamination of stored drinking water compared to the control arm. Our findings indicate that unsafe handling during storage in the household is the dominant mechanism for contamination of tubewell drinking water and that safe storage alone could substantially reduce waterborne illness among young children in rural Bangladesh.

TABLES

TABLE 1. Summary of Baseline Characteristics by Study Group

	Control (N=600 HHs)		Safe Storage (N=600 HHs)		Chlorine + Safe Storage (N=600 HHs)	
Demographics and socioeconomics	N	Mean	N	Mean	N	Mean
Number of children <2 yrs [a]		605		603		606
Number of siblings 2-5 yrs		133		130		133
Mean age of respondent	584	26	587	26	587	25
Mean number of persons per HH	584	5	587	5	586	5
Mean monthly HH income (USD)	573	92	583	95	582	93
Mean number of rooms in HH	584	2	587	2	587	2
Mean land owned by HH (acres)	578	0.5	584	0.5	582	0.5
% of HHs with:						
Kaccha walls [b]	584	34	587	35	587	36
Electricity	584	34	587	36	586	35
Cell phone	584	68	587	67	586	68
TV	584	22	587	22	586	19
% of Illiterate mothers	584	28	587	27	587	27
Water, sanitation and hygiene practices						
% of HHs with drinking water obtained:						
Directly from tubewell	582	41	587	40	586	43
From narrow-mouth container	582	45	587	44	586	42
From wide-mouth container	582	13	587	14	586	15
% of HHs that treat drinking water	584	2	587	2	587	1
% of households with:						
Improved sanitation facility [c]	584	32	587	37	587	33
Unimproved sanitation facility [d]	584	51	587	47	587	47
No sanitation facility	584	17	587	16	587	19
% of HHs where children <2 yrs defecate:						
In latrine, potty or cloth	584	24	587	26	587	28
In courtyard or living area	584	96	587	94	587	94
Outside compound area	584	4	587	7	587	6
% of HHs with:						
Handwashing station (HWS)	584	80	587	81	586	81
HWS <10 steps from latrine	584	31	587	34	586	33
HWS with water	584	72	587	72	586	72
HWS with soap	584	32	587	36	586	34
Health indicators in children < 2 yrs						
Two-day prevalence of:						
Diarrhea	605	11	603	11	606	9
Skin rash	605	14	602	15	606	15
Ear infection	605	4	602	4	604	6
Seven-day prevalence of:						
Diarrhea	605	16	603	16	606	14
Skin rash	605	16	602	17	606	16
Ear infection	605	5	602	5	604	7

HHs: Households, USD: US dollars, HWS: Handwashing station

[a] Children <2 yrs refer to children under 18 months or younger at enrollment.

[b] Kaccha walls refer to natural wall materials including jute, bamboo and mud.

[c] Improved facilities include flush/pour flush latrines that drain to piped sewer, septic tank, or off-set pit, pit latrines with slab and water seal or with slab, no water seal but lid, and composting toilets.

[d] Unimproved facilities include flush/pour flush latrines that drain into the environment, open pit, pit latrines without slab, pit latrines with slab but no water seal and no lid, and hanging toilets.

TABLE 2. Uptake Indicators in Intervention Groups (cumulative data from 10 follow-up visits)

	Safe Storage		Chlorine + Safe Storage	
	N	%	N	%
Water use from intervention container:				
Observed to retrive water for child from elsewhere	5613	11	5496	16
Reported to give <2 yr child water from elsewhere	5592	14	5473	18
Reported to give 2-5 yr child water from elsewhere	1209	22	1222	32
Observed status of intervention container:				
Container not present	5613	5	5496	7
Container empty	5613	4	5496	6
Container full but uncovered	5613	1	5496	1
Container full and covered	5613	90	5496	86
Reported to fill intervention container:				
On day of interview	5613	25	5496	40
Day before interview	5613	66	5496	49
Two or more days before interview	5613	8	5496	12
Reported to add chlorine tablets to intervention container:				
On day of interview	--	--	5496	40
Day before interview	--	--	5496	47
Two or more days before interview	--	--	5496	13
Reported having chlorinated water available:	--	--	5496	87
Free chlorine residual in intervention container:		--		
No sample available	--	--	5496	14
Residual <0.2 mg/L	--	--	5496	15
Residual 0.2-2 mg/L	--	--	5496	66
Residual 2-5 mg/L			5496	4
Residual >5 mg/L	--	--	5496	1

TABLE 3. Child Diarrhea across Study Arms (7-day recall period)

	Control		Safe Storage					Chlorine + Safe Storage							
	N	Prev %	N	Prev %	PR [a]	(95% CI)	p [b]	N	Prev %	PR [a]	(95% CI)	p [b]	PR [c]	(95% CI)	p [b]
Main Analysis (among children <2 yrs) [d]															
All	5654	10.6	5592	7.3	0.69	(0.60 , 0.80)		5505	6.7	0.64	(0.55 , 0.73)		0.92	(0.79 , 1.08)	
Interaction with Season (among children <2 yrs) [d]															
Dry season (ref)	2876	14.5	2868	10.0	0.70	(0.59 , 0.82)	--	2859	9.7	0.68	(0.57 , 0.79)	--	0.97	(0.82 , 1.16)	--
Wet season	2778	6.7	2724	4.5	0.67	(0.52 , 0.85)	0.77	2646	3.5	0.52	(0.40 , 0.68)	0.12	0.78	(0.59 , 1.04)	0.23
Interaction with Child Age at Enrollment															
06 - 12 mo (ref)	3415	11.7	3541	7.9	0.67	(0.56 , 0.80)	--	3410	7.2	0.61	(0.51 , 0.73)	--	0.91	(0.75 , 1.10)	--
12 - 18 mo	2239	9.0	2051	6.4	0.71	(0.55 , 0.91)	0.75	2095	6.1	0.67	(0.53 , 0.86)	0.56	0.95	(0.73 , 1.24)	0.81
18 - 60 mo	1169	4.4	1180	3.7	0.84	(0.49 , 1.43)	0.42	1182	3.5	0.78	(0.43 , 1.40)	0.43	0.93	(0.50 , 1.73)	0.95

[a] Prevalence ratio refers to comparison against control group.
[b] p-value for interaction term against reference category.
[c] Prevalence ratio refers to comparison against safe storage group.
[d] Children <2 yrs refer to children under 18 months or younger at enrollment.

SUPPLEMENTARY TABLES

TABLE S1. Self-Reported Iron versus Chlorine Residual at 30 Min after Chlorination

Self-Reported Iron	Chlorine Residual < 0.2 mg/L	Chlorine Residual > 0.2 mg/L	Total
Iron Reported	3	4	7
Iron Not Reported	0	45	45
Total	3	49	52

TABLE S2. Sensitivity, Specificity, PPV and NPV of Self-Reported Iron Complaints as Predictor of Chlorine Residual <0.2 mg/L vs. >0.2 mg/L at 30 Min after Chlorination

Parameter	Value
Sensitivity	3/3 (100%)
Specificity	45/49 (92%)
Positive Predictive Value (PPV)	3/7 (43%)
Negative Predictive Value (NPV)	45/45 (100%)

TABLE S3. Free Chlorine Residual at 30 Min after Chlorination (33 mg tablet in 10 L water)

Free Chlorine Residual	Number (%) of Wells
<0.2 mg/L	3 (6%)
0.2 – 1 mg/L	3 (6%)
1 – 2 mg/L	41 (79%)
>2 mg/L	5 (9%)
Total	52 (100%)

TABLE S4. CONSORT Checklist

ITEM	DESCRIPTION	REPORTED IN SECTION
Title and Abstract		
1a	Identification as a cluster randomised trial in the title; Identification as a cluster randomised trial in the title	Abstract (clustering due to longitudinal follow-up within individual participants)
1b	Structured summary of trial design, methods, results, and conclusions	Abstract
Introduction		
Background and Objectives		
2a	Scientific background and explanation of rationale; Rationale for using a cluster design	Introduction

ITEM	DESCRIPTION	REPORTED IN SECTION
2b	Specific objectives or hypotheses; Whether objectives pertain to the cluster level, the individual participant level, or both	Introduction
Methods		
Trial Design		
3a	Description of trial design (such as parallel, factorial) including allocation ratio; Definition of cluster and description of how the design features apply to the clusters	Methods (Participant Selection and Enrollment; Randomization Assignment and Allocation Concealment)
3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants		
4a	Eligibility criteria for participants; Eligibility criteria for clusters	Methods (Participant Selection and Enrollment)
4b	Settings and locations where the data were collected	Methods (Participant Selection and Enrollment)
Interventions		
5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered; Whether interventions pertain to the cluster level, the individual participant level, or both	Methods (Intervention Delivery and Promotion)
Outcomes		
6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed; Whether outcome measures pertain to the cluster level, the individual participant level, or both	Methods (Outcome Definition and Measurement)
6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample Size		
7a	How sample size was determined; Method of calculation, number of cluster(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or k), and an indication of its uncertainty	Methods (Statistical Methods)
7b	When applicable, explanation of any interim	N/A

ITEM	DESCRIPTION	REPORTED IN SECTION
	analyses and stopping guidelines	
Randomisation		
Sequence Generation		
8a	Method used to generate the random allocation sequence	Methods (Randomization Assignment and Allocation Concealment)
8b	Type of randomisation; details of any restriction (such as blocking and block size); Details of stratification or matching if used	Methods (Randomization Assignment and Allocation Concealment)
Allocation Concealment Mechanism		
9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned; Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level, or both	Methods (Randomization Assignment and Allocation Concealment)
Implementation		
10a	Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	Methods (Participant Selection and Enrollment; Randomization Assignment and Allocation Concealment; Intervention Delivery and Promotion)
10b	Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	Methods (Participant Selection and Enrollment)
10c	From whom consent was sought (representatives of the cluster, or individual cluster members, or both) and whether consent was sought before or after randomisation	Methods (Participant Selection and Enrollment)
Blinding		
11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
11b	If relevant, description of the similarity of interventions	N/A
Statistical Methods		

ITEM	DESCRIPTION	REPORTED IN SECTION
12a	Statistical methods used to compare groups for primary and secondary outcomes; How clustering was taken into account	Methods (Statistical Methods)
12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Methods (Statistical Methods)
Results		
Participant Flow		
13a	For each group, the numbers of participants/clusters who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	Results (Longitudinal Follow-Up); Figure 1
13b	For each group, losses and exclusions after randomization, together with reasons, for both clusters and individual cluster members	Results (Longitudinal Follow-Up); Figure 1
Recruitment		
14a	Dates defining the periods of recruitment and follow-up	Results (Baseline Characteristics, Longitudinal Follow-Up)
14b	Why the trial ended or was stopped	N/A
Baseline Data		
15	A table showing baseline demographic and clinical characteristics for each group; Baseline characteristics for the individual and cluster levels as applicable for each group	Table 1
Numbers Analysed		
16	For each group, number of participants/clusters (denominator) included in each analysis and whether the analysis was by the original assigned groups	Table 3, Table S7
Outcomes and Estimation		
17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval); Results at the individual and cluster levels as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	Results (Water Quality; Child Diarrhea); Table 3, Table S7
17b	For binary outcome, presentation of both absolute and relative effect sizes is recommended	

ITEM	DESCRIPTION	REPORTED IN SECTION
Ancillary Analyses		
18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	Results (Water Quality, Child Diarrhea); Table 3, Table S7
Harms		
19	All important harms or unintended effects in each group	N/A
Discussion		
Limitations		
20	Trial limitations, addressing sources of potential bias, imprecision and, if relevant, multiplicity of analyses	Discussion (Limitations)
Generalisability		
21	Generalisability (external validity, applicability) of the trial findings; Generalisability to clusters and/or individual participants (as relevant)	Discussion (Limitations)
Interpretation		
22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Conclusions
Other Information		
Registration		
23	Registration number and name of trial registry	Methods (Ethical and Other Considerations)
Protocol		
24	Where the full trial protocol can be accessed, if available	N/A
Funding		
25	Sources of funding and other support (such as supply of drugs), role of funders	Methods (Ethical and Other Considerations)

TABLE S5. Baseline Characteristics in Households that Completed Study vs. Were Lost to Follow-Up

	HHs that Completed Study (N=1649 HHs)		HHs Lost to Follow-Up (N=151 HHs)	
Demographics and socioeconomics	N	Mean	N	Mean
Number of children <2 yrs [a]		1661		153
Number of siblings 2-5 yrs		363		33
Mean age of respondent	1609	26	149	23
Mean number of persons per HH	1608	5	149	5
Mean monthly HH income (USD)	1589	93	149	96
Mean number of rooms in HH	1609	2	149	2
Mean land owned by HH (acres)	1599	0.5	145	0.6
% of HHs with:				
Kaccha walls [b]	1609	35	149	32
Electricity	1608	36	149	31
Cell phone	1608	67	149	74
TV	1608	21	149	20
% of Illiterate mothers	1609	28	149	21
Water, sanitation and hygiene practices				
% of HHs with drinking water obtained:				
Directly from tubewell	1606	42	149	36
From narrow-mouth container	1606	44	149	43
From wide-mouth container	1606	14	149	21
% of HHs that treat drinking water	1609	2	149	1
% of households with:				
Improved sanitation facility [c]	1609	34	149	31
Unimproved sanitation facility [d]	1609	49	149	46
No sanitation facility	1609	17	149	23
% of HHs where children <2 yrs defecate:				
In latrine, potty or cloth	1609	25	149	36
In courtyard or living area	1609	95	149	95
Outside compound area	1609	6	149	3
% of HHs with:				
Handwashing station (HWS)	1608	81	149	81
HWS <10 steps from latrine	1608	33	149	32
HWS with water	1608	72	149	68
HWS with soap	1608	34	149	40
Health indicators in children < 2 yrs				
Two-day prevalence of:				
Diarrhea	1661	10	153	11
Skin rash	1661	15	152	15
Ear infection	1659	5	152	9
Seven-day prevalence of:				
Diarrhea	1661	15	153	16
Skin rash	1661	16	152	19
Ear infection	1659	5	152	9

HHs: Households, USD: US dollars, HWS: Handwashing station

[a] Children <2 yrs refer to children under 18 months or younger at enrollment.

[b] Kaccha walls refer to natural wall materials including jute, bamboo and mud.

[c] Improved facilities include flush/pour flush latrines that drain to piped sewer, septic tank, or off-set pit, pit latrines with slab and water seal or with slab, no water seal but lid, and composting toilets.

[d] Unimproved facilities include flush/pour flush latrines that drain into the environment, open pit, pit latrines without slab, pit latrines with slab but no water seal and no lid, and hanging toilets.

TABLE S6. Baseline Characteristics by Study Group among Households that Completed Study

	Control (N = 565 HHs)		Safe Storage (N = 547 HHs)		Chlorine + Safe Storage (N = 537 HHs)	
Demographics and socioeconomics	N	Mean	N	Mean	N	Mean
Number of children <2 yrs [a]		568		550		543
Number of siblings 2-5 yrs		124		119		120
Mean age of respondent	550	26	534	26	525	26
Mean number of persons per HH	550	5	534	5	524	5
Mean monthly HH income (USD)	539	92	530	94	520	93
Mean number of rooms in HH	550	2	534	2	525	2
Mean land owned by HH (acres)	544	0.5	531	0.4	524	0.5
% of HHs with:						
Kaccha walls [b]	550	34	534	36	525	36
Electricity	550	33	534	37	524	36
Cell phone	550	68	534	67	524	66
TV	550	21	534	23	524	19
% of Illiterate mothers	550	29	534	28	525	28
Water, sanitation and hygiene practices						
% of HHs with drinking water obtained:						
Directly from tubewell	548	42	534	41	524	43
From narrow-mouth container	548	45	534	44	524	42
From wide-mouth container	548	12	534	14	524	15
% of HHs that treat drinking water	550	2	534	2	525	1
% of households with:						
Improved sanitation facility [c]	550	32	534	38	525	34
Unimproved sanitation facility [d]	550	52	534	47	525	48
No sanitation facility	550	16	534	16	525	19
% of HHs where children <2 yrs defecate:						
In latrine, potty or cloth	550	23	534	25	525	26
In courtyard or living area	550	96	534	94	525	94
Outside compound area	550	5	534	7	525	6
% of HHs with:						
Handwashing station (HWS)	550	80	534	81	524	81
HWS <10 steps from latrine	550	31	534	34	524	33
HWS with water	550	72	534	73	524	72
HWS with soap	550	32	534	37	524	33
Health indicators in children < 2 yrs						
Two-day prevalence of:						
Diarrhea	568	10	550	11	543	10
Skin rash	568	14	550	15	543	15
Ear infection	568	4	549	5	542	5
Seven-day prevalence of:						
Diarrhea	568	15	550	16	543	15
Skin rash	568	15	550	16	543	16
Ear infection	568	5	549	6	542	6

HHs: Households, USD: US dollars, HWS: Handwashing station

[a] Children <2 yrs refer to children under 18 months or younger at enrollment.

[b] Kaccha walls refer to natural wall materials including jute, bamboo and mud.

[c] Improved facilities include flush/pour flush latrines that drain to piped sewer, septic tank, or off-set pit, pit latrines with slab and water seal or with slab, no water seal but lid, and composting toilets.

[d] Unimproved facilities include flush/pour flush latrines that drain into the environment, open pit, pit latrines without slab, pit latrines with slab but no water seal and no lid, and hanging toilets.

TABLE S7. *E.coli* in Tubewell and Stored Water by Study Group

	Control		Safe Storage			Chlorine + Safe Storage			All Arms	
	N	Mean	N	Mean		N	Mean		N	Mean
Tubewell water										
Year-round										
% > 0 CFU/100 mL	576	44	576	38	*	574	40		1726	41
% > 10 CFU/100mL [a]	569	16	571	13		568	13		1708	14
% > 100 CFU/100mL [a]	569	3	571	4		568	3		1708	3
Dry season										
% > 0 CFU/100 mL	289	37	293	28	*	295	35		877	33
% > 10 CFU/100mL [a]	287	11	293	9		295	10		875	10
% > 100 CFU/100mL [a]	287	2	293	2		295	3		875	2
Wet season										
% > 0 CFU/100 mL	287	52	283	49		279	46		849	49
% > 10 CFU/100mL [a]	282	22	278	17		273	16		833	18
% > 100 CFU/100mL [a]	282	4	278	5		273	4		833	4
Stored water										
Year-round										
% > 0 CFU/100 mL	531	89	585	70	*	560	26	**	1676	--
% > 10 CFU/100mL [a]	520	61	583	27	*	558	9	**	1661	--
% > 100 CFU/100mL [a]	520	21	583	7	*	558	2	**	1661	--
Dry season										
% > 0 CFU/100 mL	270	84	303	59	*	292	17	**	865	--
% > 10 CFU/100mL [a]	266	47	303	20	*	292	5	**	861	--
% > 100 CFU/100mL [a]	266	13	303	5	*	292	1	**	861	--
Wet season										
% > 0 CFU/100 mL	261	94	282	82	*	268	35	**	811	--
% > 10 CFU/100mL [a]	254	75	280	33	*	266	13	**	800	--
% > 100 CFU/100mL [a]	254	29	280	9	*	266	3	**	800	--

CFU: Colony forming units.

[a] N different from the N for > 0 CFU/100 mL because of confluent (positive uncountable) samples.

* p-value <0.05 in comparison against control group using the $\chi 2$ test.

** p-value <0.05 in comparison against control group and safe storage group using the $\chi 2$ test.

TABLE S8. Diarrhea in Children <2 yrs across Study Arms (2-day and 7-day recall period) [a]

	Control		Safe Storage				Chlorine + Safe Storage					
	N	Prev %	N	Prev %	PR [a]	(95% CI)	N	Prev %	PR [a]	(95% CI)	PR [b]	(95% CI)
2-day recall	5654	6.8	5592	4.4	0.65	(0.54 , 0.77)	5505	4.4	0.65	(0.54 , 0.77)	1.00	(0.83 , 1.21)
7-day recall	5654	10.6	5592	7.3	0.69	(0.60 , 0.80)	5505	6.7	0.64	(0.55 , 0.73)	0.92	(0.79 , 1.08)

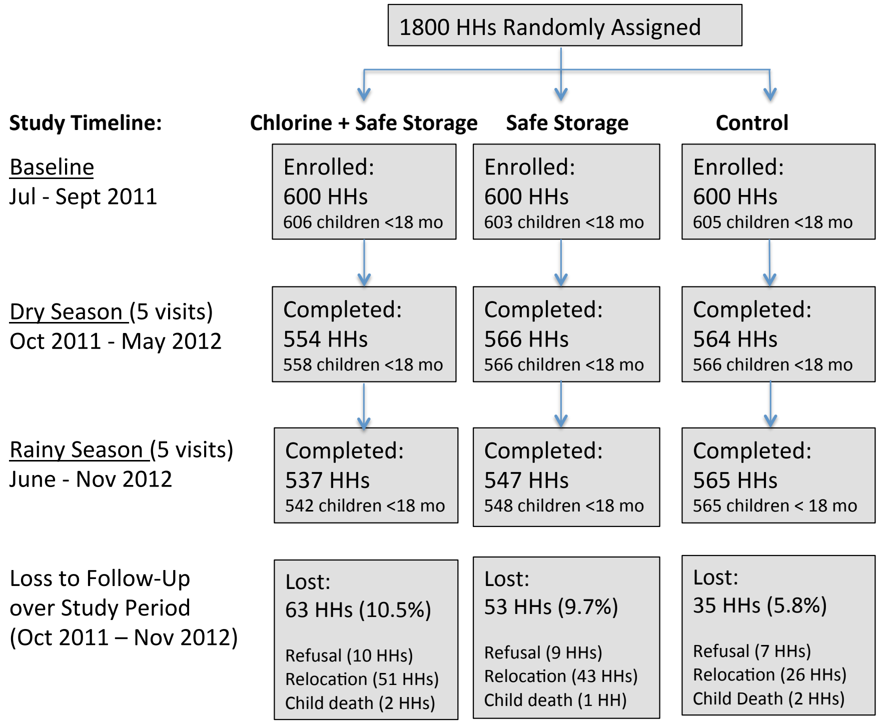
[a] Children <2 yrs refer to children under 18 months or younger at enrollment.
[b] Prevalence ratio refers to comparison against control group.
[c] Prevalence ratio refers to comparison against safe storage group.

TABLE S9. Negative Control Outcomes in Children <2 yrs across Study Arms [a]

	Control		Safe Storage				Chlorine + Safe Storage					
	N	Prev %	N	Prev %	PR [a]	(95% CI)	N	Prev %	PR [a]	(95% CI)	PR [b]	(95% CI)
2-day recall												
Skin rash	5655	3.9	5592	3.5	0.89	(0.67 , 1.17)	5505	3.3	0.86	(0.65 , 1.12)	0.96	(0.73 , 1.28)
Ear infection	5655	1.7	5590	2.3	1.38	(0.88 , 2.17)	5504	1.7	1.03	(0.64 , 1.64)	0.74	(0.47 , 1.17)
7-day recall												
Skin rash	5655	4.4	5592	3.8	0.88	(0.68 , 1.14)	5505	3.7	0.86	(0.66 , 1.10)	0.97	(0.75 , 1.26)
Ear infection	5655	2.1	5590	2.6	1.26	(0.84 , 1.91)	5504	1.9	0.94	(0.61 , 1.45)	0.74	(0.48 , 1.14)

[a] Children <2 yrs refer to children under 18 months or younger at enrollment.
[b] Prevalence ratio refers to comparison against control group.
[c] Prevalence ratio refers to comparison against safe storage group.

FIGURES



Note: <18 months refers to the child age at enrollment

FIGURE 1. Flowchart of Study Participation

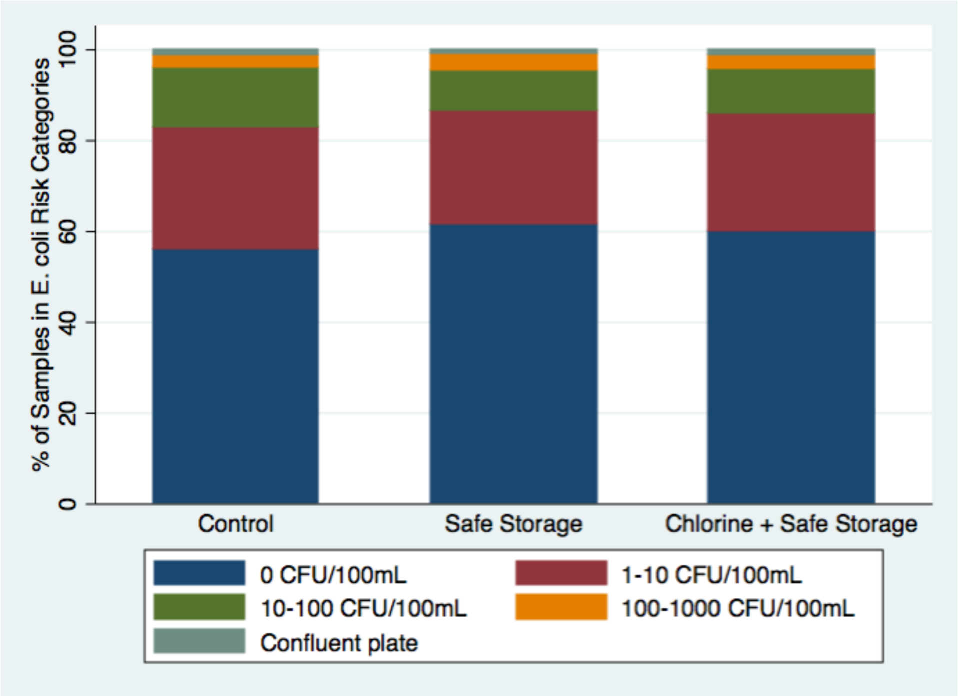


FIGURE 2. Categories of *E. coli* Counts in Tubewell Water across Arms (see Table S7)

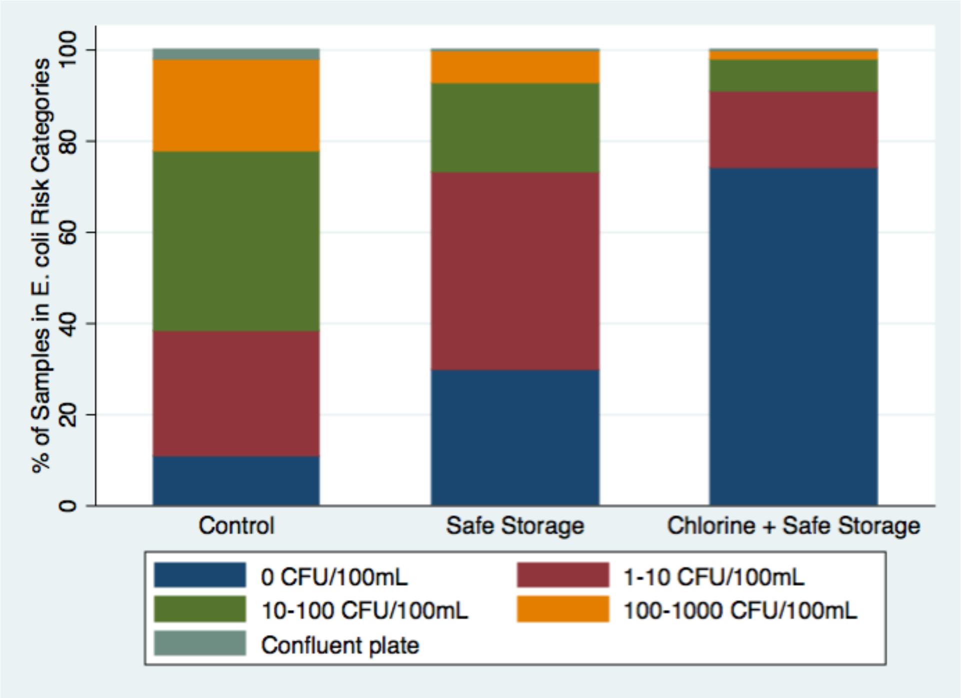


FIGURE 3. Categories of *E. coli* Counts in Stored Water across Arms (see Table S7)

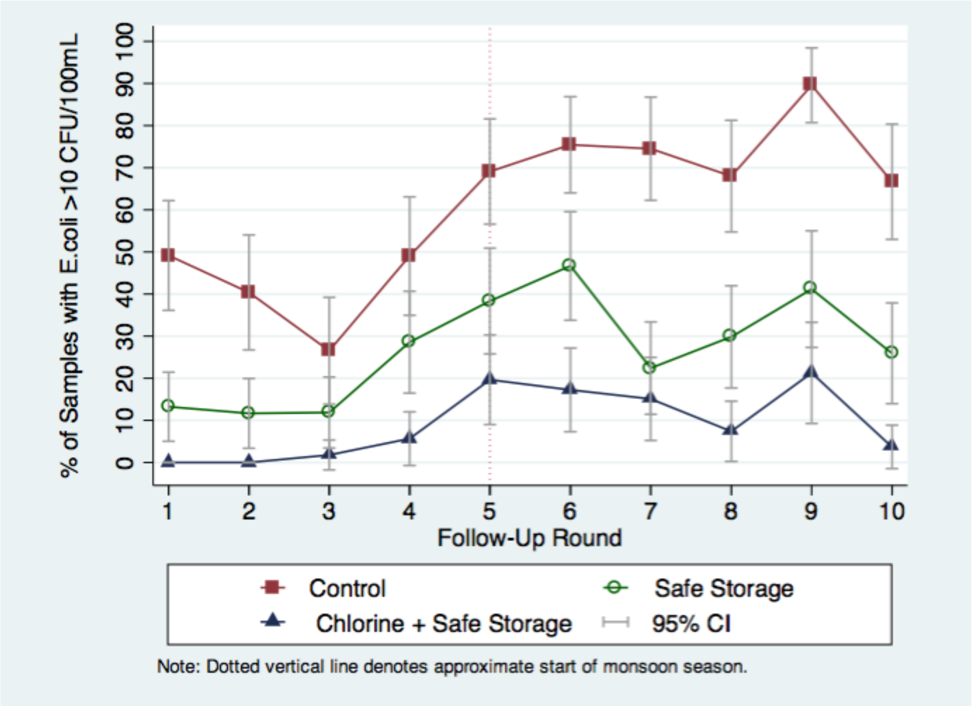


FIGURE 4. Temporal Trend in Percentage of Stored Water Samples Exceeding Low Risk (*E. coli* >10 CFU/100 mL)

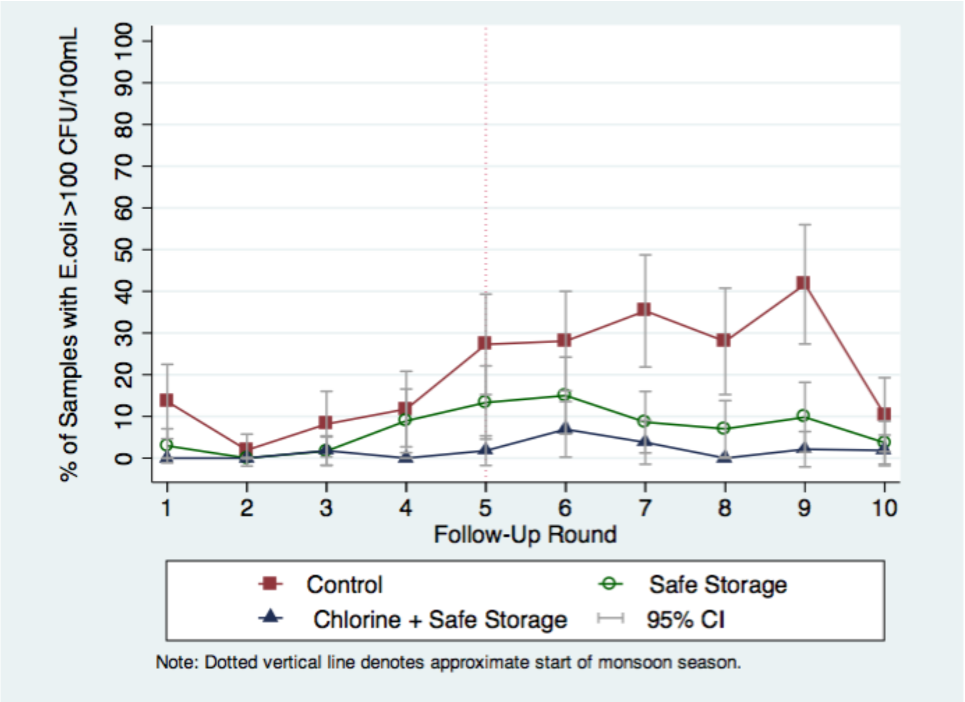
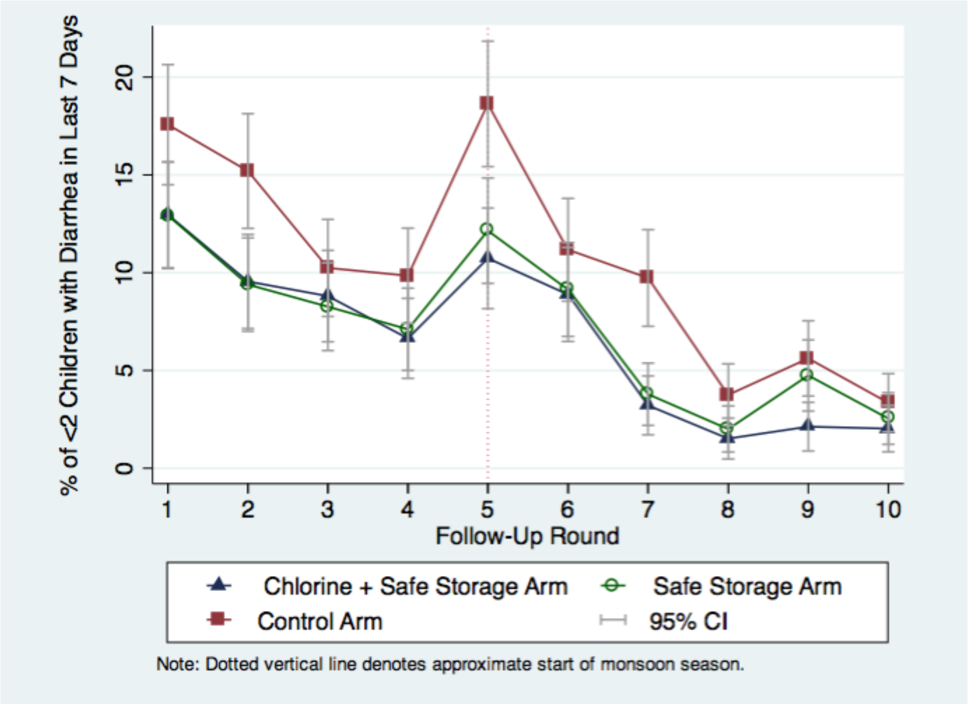


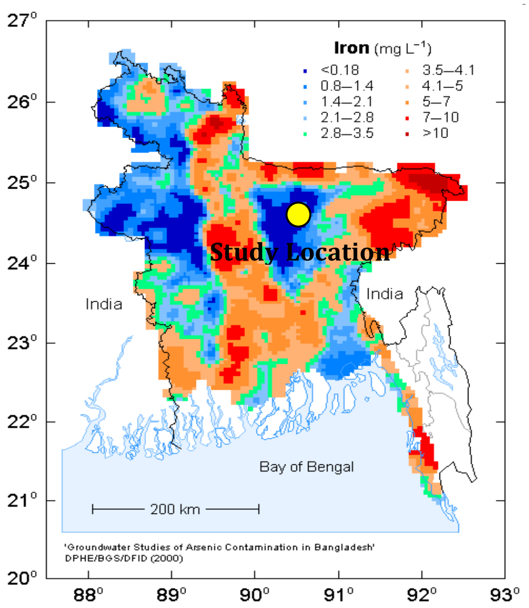
FIGURE 5. Temporal Trend in Percentage of Stored Water Samples Exceeding Moderate Risk (*E. coli* >100 CFU/100 mL)



Note: Dotted vertical line denotes approximate start of monsoon season.

FIGURE 6. Temporal Trend in Diarrhea Prevalence in Children <2 yrs

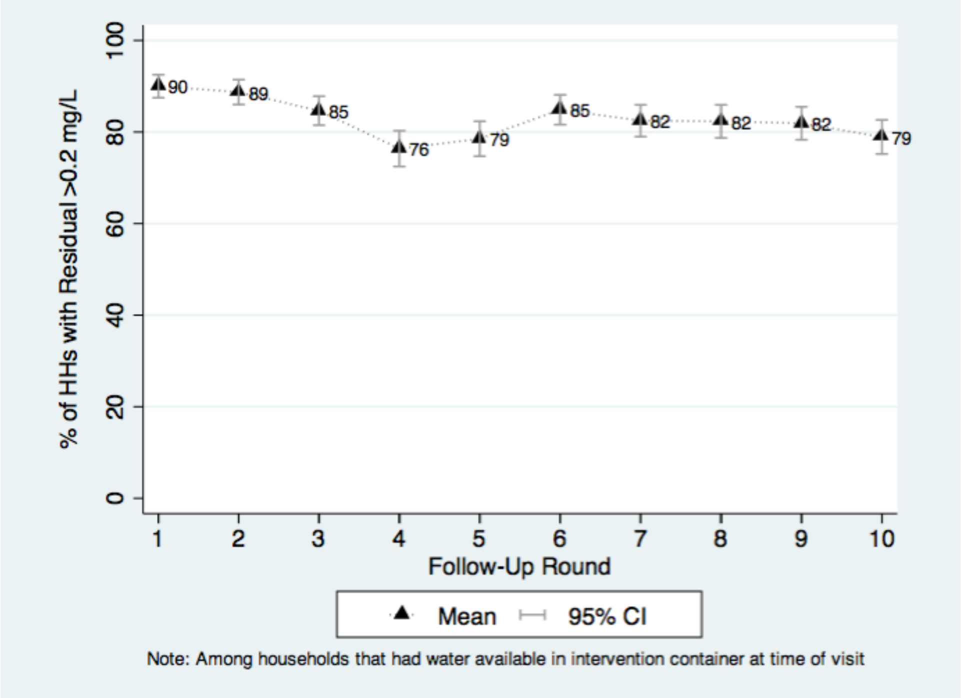
SUPPLEMENTARY FIGURES



'Groundwater Studies of Arsenic Contamination in Bangladesh'
DPHE/BGS/DFID (2000)

FIGURE S1. Iron Map of Bangladesh (Source: BGS&DPHE 2001)

FIGURE S2. Safe Storage Container with Tightly Fitting Lid, Narrow Mouth and Tap



Note: Among households that had water available in intervention container at time of visit

FIGURE S3. Temporal Trend in Percentage of HHs with Chlorine Residual >0.2 mg/L

Chapter 5. Conclusions

Our findings from our systematic review and meta-analysis, and our field studies in two different settings in two less developed countries, one in urban India and the other in rural Bangladesh, both indicate that use of water from improved water sources as classified by the JMP is not sufficient to prevent child waterborne illness as secondary contamination mechanisms can present a health risk.

In our systematic review, we assessed the association between waterborne illness and (re)contamination of piped water due to distribution system deficiencies (Chapter 2). Our findings suggest that direct consumption of tap water, as compared to consumption of tap water that has been further treated at the point of use, is associated with 34% increase in the incidence of gastrointestinal illness (IDR = 1.34, 1.00-1.79) in settings where centrally treated water meeting water quality regulations is distributed via a piped network that has deficiencies such as pressure loss or lack of adequate disinfectant residual. Increases in gastrointestinal symptoms were also associated with short-term service interruptions in continuously operated distributions systems (RR = 3.26, 1.48-7.19) as well as chronically intermittent water supply (OR = 1.61, 1.26-2.07). Our findings indicate that deterioration of water quality within the distribution system can pose a health risk associated with the consumption of water delivered by piped networks.

In Hubli-Dharwad, India (Chapter 3), we focused on a specific distribution system deficiency; we assessed the health impact associated with intermittent versus continuous delivery of water that is supplied through a piped distribution network in an urban setting and typically accessed by consumers through private connections. A piped connection on the premises is considered the top rank on the JMP water access ladder ascending from unimproved to improved sources [WHO-UNICEF 2013]. We found that switching from intermittent to continuous delivery of piped water, augmented by an upgrading of the distribution network and customer connections, led to reduced waterborne illness in children under five. Children in households with continuous supply had 7% reduction in diarrhea prevalence (PR = 0.93, 0.83-1.04) and 22% reduction in the prevalence of blood or mucus in stool (PR = 0.78, 0.60-1.01). Continuous supply also led to 42% reduction in the percentage of households with at least one case of typhoid fever (CIR = 0.58, 0.41-0.78) and 49% reduction in the percentage of households with at least one under-two child death (CIR = 0.51, 0.22-1.07) since the implementation of continuous supply. These findings are consistent with our systematic review and meta-analysis on the impact of distribution system deficiencies on gastrointestinal disease, which suggested that intermittencies in water delivery can lead to elevated levels of waterborne illness in consumers of piped water. Another important finding from Hubli-Dharwad was that households with continuous supply continued to store drinking and cooking water in their home despite the uninterrupted availability of tap water. We found evidence of point-of-use contamination during collection, storage and handling in households, counteracting the improvements in tap water quality delivered by continuous water supply and potentially preventing households from achieving the full potential of health benefits from the conversion to continuous supply.

We had similar findings on the role of point-of-use contamination in rural Bangladesh (Chapter 4), where we assessed the health impact of treating and safely storing tubewell drinking water. Private tubewells on the premises are the primary drinking water source for the majority of rural Bangladeshis and are categorized as an improved water source [WHO-UNICEF 2013]. Given that the provision of piped water on the premises to remote rural populations is not realistically feasible in the near future, tubewells present one of the highest achievable ranks on the water access ladder for rural populations, and groundwater is typically considered microbiologically safe as the percolation process leads to pathogen removal and inactivation. We found that safely storing tubewell water in a container with a narrow mouth, tightly fitting lid and tap for hygienic removal of water led to 31% reduction in diarrhea prevalence (PR = 0.69, 0.60-0.80) in children under two; combining safe storage with chlorination led to a 36% reduction (PR = 0.64, 0.55-0.73), suggesting no additional health benefits from the addition of chlorine. We also found that safe storage, both alone and in combination with chlorine, was effective in preventing heavy microbiological contamination of household stored water.

Taken together, this body of evidence confirms previous findings that, even for water sources categorized as improved by the JMP, there are water quality problems that can pose a public health threat [Onda 2012]. Notably, in both settings that we investigated, we documented waterborne illness associated with deficiencies in the distribution and handling of drinking water from the point of source to the point of consumption, rather than contamination at the water source. In the urban Indian setting with piped water delivery, refurbishing the distribution system and changing the water delivery frequency led to reductions in waterborne illness; our findings on continued household storage and contamination of stored water suggested that these health benefits could be enhanced by elimination of storage or adoption of safe storage practices. Similarly, in the rural Bangladeshi setting with private tubewells as the primary drinking water source, we found that point-of-use handling was the dominant mechanism for contamination of tubewell water as evidenced by marked reductions in child diarrheal illness due to safe storage and no additional health benefits when safe storage was combined with chlorination. These findings suggest that efforts to improve drinking water quality should place emphasis on preventing contamination at each step of the chain leading from the water source to the point of consumption, including the distribution system and household storage containers, to maximize the protection against waterborne illness.

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