This research involves the analysis of existing data from studies originally conducted at the University of California, Berkeley (termed "UCB-water") and at the University of Michigan (termed “UMich-water”). The UCB-water studies were funded by two sequential NIH grants (Award Nos.: R01AI068854 and R01AI50612; Titles: *The Socio-Environmental Determinants of Schistosomiasis Re-emergence*, and *Local Strategies for Schistosomiasis Control*; PI: Robert Spear), which have ended, all data have already been collected, and no additional interaction with human subjects will be pursued. The UMich-water study was funded by an NIH grant (Award No.: R01AI050038; Title: *Environmental Change and Diarrheal Disease*; PI: Joseph Eisenberg), which has ended, all data have already been collected, and no additional interaction with human subjects will be pursued. Drs. Spear and Eisenberg are collaborators on the present study.

The UCB-water data were collected under the oversight, and with the approval, of the University of California, Berkeley, Committee for the Protection of Human Subjects (approved protocols #2004-5-129 and #2010-12-2645). The objectives of the secondary analysis are in keeping with those for which consent was originally obtained. The original consent forms stated “The purpose of this study is to understand how schistosomiasis spreads (R01AI068854),” and “The purpose of this study is to try to develop better ways of controlling this type of infection (R01AI50612).” The new, re-analysis of these data will add additional detail to our understanding of how environmental factors, including climate and hydrology, contribute to the spread of this waterborne disease. Assessing these factors was a primary objective of the original study, but the investigators lacked the sophisticated environmental modeling capabilities that we are pursuing in the current project. With improved understanding of the environmental factors that contribute to disease spread, new management strategies may be possible to better control waterborne infections.

The UMich-water data were collected under the oversight, and with the approval, of the University of Michigan Health Sciences and Behavioral Sciences Institutional Review Board (IRB-HSBS; approved protocol #HUM00004835). The objectives of the secondary analysis are in keeping with those for which consent was originally obtained. The original consent forms stated “Our goal is to better understand why people get diarrheal disease,” and the new, re-analysis of these data will add additional detail to our understanding of how environmental factors, including climate and hydrology, contribute to waterborne diarrheal disease risk. Assessing these factors was a primary objective of the original study, but, as with the UCB-water study, the UMich-water investigators lacked the sophisticated environmental modeling capabilities that we are pursuing in the current project. With improved understanding of the environmental factors that contribute to disease spread, new management strategies may be possible to better control waterborne infections.

The investigators on the current project will not interact with human subjects, and will not receive and new data. The investigators on the current project currently possess the UCB-water and UMich-water study datasets.

**Background**

Climate is known to be a principal driver of microbiological water quality (e.g., John and Rose 2005; Koirala et al. 2008), and climate factors have direct impacts on the survival of waterborne pathogens and incidence of waterborne diseases (Drasar, Tomkins, and Feachem 1978; Levy, Hubbard, and Eisenberg 2009; Singh et al. 2001; Rose et al. 2001; Easton et al. 1999; Vezzulli, Colwell, and Pruzzo 2013). Yet despite strong statistical evidence of associations between climate and water quality or waterborne disease, mechanistic explanations for these links are currently lacking. A more thorough understanding of causal mechanisms linking climate and environmental pathogens is critical for generating robust predictions of the impact of future climate conditions on microbiological water quality, especially in the developing world (Lafferty 2009; Remais, Liang, and Spear 2008; Moore et al. 2012). To this end, improved models are needed that address the structural, computational, and data challenges involved in establishing causal relationships between meteorological phenomena and water quality, and ultimately waterborne disease.

Waterborne disease outbreaks have been associated with both wet and dry periods (Curriero et al. 2001; Thomas et al. 2006; Shiffman et al. 1976), and both high and low extremes of rainfall (Singh et al. 2001). Meanwhile, major floods have been associated with increased waterborne disease (Kondo et al. 2002; Schwartz et al. 2006; Qadri et al. 2005), and seasonal effects have been observed to be a major source of variability in concentrations of indicator organisms (Solo-Gabriele et al. 2000; George, Anzil, and Servais 2004; Wright 1986; Levy et al. 2009). That both wet and dry conditions are known to impact waterborne disease can be understood via four mechanistic relationships (which this project examines) between climate, hydrology and water quality: The *runoff effect* relates to the increased microbial contamination associated with wet conditions caused by the flushing of fecal material from sources into waterways following heavy rainfall, and/or mobilization of bacteria or parasitic ova resident in soil. Rainfall can affect soil saturation, which influences the rate of transport of microbial organisms. *E.coli*, for instance, can be transported via shallow subsurface flows and scouring of riverbank soils in the wet season, releasing bacteria that are associated with sediments or that have survived or grown in the soil. In addition, a heavy pulse of rain can cause the rapid and distant transport of pathogens via overland flow, particularly in the presence of inadequate sanitation. As opposed to the “first flush” effect, the runoff effect is not limited to the first heavy rains of the year in areas of poor sanitation because of the constant source of fecal contamination in these areas (Burns 2005).

The *dilution effect* represents the phenomenon where high surface water flows dilute the concentration of contaminantsin waterways. This effect occurs at an intermediate timescale, on the order of days or weeks, and can act to moderate increases in contaminants from the runoff effect and other processes (Burns 2005).

The *concentration effect* (also called the “accruing-input effect”) is where dry conditions cause an increase in the density of microorganisms in water bodies due to lack of flows to dilute these contaminants (Wright 1986). This effect occurs at a seasonal timescale, and has been used to explain cases of dry season epidemics of diarrheal disease (e.g., Drasar, Tomkins, and Feachem 1978). Dry season contamination peaks can occur independent of rainfall pulses, likely driven by local contamination events that are not flushed out of the waterway as they would be during rainy periods.

The *survival effect* describes the how microbial viability during transport is influenced by environmental variables. Broadly speaking, low temperatures tend to prolong viability while high temperatures reduce time to inactivation (Ferguson et al. 2003). This effect is ubiquitous in its implementation in watershed-scale models (e.g., BASINS, GWLF, etc.), but generally these platforms were designed for other applications (e.g., sediment transport), and thus represent pathogen transport using simplistic first-order decay processes (Haydon and Deletic 2006).

This project will develop and test methods for conceptualizing, quantifying and predicting the effects of these mechanisms on water quality at varying scales. Key questions will be addressed: how can we make reliable predictions about the effects of future environmental change on water quality in diverse settings? How can we direct social-economic decision-making to offset increased water quality problems under future climate conditions? Addressing these questions is crucial to identifying management strategies that may moderate future risk, but answering them poses major data, methodological and theoretical challenges that this project aims to address.

We are beginning year 3 of a series of interlinked research activities examining the interactions between pathogens, hydrology, climate, management decisions, and social organization using existing data from the UCB-water and UMich-water studies on waterborne disease transmission. The central hypotheses are that 1) climate change can affect water quality by altering the dynamics of surface water flows and the fate and transport of pathogens in the water column, and that 2) both management decisions and social organization can limit or exacerbate climate's influence. To test these hypotheses, we are assessing the impact of climate change on processes that determine water quality, and identifying management decisions that can mediate climate-related changes in water quality.

**Study Personnel**

Dr. Justin Remais (PI) is an expert on mathematical and statistical modeling of case data for environmentally-mediated infectious diseases, and has extensive experience in statistical and simulation studies on the dynamics of waterborne disease transmission, with a specific focus on the environmental modifiers of transmission.

**Subject Population**

This project is assessing the relationship between multiple environmental drivers and schistosomiasis and infectious diarrhea infections, by performing a secondary data analysis of epidemiological records between January 1, 2000 and June 30, 2014.

The secondary data consists of: **(1)** a dataset (termed **UCB-water**) collected during previous social survey and epidemiologic studies at the University of California, Berkeley between January 1st, 2000 and May 31st, 2011 (protected under UCB CPHS protocols #2004-5-129 and 2010-12-2645); and **(2)** a dataset (termed **UMich-water**) collected during previous social survey and epidemiologic studies at the University of Michigan between January 1, 2000 and June 30, 2014 (protected under University of Michigan IRB approved protocol #HUM00004835). Both of these datasets are already owned and in the possession of the Principal Investigator, and are subject to ongoing analysis as part of federally-funded research that is being transferred from Emory University to UC Berkeley.

The records contained in the datasets consist of both child and adult individuals (including the elderly) from all ethnic groups (eg. Han, Yi, Qiang in China; Chachi, Colono, in Ecuador). It has been demonstrated that children are less likely to be infected with certain tropical parasitic infections than their adult counterparts, and that prevalence of infection increases with age, with one study, for instance, finding the highest prevalence in populations between the age of 40 and 49 years (Zhou 2007). Thus, children are less represented in the dataset than their adult counterparts in the UCB-water dataset (Carlton 2010). Children are overrepresented in the UMich-water dataset. We will take measures to protect the confidentiality of the data for all of our participants, including child participants, as is fully described in a separate section of this protocol.

With respect to ethnicity, the datasets contain records reflecting the ethnic diversity of residents of the respective study regions. In terms of ethnic diversity in the UCB-water dataset, the majority of the records represent the Han Chinese majority population, but other ethnic minorities (e.g. Yi, Qiang, Tibetans) were also included in the study population. In the UMich-water dataset, the majority of the records represent the Chachi and Colono ethnicities, but other ethnic minorities are included in the study population. In both datasets, the exact proportion of records of women and minority participants differs by outcome. We will take measures to protect the confidentiality of the data for all of our participants, including women and minorities, as is fully described in a separate section of this protocol.

In the datasets, no information is available on the status of individuals as to their being prisoners, pregnant, having physical or cognitive impairments or their membership in other vulnerable groups. The datasets do contain records on child participants, and there was no exclusion of records in the datasets based on age. For schistosomiasis, it has been demonstrated that children are less likely to be infected with *S. japonicum* than their adult counterparts, and that prevalence of infection increases with age, with highest prevalence found in populations between the age of 40 and 49 years (Zhou 2007). Therefore, children are less represented in the UCB-water dataset than their adult counterparts (Carlton 2010). In contrast, children are overrepresented in the UMich-water dataset.

Pregnant or breastfeeding women were not eligible to be included in research performed in the creation of the **UCB-water** dataset, but were eligible to be included in research performed in the creation of the **UMich-water** dataset. No information is available on the status of individuals as to their being pregnant or breastfeeding. With respect to schistosomiasis, records of female participants have been included in the UCB-water dataset, however, they are not as strongly represented in the dataset as their male counterparts, as previous studies have shown that the prevalence of parasiticinfections is higher in male study participants than in female study participants (Zhou 2007), with one such study, for example, showing that men were 2.89 times as likely to be infected with *S. japonicum* as their female counterparts (Carlton 2010). Men and women are generally evenly distributed in the UMich-water dataset with respect to sex.

**Recruitment**

There will be no direct recruitment of any individuals into this study. All case detection and data collection was carried out without involvement of the current project PI; will have been completed by the start date of the transfer of this project to Berkeley; and no additional data will be collected for the purposes of this study. Over the course of this study, no contact will be made with individual participants included in this study.

**Study Procedures**

In order to assess the relationship between multiple environmental drivers and water quality and quantity, we have developed community-scale and regional-scale mechanistic socio-environmental models that include the social survey and human infection survey data extracted from the UCB-water and UMich-water datasets, aggregated at the community level. We hypothesize that climate change can affect water quality by altering underlying hydrology parameters that determine the runoff, dilution and survival of pathogens in the water column. We have developed an open-source hydrology model to examine water quantity response to climate variability; we will develop a water quality extension to the model that represents pathogen-specific fate and transport, and an analytics toolkit for investigating the climate sensitivity of water quality across networks; and will are testing how changes to climate or environmental management influences the relationships between climate, water quantity and quality, using the full model to examine management options.

We hypothesize that climate change can affect the water budget of the two study regions by altering underlying hydrology parameters that determine total discharge and discharge variability at key locations. To analyze the role of climate forcing on water *quantity* (and in Objective 2, water *quality*), we are expanding on our previous work (Remais, Liang, and Spear 2008; Abdelnour et al. 2011; Abdelnour et al. 2013) by developing customized, catchment-scale hydrological models for each region, allowing us to explicitly simulate the response of hydrodynamics to exogenous environmental drivers and endogenous environmental characteristics. We are using a spatially distributed eco-hydrology model, VELMA (Visualizing Ecosystems for Land Management Assessment; Abdelnour et al. 2011; Abdelnour et al. 2013), which links hydrological and biogeochemical processes within catchments. The model is forced with time-series of air temperature and precipitation, and model outputs at every grid cell include stream flow, soil moisture, soil temperature, soil heterotrophic respiration, and ecosystem net primary productivity. Flow outputs from VELMA simulations driven by current climate have been compared between and within the sites, including runoff timing, maximum flow, maximum n-day flow, and number of days in which the flow is in the upper quintile; these are expressed per unit basin area and aggregated at daily, monthly, seasonal and annual timescales. For future climate, our team has carried out work on decadal-scale changes in temperature, precipitation, variability of these terms, and other key variables of interest (e.g., Moore et al. 2012; Dhingra et al. 2013; Zhou, Chang, and Fuentes 2012). The climate components we are exploring in this proposal include temperature and precipitation (and their variability), seasonal effects (e.g., warmer winters, drier summers) and the intensity and frequency of episodic events (e.g., heavy rainfall).

We hypothesize that climate change can affect water *quality* by altering the underlying runoff, dilution, concentration and survival mechanisms. Waterborne pathogens are highly sensitive to changes in water temperature (Noble, Lee, and Schiff 2004) and may be shielded from inactivation through particle association (Ward, Ashley, and Moseley 1976; Liew and Gerba 1980) facilitated by discharge variability. We have added to VELMA a major extension, the PATHFATE module, which will simulate the fate and transport of pathogens in response to environmental characteristics of the water column. PATHFATE replaces VELMA’s current soil temperature model with a scheme that allows us to explicitly track soil water and soil water heat as it moves vertically through the soil column and laterally from hillslope to riparian zone and into the stream (Stieglitz et al. 1997; Stieglitz et al. 2000; Ducharne et al. 2000; Shaman et al. 2004; Shaman, Day, and Stieglitz 2002; Shaman et al. 2002). With water column temperature estimated in this manner, PATHFATE implements a comprehensive suite of pathogen fate and transport processes in VELMA: 1) microbial deposition within stores (cells) in the catchment based on a contamination source layer; 2) microbial loss from the surface store due to inactivation or physical factors (e.g., settling); 3) microbial exchange between cells via surface water flows; 4) microbial transport into sub-surface stores via infiltration; 5) microbial loss from sub-surface stores due to inactivation or physical factors (e.g., desiccation); 6) microbial exchange between cells via sub-surface flows; 7) removal from the sub-surface store by sub-surface overflows into the surface store; and 8) microbial attachment as a function surface chemistry, hydrophobicity, and electrostatic interactions (Schijven and Hassanizadeh 2000) drawing on empirical data on microbial attachment and deposition (Krometis et al. 2010; Bhattacharjee, Ryan, and Elimelech 2002; Loveland et al. 1996).

With pathogen sources estimated at the township-level using the environmental modeling procedures described above, we are now examining the association between microbial deposition within stores in the catchment and epidemiologic risk as captured by the UCB-water and UMich-water datasets. We are combining our community-level social survey data on sanitation resources, water use, hygiene practices, population size, and infection incidence to estimate risk of disease given the underlying hydrology at the sites and estimated pathogen source loading using a probabilistic pathogen loading model (Dorner et al. 2006). One way in which environmental change may play a role in determining the spatial distribution of disease incidence is by facilitating survival and transport of pathogens from specific sources, or along specific pathways. For instance, are there key sites of transmission that are intensified by climate change? Attenuated? How is the spatial scale of transmission altered under future climate? We are developing an analytics toolkit (NETFATE) for characterizing changes in hydrological connectivity under altered climate conditions, and assessing the degree to which connectivity influences disease transmission under current and then altered environmental conditions, building on our novel application of network theory (Remais et al. 2010). The approach accounts for the strength of hydrological connections between transmission sites, as well as connection asymmetries that arise from directional (i.e., hydrological) flows (Remais et al. 2010).

The overall objective of our ongoing epidemiological analyses is to test specific correlations between hydrological drivers and disease transmission as assessed in the UCB-water and UMich-water datasets. We will use a range of statistical tools, including hierarchical, longitudinal mixed models and time-series approaches to explore mutli-scale associations. For instance, we are modeling the association between hydrological drivers and incidence using a Poisson generalized estimating equations (GEE) approach with an autoregressive correlation structure to accommodate autocorrelation in incidence within villages (Liang and Zeger 1986; Zeger and Liang 1986). At the regional scale, we are testing the hypothesis that detrended and lagged temperature, rainfall and hydrological flow variables are associated with incidence by applying scale-dependent correlation techniques, which can reveal transient correlations between two series (Rodriguez-Arias and Rodo 2004; Rodó and Rodríguez-Arias 2006; Remais et al. 2009).

We are assessing the sensitivity of model predictions to management decisions and social processes that mediate the influence of environmental change by incorporating mechanisms related to water management practices, land use, changes in population size, hygiene and sanitation into our epidemiological models. The ability of communities to respond to future climate, and to potentially poorer water quality is hypothesized to be determined in part by management decisions (e.g., to build latrines, cut forest, mitigate flooding) that affect physical infrastructure. Using the models described above, we are developing management scenarios and explore their effects on water quantity and quality.

**Risks and Discomforts**

There should be no more than minimal risks to participants’ confidentiality for participating in this study; the main risk is that personal health information might be inadvertently divulged. In all cases with personal identifiers, in order to minimize risks we will take measures to keep data confidential and secure, and maintain only data that are stripped of personal identifiers unnecessary for our analysis. To ensure the confidentiality and integrity of the data, the UCB-water and UMich-water datasets are free of names and other personal identifiers unnecessary for our analyses.

In order to ensure confidentiality, digital data at Berkeley will be stored on a secure, password-protected file server. Passwords will be strong, containing a mix of upper- and lower-case letters, and combinations of numbers and symbols. All Berkeley staff members working on this project will have appropriate CITI training.

**Benefits**

Since we will have no direct contact with the study participants, we will not be able to directly inform participants of new findings that might affect their health. Benefit to the population of subjects may result through indirect communication of study findings. The results of our project will be used to inform best practices for schistosomiasis and infectious diarrhea surveillance and control, and therefore will we communicate the results of our study to relevant health officials and the public health community more broadly through publication of results and recommendations. Most importantly, we will share the findings of our research with our colleagues in public health disciplines who work directly with populations affected by waterborne infections. Participants may thus receive indirect benefits from this study with respect to improved disease control and surveillance.

**Informed Consent**

We request a waiver of informed consent for this study (a) because the study poses no more than minimal risk to the participants; (b) the waiver will not adversely affect the rights and welfare of the subjects; and (c) the study could not feasibly be conducted without a waiver of informed consent. As we have described above, personnel other than the Berkeley PI collected the data used in the study prior to our analysis. No interaction has occurred or will occur between Berkeley personnel and the study participants at any point during the course of this study. Since the dataset contains tens of thousands of historical records collected over a 15-year time period, it would not be possible to locate all of the participants in order to obtain informed consent. Due to the nature of the data collection and the structure of the datasets, it would not be possible to conduct this study without a waiver of informed consent.

**Assent waiver**

We request a waiver of assent for this study (a) because the study poses no more than minimal risk to the participants; (b) the waiver will not adversely affect the rights and welfare of the subjects; and (c) the study could not feasibly be conducted without a waiver of assent. As we have described above, personnel other than the Berkeley PI collected the data used in the study prior to our analysis. No interaction has occurred or will occur between Berkeley personnel and the study participants at any point during the course of this study. Since the dataset contains tens of thousands of historical records collected over a 15-year time period, it would not be possible to locate all of the participants in order to obtain assent. Due to the nature of the data collection and the structure of the datasets, it would not be possible to conduct this study without a waiver of assent.

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