

Toward a Systems Approach to Enteric Pathogen Transmission: From Individual Independence to Community Interdependence

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Abstract

Diarrheal disease is still a major cause of mortality and morbidity worldwide; thus a large body of research has been produced describing its risks. We review more than four decades of literature on diarrheal disease epidemiology. These studies detail a progression in the conceptual understanding of transmission of enteric pathogens and demonstrate that diarrheal disease is caused by many interdependent pathways. However, arguments by diarrheal disease researchers in favor of attending to interaction and interdependencies have only recently yielded more formal systems-level approaches. Therefore, interdependence has not yet been highlighted in significant new research initiatives or policy decisions. We argue for a systems-level framework that will contextualize transmission and inform prevention and control efforts so that they can integrate transmission pathways. These systems approaches should be employed to account for community effects (i.e., interactions among individuals and/or households).

INTRODUCTION

Diarrheal disease and its risk factors have been the focus of a substantial volume of literature for the past four decades. These studies contain valuable information about how the enteric pathogens that cause diarrheal disease are transmitted. The research frameworks used have progressed through time, moving from early attention to environmental transmission pathways, to a better delineation of risk between private and public domains, to increased focus on social and ecological processes. The idea of interdependencies among these realms has been posed but not embraced as a standard approach.

We review the literature on diarrheal disease epidemiology from the past four decades and detail a progression in the conceptual understanding of enteric pathogen transmission. We divide the research evidence into three overlapping periods, the first of which was composed largely of risk-factor observational studies, some of which were influential in intervention design and health policy development. In the second period, intervention studies became prevalent and began to replace observational studies as a basis for policy making. In the third period, meta-analyses, which provided a quantitative summary of the large numbers of intervention and observational studies, became influential. We describe this literature in terms of the evolving conceptual thinking about how transmission affects risk and how it can inform policy decisions on intervention and sustainable control efforts. These four decades of work have resulted in significant progress in such efforts, as evidenced by a 50% decrease in childhood mortality (see Disease Burden section, below). But to continue progress in reducing the disease burden, we argue that research should move in the direction of a systems perspective, where transmission pathways are viewed as interdependent processes that are affected by social and ecological factors.

The history of conceptual frameworks in diarrheal disease research is marked by the changing role of the environment in disease causation, which recapitulates larger debates in public

health about disease causation. The argument between miasmatisms and contagionists in the mid-nineteenth century was focused largely on the environmental origins of diarrheal diseases, especially cholera. Edwin Chadwick, a proponent of miasma theory, did groundbreaking work with the sanitary reform movement in England in the 1840s. This work launched large-scale infrastructure improvements that diminished environmental transmission, causing significant advancements in health (21). Shortly thereafter, the link between the environment and diarrheal disease was clearly established by John Snow (123), and contagionist theories were validated. Through a series of epidemiological studies, Snow (133) demonstrated that a waterborne pathogen was the cause of the cholera epidemics in England, implicating contaminated drinking water. By the late 1800s, however, germ theory had supplanted this environmental focus with a biomedical perspective.

For the field of diarrheal disease epidemiology, it was not until the 1970s that a concerted effort developed to return focus to the environment. This shift was initially illustrated by the F-diagram, an innovative outline highlighting the role of the environment in waterborne disease transmission. The F-diagram promoted the idea that diarrheal disease was transmitted through, for example, food, flies, fields, fingers, and fluids (75). As noted by Kawata, “the focus of treatment must shift from the host to the environment if a permanent reduction in acute diarrheal disease is to be achieved. To this end, a long-range strategy of investment in the construction and maintenance of safe water supply and sewerage facilities is a necessity” (75, p. 2122). Influenced by the F-diagram, the 1980s marked the beginnings of establishing systematic evidence for the multiple pathways of environmental transmission (49).

In the mid-1990s, Cairncross et al. (20) advanced thinking about transmission of water-related infections even further toward group-level causation by dividing transmission into the domestic domain—under the control of the household—and the public domain, including education, work, recreation, and economic

production. Cairncross et al. (20) reviewed estimates of the relative importance of each domain in disease transmission, as well as the types of interventions that might prevent transmission in each domain and the politics surrounding them. They emphasized that interventions in both domains are often needed to control infectious disease. In another refinement of the environmental approach, some of these studies attended to causes related to power [socioeconomic factors (42, 129, 148) and gender and gender roles (39, 136)] and others to causes related to geographic space [roads and remoteness (14, 36, 72)]. These represent more complex and explicit causal frameworks beyond a simple dichotomy of proximal and distal (83).

Although interaction terms are often included in analysis of observational datasets, explicit conceptual attention to the meaning of interaction among these multiple transmission pathways was explored only sporadically. Some evaluated how sanitation and water pathways interact (43, 45, 46, 60, 138); others investigated the protective community effects of household latrine use (116), piped water, and sanitation (95), as well as the deleterious effects of poor community sanitation on household risk regardless of improved water and sanitation in the household (44, 49). Community effects are a result of the interdependencies among people and households; therefore, risks are manifested not only at the individual or household level but also at the community level. More recent studies have emphasized these interdependencies in the causation of diarrhea (37).

This focus on interdependencies raises the analysis from an individual level where outcomes among individuals are assumed to be independent to a systems level where outcomes are assumed dependent. Specifically, when outcomes (e.g., diarrhea) influence exposures (e.g., fecal contamination), which in turn influence outcomes (e.g., diarrhea), the assumption of independence no longer holds. In systems theory, this phenomenon is known as feedback. We define a systems-level approach here as one that can account for population-level effects that are not obtained by a simple linear aggregation

of individual-level effects. A systems-level approach requires models that can account for the dependencies associated with infection transmission (81). We argue that this systems-level approach is important for accurately identifying optimal intervention strategies, quantifying their health effects on diarrhea, and presenting this information in a way that informs public policy and resource allocation decisions.

In the sections below, we give a thematic overview of the research on enteric pathogen transmission and how trends have changed over time. We present this research organized by study design. The first section focuses on observational studies that fall into three categories. The first two categories are concerned with either single transmission or multiple transmission pathways, whereas the third category reviews studies that have addressed social (e.g., socioeconomic status, gender, and gender roles) and geographical factors. The second section focuses on intervention studies and is structured temporally to highlight an early emphasis on large-scale water systems in the 1970s and 1980s, followed by an emerging interest in hygiene during the 1990s, and an increasing interest in household water treatment in the 2000s. The third section highlights the emergence of meta-analyses and systematic reviews that summarize the research conducted in prior decades. These reviews tend to focus on one type of intervention at a time, and only a few of them emphasize the importance of interdependence in transmission. Finally, we argue for a systems-level framework that will contextualize transmission and inform prevention and control efforts so that they can integrate transmission pathways.

DISEASE BURDEN OF ENTERIC PATHOGENS

Enteric disease has been and continues to be a major cause of morbidity and mortality worldwide. Over the past four decades, oral rehydration therapy has helped reduce diarrhea-associated mortality from ~5 million to 2.5 million deaths per year; however, it is still

the second leading cause of childhood mortality worldwide (82). The magnitude and specific causes of this disease burden vary geographically, depending on a variety of socioeconomic and demographic factors. Developing countries suffer the bulk of the disease burden worldwide. Prior to the introduction of oral rehydration therapy, diarrheal disease was the leading cause of childhood mortality. This disease burden is due primarily to overcrowding as well as to substandard water and sanitation facilities. Diseases are caused by a variety of viral, bacterial, and protozoan agents, a large proportion associated with *Escherichia coli* pathotypes (e.g., enterotoxogenic, enteropathogenic, and enteroaggregative), *Shigella*, and rotavirus. *Cryptosporidium* has emerged in the past few decades as a major protozoan causing persistent diarrhea (17).

In the developed world, food contamination is a principal mode of transmission in which *Salmonella* and *Campylobacter* are often implicated. Viral pathogens are also common in developed countries. Since the 1990s, norovirus has been increasingly identified in outbreaks associated with food and water contamination as well as nursing homes and daycare centers (125). However, since the introduction of the rotavirus vaccine in 2006, there has been a dramatic decrease in rotavirus incidence in the developed world. Many of the future reductions in diarrhea mortality will depend on appropriate attention to the specific details of modes of transmission in different ecological and socioeconomic contexts.

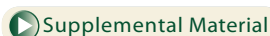
METHODS

Database searches were conducted using the Cochrane Library, Web of Science, PubMed, and Scopus. All searches included a mode of enteric pathogen transmission (e.g., water, hygiene, food), a pathogen name or disease outcome (e.g., *Giardia*, diarrhea), and the term “epidemiology.” (For a complete list of search terms, follow the **Supplemental Material** link from the Annual Reviews home page at <http://www.annualreviews.org>.) The

initial search yielded more than 32,000 unique results. Approximately 88% of these articles were excluded because they did not investigate human enteric pathogens or focused only on clinical treatment; additional exclusion criteria were outbreak investigations (eliminated 9%) and articles in a language other than English/Spanish (eliminated <1%). The 823 articles that remained (~3%) were then categorized by pathogen, developing/developed country, rural/urban, mode of transmission, environmental/health (i.e., whether there was a health variable analyzed versus only environmental outcome variables analyzed), and study design (see **Supplemental Material** for a list of categorizations). These 823 studies were narrowed down using the following additional exclusion criteria: modeling articles, editorials, nonsystematic reviews of disease, and policy/economic analyses. A final list of 415 articles was reached by cross-referencing our list with the reference list of meta-analyses and systematic reviews, as well as those articles that cited these same meta-analyses and systematic reviews. Any relevant article that had not been found previously was added to our reference list. If an abstract or article was unavailable, we excluded the article. Of these 415, 246 were observational studies, 78 were intervention trials, 20 were meta-analysis/systematic review studies, and 71 were conceptual in nature. Most of these articles were characterized by reading the articles in their entirety, and all abstracts were read. These citations can be viewed in the **Supplemental References** online. Because of space constraints only a representative subset is cited here.

HISTORY OF WATER, SANITATION, AND HYGIENE RESEARCH

The following review sorts research findings by study design through time. We note the relative lack of attention to multiple transmission pathways and interdependencies among pathways, and highlight the need to widen the causal lens and pay more conceptual attention



to socioeconomic status, gender, remoteness, and ecosystem changes.

Observational Studies

During the second half of the twentieth century, researchers made a concerted effort to identify risk factors for diarrheal disease through observational studies, examining many pathways of transmission. It was common knowledge throughout this time that there were multiple causes of diarrhea and that these causes interacted (80). Yet more than half of the 246 observational studies identified for this review focused on only one transmission pathway: person to person (17 studies), sanitation (19 studies), food and food hygiene (16 studies), domestic hygiene (21 studies), and water (72 studies). Of the remaining 101 articles that included multiple transmission pathways, 26 explored the classic trinity of water, sanitation, and hygiene. However, 95% of all 101 studies investigating multiple pathways compartmentalized risks in their analysis, assuming each transmission route was independent of the others. The other 5% explored dependencies between pathways, usually water and sanitation. This reflects, in part, the prevalent statistical methods used in this area of research, which assume factors to be independent. In all but this final 5%, it was as though researchers sought the holy grail of risk, the single factor that could account for the bulk of the incidence and would be readily amenable to intervention (57), or the single at-risk population that could be separated out as the target for prevention campaigns.

Single Transmission Pathways

Water. Within the water transmission pathway, there was a clear division between themes of studies done in developing countries and those in developed countries. Studies in developed countries generally comprised two themes. The first was swimming and water sport-related disease and the need to reevaluate the standards used to regulate the quality of water used for these sports (see examples in Reference 142). The second was quality of

municipal water supplies and the merits of chlorine versus filtering or a combination of the two (51, 101). Developed countries have historically had sophisticated water treatment plants and lower likelihood of recontamination in the household. There the research focus has consistently been on municipal water supplies and regulatory questions with respect to managing community supplies. However, with the increasing deterioration of drinking water distribution systems even in developed countries, increased attention has been paid to risks associated with contamination of drinking water between the treatment plant and the home (86).

In developing countries, however, articles about transmission by water focused on both quality and quantity of water. The water-quality research focused on the importance of supply (71) or point-of-use (117); several articles compared the two (54, 104). (The debate between advocates for intervening on the water supply versus at point-of-use is discussed in Intervention Trials, below.) Observational studies focused on measuring the quality of water at the source and/or point-of-use using fecal coliforms or other indicator organisms (146). A few studies have argued that quality of water extends beyond drinking, for use in cleaning, bathing, etc. (67). In addition, many have argued that quantity and access to water are important for drinking as well as for hygiene purposes such as hand washing (52). Jagals et al. (70) noted that when large sections of the population do not have access to water it can lead to unsafe and improper use of supplied water and reliance on other unsafe sources of water. Another aspect of access was distance traveled to obtain water (see examples in Reference 143).

Food. Levine & Levine (88) noted that one of the main changes in human ecology in the developed world has been a shift in the production, distribution, and retailing of food. This shift has resulted in the growth of large-scale industrial agriculture characterized by huge centralized farms, as well as large-scale food service such as fast-food chains, creating a

possibility for widely disseminated outbreaks if breakdowns in food hygiene occur. These changes, which have led to economies of scale, have also facilitated the emergence of diarrheal pathogens such as *Salmonella enterica* (77, 79) and *E. coli* O157:H7 (102, 115), which have become a problem in the developed world.

In the developing country context, the food pathway was less emphasized compared with other pathways. When it was considered, it was in the context of exploring multiple risk factors. The few studies that did focus on the food and food hygiene pathway in developing countries explored contamination, for example contamination of weaning foods (16) and issues related to food storage (119).

Hygiene. Articles from developed countries exploring the hygiene pathway presented different issues than did those from developing countries. Studies in the developed world tended to focus on the public domain, for example examining issues of daycare staff both diapering children and serving food (87, 134), and hand washing on cruise ships (105). Larson (85) argued that all studies about the developed world have focused on the community level and that more attention to domestic hygiene behavior in the household is needed. Articles within the home have explored the risks of pets (5) and changing diapers (66).

In contrast, hygiene research in the developing world focused on the private domain. One major theme was the importance of hand washing (73, 122); other studies evaluated additional hygiene aspects such as the presence of soap (144), cleaning utensils and the kitchen (58), and safe disposal of children's feces (12). Finally, studies in both the developed (107) and the developing world (55) cited the importance of flies contaminating food in the transmission of pathogens.

Person-to-person. The studies evaluating person-to-person transmission presented two themes: general person-to-person transmission and sexual transmission. The first examined the spread of disease within households or with household contacts and included articles about

both the developed and developing world (106). However, very few of these studies discussed the mechanism of transmission. Those that did focused on children attending daycare centers becoming infected both through child-to-child fecal-oral contact as well as through fomites (84). Others explored the importance of asymptomatic carriers, for example in the spread of cholera (132). All other articles used index cases to describe the spread of disease without actually focusing on the mechanisms (139). The second theme was sexually transmitted enteric pathogens by oral-anal contact in developed countries. Some studies compared heterosexual and homosexual men (76), whereas the others focused only on homosexual men (98).

Sanitation. In contrast with studies discussing the other pathways, all studies exploring only sanitation were about developing countries. Many focused on the importance and use of latrines as they impacted sanitation at the household level (1, 97). Age of latrine users, the location where children defecated, and how mothers disposed of the feces were discussed (12). Others evaluated the effect of improved sewage systems on the health of the community (13, 108). A final theme was the transmission of disease from irrigating crops using wastewater (22).

Multiple Transmission Pathways

Whereas numerous articles focused on the multiple causes of diarrheal disease, few paid attention to the interdependencies between pathways. The vast majority of studies exploring multiple transmission pathways were about developing countries. Many of these studies merely characterized diarrhea as a problem. The authors used a combination of surveys and observational data to theorize risk factors for disease, including water, sanitation, and hygiene practices. The researchers typically analyzed these risk factors using logistic regression to find which factors were statistically significant.

Even more strikingly, very few studies about developed countries explored multiple

transmission pathways, suggesting an even stronger bias toward the single independent pathway causes. Several of the few studies that did focus on these multiple pathways fit the Levine & Levine (88) concept that there are developing world ecological niches in the developed world, such as daycare centers, where risks are elevated (47). Another such location was agricultural camps, with studies emphasizing availability of water for hygiene (64) and need for increased quality of water and sanitation measures (6).

Of articles addressing multiple transmission pathways, few examined interdependencies among these pathways. Most tested for multiple risk factors assuming that they were all independent. Few observational studies identified in this review addressed the possibility of interactions between water and sanitation, and none broadened this scope to examine interdependencies among other pathways. Furthermore, many of these articles were written prior to 2000, indicating a shift away from this type of thinking. Some evaluated the joint effects of improved sanitation and water (11, 61), concluding that future studies should account for both pathways. Others evaluated water and sanitation independently and then used interaction terms in regression analysis to evaluate the synergistic effect of the two pathways above and beyond the effect of water or sanitation individually (43, 45, 138), finding that the interaction was highly significant. In addition, VanDerslice and Briscoe (138) found an effect of sanitation at the community level, but not at the household level, further demonstrating the need to look at community-level risk when examining transmission pathways. A final article concluded that flies do not present an independent pathway of disease transmission but are tied to the sanitation pathway with flies drawn to feces (145).

Widening the Lens

One major critique of observational studies is the need to widen the lens through which we view diarrheal disease. Current study designs focus on pathways through which pathogens are

transmitted and pay less conceptual attention to factors such as socioeconomic status, gender, remoteness, and ecosystem changes, which may be more difficult to operationalize but are no less important.

Socioeconomic status was often addressed; however, most studies did not consider poverty as an underlying cause of disease. Some articles simply mentioned that their study population had a low socioeconomic status or included tables of socioeconomic characteristics without mentioning this issue further in their analysis or discussion (149). Some used socioeconomic status as a confounder for which to control in measuring the effects of water quality or sanitation (33). Finally, some articles mentioned socioeconomic factors such as crowded housing or low levels of education as one of many risk factors for disease (110, 140).

Few studies actually explored how low socioeconomic status might act as a major underlying cause of diarrheal disease. Several studies cited poverty as an important indirect cause of diarrheal disease because it was the root cause of other factors such as lack of clean water and sanitation or lack of education about good hygiene behavior (129, 148). Another theme was the need to combine infrastructure improvements with poverty-reduction projects (71). Others cited cost of water and availability of water to low-income families as major risk factors for disease (56, 120). Genser et al. (53) went further to quantify attributable risk due to low socioeconomic status before and after a citywide sanitation improvement.

Other articles noted that diarrheal disease is a specifically gendered problem: Female children were more likely to become ill than male children (39), and women were more at risk than men (103). Some studies used all female populations without commenting further on how gender influenced the results (31). Finally, some studies cited a mother's age or lack of education as risk factors without considering whether a father's level of education might matter (113).

Some studies did not explicitly include the important role of women in both the

household and the community. In a review of the roles of women in water supply and sanitation programs, Elmendorf (40) noted that all water and sanitation improvements are influenced by women's behavior: "It is she who forms a constant link in the chain of contamination from feces to fingers to food, and she who in turn can break the chain by latrine use, hand washing, and protection of leftover food" (p. 199). Some of the studies addressed the role of women in this "chain of contamination" (3, 147). In addition to the mothers' actions, many studies also explored their perceptions of disease in addition to their actions (58, 136). Another group of studies examined women as agents of behavioral change. For example, educating women about soap (144) changed not only mothers' behaviors, but the behaviors of the entire household. A final theme was mothers as acceptors and primary users (40) of new technology such as solar disinfection (117).

Transmission of diarrheal pathogens was also affected by remoteness. Examining a very isolated community in Papua New Guinea, Jenkins et al. (72) found that as contact with outsiders increased in the 1980s, so too did epidemics of diseases including rotavirus. Eisenberg et al. (36) quantified the effect of new roads in Ecuador on remoteness, finding higher diarrheal disease and pathogen infection rates in nonremote villages. They hypothesized that the effect of remoteness can be explained by both the increased rates of introduction of new pathogens from travel outside the region and decreased social cohesion observed in the nonremote villages. Bates et al. (14) examined social space, measured by both social networks and geographic distance, as a community-level determinant of diarrheal disease.

Beyond community-level and regional effects, ecosystem changes are also important to consider when examining larger scale forces that influence disease burden. For example, Curriero et al. (28) examine the impact of extreme precipitation events on waterborne disease outbreaks in the continental United States. This study and others that examine the relationship between climate variability and diarrheal

disease highlight the need to include ecosystem scale factors when characterizing transmission.

Intervention Trials

Intervention trials in the 1970s followed the traditional wisdom that water quality at the source is most important in preventing diarrheal disease. These studies typically evaluated the effect of an expansion in public water services on the incidence of diarrhea (10). The emphasis on water source has historical roots that go back to the nineteenth century with John Snow and the Broad Street pump, which resonated with water resource engineers' numerous experiences with point source epidemics (80). During this time, the international health community was concerned with improving the primary health care system, and a commitment to address it was formalized with the Alma Ata Declaration signed in 1978. Following this trend, investments in water as a public good were more easily justified.

The interest in water source continued into the 1980s, driven in large part by its designation as the "International Drinking Water Supply and Sanitation Decade," with the goal of safe water supply and sanitation for most of the world's population by 1990. As such, these years saw the vast majority of studies focusing on the effect of water supply alone (118, 150), in addition to a few studies on sanitation alone (30) and the combination of water supply and sanitation (59). Studies focusing on behavior change underscored the importance of community education in supporting water supply and sanitation interventions (130). Promising studies on personal hygiene behaviors also began to be published (130).

The emphasis on personal hygiene gained momentum during the 1990s, as growing evidence showed that hand washing (121) and simple hygiene education (144) could yield dramatic reductions in diarrheal disease. Studies exploring multiple transmission pathways began to incorporate hand-washing and hygiene education, in addition to water and sanitation interventions (9, 124). During the

latter half of the 1990s, attention began to shift toward household water interventions (63) in response to a growing awareness of possible contamination between water source and point-of-use.

This move from the public to the private domain may also have reflected a shift in policy focus toward cheap and simple interventions targeting single households (126) instead of larger, more complex, and more expensive interventions that target larger population groups. Thus the period of 2000 to 2010 saw an explosion of research on point-of-use water interventions. These studies typically focused on household water treatment (HWT) through chlorination (112, 127), solar disinfection (27, 100), and flocculation (22, 114). Filtration methods were also commonly assessed, using ceramic filters (32) and sand filters (131). Some of these household interventions were undertaken with HIV-positive persons (26) and the elderly (25). Other household interventions were tested as personal filtration devices well-suited for natural disaster conditions (41).

Some studies integrated additional intervention components to HWT, thereby interrupting more transmission pathways. One important strategy that addressed multiple transmission pathways was the “Safe Water System,” designed by the U.S. Centers for Disease Control and Prevention (91, 111). The strategy involved water treatment with sodium hypochlorite solution, safe water storage in narrow-mouthed plastic containers, and behavior change through social marketing and motivational interviewing (96). On the whole, interventions that have addressed multiple transmission pathways have been met with mixed success. Some studies showed no additional benefit over single interventions, for example, adding hand washing to HWT (93). However, others have found that “multi-barrier” interventions perform best where there are many opportunities for contamination (109).

Study designs for diarrheal disease interventions have generally become more rigorous over time. Randomization was rare for intervention

studies in the 1980s and 1990s. Of the studies that did randomize, most focused on behavioral interventions such as handwashing and hygiene rather than water treatment and storage. With the surge of interest in HWT in the 2000s, randomization became the rule rather than the exception. Blinding was rare until recently, with only one study blinded prior to 2000 (78).

Currently (in 2011) HWT interventions are being examined more critically. For example, although HWT interventions addressed the issue of recontamination, individual-level compliance is necessary to obtain sustained reduction in diarrheal disease (7, 65, 94). Because these intervention trial designs created a condition in which compliance was artificially high, they measured efficacy as opposed to effectiveness. Trials of short duration exacerbated this problem (68); several authors have called for research on long-term sustainability in developing countries (8, 92, 141), whereas others have called for re-examining the benefits of infrastructural improvements at the community level that do not require individual-level compliance, much like the thinking in the 1970s and 1980s.

Meta-Analyses and Systematic Reviews

Reviews and meta-analyses reflected current policy priorities aimed at the domestic sphere, namely point-of-use water treatment and handwashing interventions. They focused predominantly on the effect of each intervention in isolation (24, 50). Examining the heterogeneity observed among these single pathway intervention trials gives insight into the interdependent nature of transmission pathways. Given this evidence, interventions should not be considered in isolation. The question as to whether single or multiple interventions are most effective has direct implications for research and policy.

Several authors of meta-analyses note heterogeneity in diarrheal disease reduction among intervention trials but few have tried to explain it. Gundry et al. (60) found that point-of-use interventions had a greater impact on diarrhea where a high proportion of

households had adequate sanitation, concluding that interdependencies between pathways played a key role in explaining heterogeneity. Gundry et al. argued that multiple interventions are necessary. An early review by Esrey & Habicht (44) similarly found that the effect of water-quality interventions is relatively small where sanitation and hygiene are poor. They recommend that water-quality interventions take priority only after sanitation and water-quantity standards have been met. A recent meta-analysis by Waddington & Snilstveit (141) found that adding either hygiene or sanitation resulted in health benefits beyond the use of water supply or quality interventions alone.

Other authors focused on different causes of heterogeneity. Both Arnold & Colford (8) and Waddington & Snilstveit (141) found an attenuated effect of HWT interventions for longer trials, suggesting that gradual loss of interest and noncompliance over time may explain heterogeneity of results; in contrast, Waddington did not observe this attenuation for hygiene interventions. Hunter (68) similarly found that duration of follow-up, as well as whether the study was blinded, significantly predicted the effectiveness of HWT interventions. These authors who looked at heterogeneity among intervention trials advocated for improved study designs, including the need to examine multiple and interdependent interventions, to quantify compliance better, and to develop new ways to effectively blind both participants and researchers.

Water recontamination, for example, when poor hygiene coexists with unsafe water storage, provides additional evidence of interdependence. Wright et al. (146) conducted the first systematic review of the literature on this topic, finding a significant increase in microbial contamination of household drinking water between source and point-of-use in developing countries. Subsequent meta-analyses showed that point-of-use interventions are effective (24, 50, 60). This result further supported the contention that recontamination plays an important role and contradicted the argument by VanDerslice & Briscoe (137) that household

recontamination is not as dangerous as water source contamination. They argued that in-house contamination creates immunity within the household, whereas source contamination brings in new pathogens, and that other in-house transmission pathways are more efficient than water recontamination. This reinforces the need to understand better the specific mechanisms governing pathway interdependency.

Finally, with the increased interest in the domestic sphere and behavioral practice, several meta-analyses were conducted to synthesize the many hand hygiene intervention studies published in the 1990s. Although all showed a consistent reduction of diarrheal disease by more than 30%, the various reviews differed mainly in the specific details of how hands were washed: with soap, antibacterial soap, or alcohol-based sanitizers, etc. (2, 29, 38). As with the water intervention trials, these interventions have not evaluated how hygiene might interact with other transmission pathways.

The future of systematic reviews and meta-analyses should move toward evaluating the sustainability of diarrheal disease interventions, as demonstrated by Hunter (68) and Arnold & Colford (8). Researchers are increasingly concerned with how an intervention's efficacy under controlled conditions may or may not translate into effectiveness in real-world conditions (7). The above systematic reviews and meta-analyses showed that HWT interventions and hand hygiene studies consistently yield dramatic positive results under artificial study conditions. Nonetheless, Waddington & Snilstveit (141) challenged the notion that HWT and domestic hygiene interventions are necessarily the most efficacious, suggesting the need to reexamine community or regional scale infrastructural interventions.

CURRENT THINKING AND MOVING FORWARD

We have described an extensive literature in diarrheal disease research that has documented the many pathways through which enteric pathogens are transmitted. Over the past

decades, this research has largely comprised single independent determinants of transmission. How are these pathways and levels of causation connected, and how does this interaction affect intervention design? Answering this question requires a systems analytical approach where one explicitly acknowledges the interdependencies among these pathways. We have shown that attention to interdependencies has arisen sporadically over the past four decades in the diarrheal disease literature. However, unlike the cases of research on measles, malaria, and sexually transmitted diseases, these arguments by diarrheal disease researchers in favor of attending to interaction and interdependencies (19) have only recently yielded more formal systems-level approaches. We argue that these systems approaches should be employed to identify community effects (i.e., interactions among individuals and/or households) and the transmission mechanisms that lead to these effects. The implications speak to the need for alternative study designs and analytical tools as well as an interdisciplinary approach to research.

Over the past decade, a few researchers have used systems analysis to explain enteric pathogen transmission dynamics, often focusing on cholera (19), but also on other pathogens such as *Cryptosporidium* (34), *E. coli* O157 (99), and *Giardia* (35). Systems analysis has received attention within the Environmental Protection Agency, where it has been used to support regulations (128). However, a formal framework for including the environment in these systems models has only recently been put forward (90). Applying this approach to diarrheal disease requires an explicit acknowledgment of the fact that the processes are interdependent; for example, poor sanitation leads to the contamination of water sources, contaminated water sources can spread pathogens to food, and food-sharing practices within communities can cause pathogens to reach other households. Intervention and control efforts must account for these interdependent processes (37).

Thus diarrheal disease risk is established not only by a person's behavior, or that of

his/her household, but also by the practices of neighbors and the surrounding community. This community effect has been empirically documented; for example, households without latrines were shown to have health benefits if they were adjacent to households with latrines (116), those not receiving the cholera vaccine nonetheless received benefits when they resided within a community that had high vaccine coverage (4), and water filtration in one household provided benefits for neighboring nonfiltering households (69). All these examples illustrate that pathogens move within communities through multiple pathways: Interventions that decrease transmission of one or more pathways can also decrease transmission through other pathways, thereby providing additional indirect benefits. Some researchers have echoed this concept by arguing that interventions at the community level are more effective because they address the interdependencies among people and households (13, 53); clustered randomized experiments have empirically shown the importance of the community effect (74).

Despite the evidence that community effects are important, recognition of these effects in research designs and analyses is still uncommon. For example, the indirect effects of cholera immunizations cannot be measured with designs that include vaccinated and unvaccinated individuals in the same village. Additionally, these designs cannot address an important implication of a community effect: whether percent coverage has a threshold effect analogous to herd immunity. We must elevate the design to the community level (62) and include both vaccinated and unvaccinated villages, as illustrated in the study by Ali et al. (4). To study these kinds of complex interconnections among individuals, households, communities, and regions, regional-level designs need to be implemented more often (36, 37, 42, 72). Additionally, to improve our understanding of transmission, we need study designs that elucidate social patterns of interaction (135) and the movement of pathogens through the environment (89).

Study designs must be appropriate for collecting relevant data, but so also must

appropriate statistical tools be chosen for analyzing those data. The statistical tools often used to analyze population data assume that outcomes are independent. Yet we know from studies that document a community effect, such as those discussed above, that outcomes are dependent. One way researchers have attempted to address this dependency is to examine the interaction among transmission pathways (45, 60, 138). Although this has provided evidence for interdependencies, the analytic tools often used (logistic or linear regression) still assume independent outcomes. Alternatively, dynamic transmission models explicitly acknowledge these interdependencies and are a more appropriate tool to examine the impact of intervention and control strategies at the population level.

Four decades of research show that diarrheal disease is caused by many interdependent transmission pathways. However, this interdependence has not yet been highlighted in significant new research initiatives or policy

decisions. Studying how enteric pathogens are transmitted through the environment requires understanding ecological processes, sociological processes and the built environment, and the interactions among these (48). Yet research is still dominated by single disciplines. Few research efforts have assembled the interdisciplinary resources required to understand the many complexities of the causal pathways, community effects, regional designs, and analytic models described above (15).

If these complexities were to be included, health policies would need to pay more attention to how recommendations must be modified according to context, for example, the effect of sanitary conditions on water interventions or the influence of socioeconomic status on hygiene education. Policy makers should specify the contingencies that influence a policy's probability of success. Furthermore, policies themselves are interdependent; their evaluations must consider their joint effect, sometimes synergistic and sometimes antagonistic.

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Contents

Symposium: Comparative Approaches to Reducing Health Disparities

Health Disparities Research in Global Perspective: New Insights and New Directions <i>Shiriki Kumanyika</i>	1
Health Inequalities: Trends, Progress, and Policy <i>Sara N. Bleich, Marian P. Jarlenski, Caryn N. Bell, and Thomas A. LaVeist</i>	7
Conceptual Approaches to the Study of Health Disparities <i>Ana V. Diez Roux</i>	41
How Society Shapes the Health Gradient: Work-Related Health Inequalities in a Comparative Perspective <i>Christopher B. McLeod, Peter A. Hall, Arjumand Siddiqi, and Clyde Hertzman</i>	59
Disparities in Infant Mortality and Effective, Equitable Care: Are Infants Suffering from Benign Neglect? <i>Diane L. Rowley and Vijaya Hogan</i>	75
Clinical Care and Health Disparities <i>B. Starfield, J. Gervas, and D. Mangin</i>	89

Epidemiology and Biostatistics

A Review of Spatial Methods in Epidemiology, 2000–2010 <i>Amy H. Auchincloss, Samson Y. Gebreab, Christina Mair, and Ana V. Diez Roux</i> ...	107
Early Intervention to Reduce the Global Health and Economic Burden of Major Depression in Older Adults <i>Charles F. Reynolds III, Pim Cuijpers, Vikram Patel, Alex Cohen, Amit Dias, Neerja Chowdhary, Olivia I. Okereke, Mary Amanda Dew, Stewart J. Anderson, Sati Mazumdar, Frank Lotrich, and Steven M. Albert</i>	123
Preventability of Cancer: The Relative Contributions of Biologic and Social and Physical Environmental Determinants of Cancer Mortality <i>Graham A. Colditz and Esther K. Wei</i>	137

The Hurrier I Go the Behinder I Get: The Deteriorating International Ranking of U.S. Health Status <i>Stephen Bezruchka</i>	157
---	-----

Unintentional Injuries: Magnitude, Prevention, and Control <i>Sarah Stewart de Ramirez, Adnan A. Hyder, Hadley K. Herbert, and Kent Stevens</i>	175
--	-----

Environmental and Occupational Health

Community-Based Approaches to Controlling Childhood Asthma <i>Noreen M. Clark</i>	193
--	-----

Future Challenges to Protecting Public Health from Drinking-Water Contaminants <i>Eileen A. Murphy, Gloria B. Post, Brian T. Buckley, Robert L. Lippincott, and Mark G. Robson</i>	209
--	-----

Speed Limits, Enforcement, and Health Consequences <i>Rune Elvik</i>	225
---	-----

Toward a Systems Approach to Enteric Pathogen Transmission: From Individual Independence to Community Interdependence <i>Joseph N.S. Eisenberg, James Trostle, Reed J.D. Sorensen, and Katherine F. Shields</i>	239
---	-----

Public Health Practice

Advertising of Prescription-Only Medicines to the Public: Does Evidence of Benefit Counterbalance Harm? <i>Barbara Mintzes</i>	259
--	-----

Economic Evaluation of Pharmaco- and Behavioral Therapies for Smoking Cessation: A Critical and Systematic Review of Empirical Research <i>Jennifer Prah Ruger and Christina M. Lazar</i>	279
--	-----

Policies for Healthier Communities: Historical, Legal, and Practical Elements of the Obesity Prevention Movement <i>Samantha K. Graff, Manel Kappagoda, Heather M. Wooten, Angela K. McGowan, and Marice Ashe</i>	307
---	-----

Public Health and the Epidemic of Incarceration <i>Dora M. Dumont, Brad Brockmann, Samuel Dickman, Nicole Alexander, and Josiah D. Rich</i>	325
--	-----

Quitlines and Nicotine Replacement for Smoking Cessation: Do We Need to Change Policy? <i>John P. Pierce, Sharon E. Cummins, Martha M. White, Aimee Humphrey, and Karen Messer</i>	341
Systems Science Methods in Public Health: Dynamics, Networks, and Agents <i>Douglas A. Luke and Katherine A. Stamatakis</i>	357
Health Inequalities: Trends, Progress, and Policy <i>Sara N. Bleich, Marian P. Jarlenski, Caryn N. Bell, and Thomas A. LaVeist</i>	7

Social Environment and Behavior

Health Disparities Research in Global Perspective: New Insights and New Directions <i>Shiriki Kumanyika</i>	1
Health Inequalities: Trends, Progress, and Policy <i>Sara N. Bleich, Marian P. Jarlenski, Caryn N. Bell, and Thomas A. LaVeist</i>	7
Conceptual Approaches to the Study of Health Disparities <i>Ana V. Diez Roux</i>	41
How Society Shapes the Health Gradient: Work-Related Health Inequalities in a Comparative Perspective <i>Christopher B. McLeod, Peter A. Hall, Arjumand Siddiqi, and Clyde Hertzman</i>	59
Disparities in Infant Mortality and Effective, Equitable Care: Are Infants Suffering from Benign Neglect? <i>Diane L. Rowley and Vijaya Hogan</i>	75
Suicide Mortality in the United States: The Importance of Attending to Method in Understanding Population-Level Disparities in the Burden of Suicide <i>Matthew Miller, Deborah Azrael, and Catherine Barber</i>	393

Health Services

From Small Area Variations to Accountable Care Organizations: How Health Services Research Can Inform Policy <i>Harold S. Luft</i>	377
Suicide Mortality in the United States: The Importance of Attending to Method in Understanding Population-Level Disparities in the Burden of Suicide <i>Matthew Miller, Deborah Azrael, and Catherine Barber</i>	393

The Medicalization of Chronic Disease and Costs <i>Kenneth E. Thorpe and Meredith Philyaw</i>	409
The Methods of Comparative Effectiveness Research <i>Harold C. Sox and Steven N. Goodman</i>	425
Clinical Care and Health Disparities <i>B. Starfield, J. Gervas, and D. Mangin</i>	89

Indexes

Cumulative Index of Contributing Authors, Volumes 24–33	447
Cumulative Index of Chapter Titles, Volumes 24–33	452

Errata

An online log of corrections to *Annual Review of Public Health* articles may be found at <http://publhealth.annualreviews.org/>