Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Rachel A. Silver Date

Climatic Drivers and Heterogeneity of Diarrheal Disease, according to Pathogenic Class

By

Rachel A. Silver

Master of Public Health

Global Epidemiology

Karen Levy, PhD, MPH, MSc

Faculty Thesis Advisor

Climatic Drivers and Heterogeneity of Diarrheal Disease, according to Pathogenic Class

By

Rachel A. Silver

B.S., The Ohio State University, 2015

Thesis Committee Chair: Karen Levy, PhD, MPH, MSc

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Global Epidemiology

2017

Abstract

Climatic Drivers and Heterogeneity of

Diarrheal Disease, according to Pathogenic Class

By: Rachel A. Silver

Purpose: Global research that examines the relationship between climate and diarrheal diseases is lacking, especially regarding studies that demonstrate a link between climate and specific disease-causing agents. Among the existing data, positive associations between temperature and diarrheal disease incidence have been found, but uncertainty remains due to a lack of quantitative data on the effect that meteorological conditions have on risk by the specific individual pathogens responsible for causing diarrheal illness. In order to understand the effects that a changing climate is having on the incidence of infection, it is necessary to quantify and assess pathogen-specific seasonal patterns over a period of time, and the influence various weather factors have on this relationship.

Methods: This issue was examined through a systematic review of the literature focusing on three pathogens – *E. coli*, *Cryptosporidium*, and norovirus. Studies meeting specific inclusion and exclusion criteria that were conducted for a minimum of one full year were used for characterization of seasonal patterns. Available temperature and precipitation data for each study location was assessed through univariate, log-linear Poisson regression models and a pooled dataset for each pathogen was created for a meta-analysis using a generalized estimating equation modeling technique on each dataset.

Results: A positive correlation between mean monthly temperature and incidence of diarrheagenic *E. coli* and *Cryptosporidium* was found across all studies included in the pooled data analysis. Increases in the incidence of disease was found to be associated with a 1°C increase in mean monthly temperature for *E. coli* (8% increase, 95% CI: 5%-11%; P<0.0001) and mean 1-month lagged temperature *Cryptosporidium* (6% increase, 95% CI: 2%-10%; P=0.003) controlling for precipitation and country development stratum. Norovirus displayed a negative correlation between mean monthly temperature and incidence of disease, with (4% decrease, 95% CI: 0%-8%; P=0.05) per 1 degree Celsius increase, controlling for precipitation, country development, and new strain year.

Conclusions: These results demonstrate a heterogeneous relationship across pathogen class with ambient temperature, and suggests that an increase in mean monthly temperature corresponds to an increased incidence of diarrheagenic *E. coli*, and *Cryptosporidium*, and a decreased incidence of norovirus.

Climatic Drivers and Heterogeneity of Diarrheal Disease, according to Pathogenic Class

By

Rachel A. Silver

B.S., The Ohio State University, 2015

Thesis Committee Chair: Karen Levy, PhD, MPH, MSc

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Global Epidemiology

2017

TABLE OF CONTENTS

FIGURES AND FIGURE LEGENDS

INTRODUCTION

Background

The global burden of diarrheal disease is estimated at 1.7 billion cases per year in children under five years of age (1). Of those cases, over half a million children will die from diarrhea-related causes, accounting for 8-10% of all deaths in this age group, and causing approximately 1.2-1.4 million deaths across all age groups worldwide (1, 2). Though rates of diarrheal disease are decreasing from an uptake of treatment and implementation of prevention methods, it remains the second leading cause of death among children under five and a primary cause for global years of life lost (YLL), ranking as number five in 2015 (2, 3). Long-term morbidity outcomes can also occur as a result of enteric (diarrheal) diseases, including stunted growth and impaired cognitive development, the former leading to a predisposition to an increased risk for some of the world's leading non-communicable diseases later in life – obesity, type 2 diabetes, metabolic syndrome or cardiovascular disease – as well as premature death in moderate to severe stunting cases (3, 4).

Morbidity and mortality rates from enteric infections are highest in low and middle income countries (2). Several studies cite a perpetual cycle between malnutrition, poverty, and enteric disease in which malnourishment increases incidence, duration, and severity of infection while height and weight impairments occur because of diarrhea, all of which are exacerbated by the effects of living in poverty (4, 5). Such populations are characterized by crowded living conditions and will undoubtedly face widespread fecal contamination, inadequate

water sanitation, and minimal refrigeration options for preservation of food, thus allowing for the growth and transmission of various enteric pathogens that cause diarrheal disease (3).

Water availability and sanitation, as well as the emergence and re-emergence of etiologic pathogens, are largely affected by environmental factors, one of rapidly growing importance being climate change. The Intergovernmental Panel on Climate Change (IPCC) has found that each of the last three decades have successively increased in surface temperature and have all been warmer than any prior decade since 1950 (6). The IPCC predicts that the global surface temperature change for the end of the 21st century is likely to exceed 1.5 degrees Celsius relative to the period from 1850 to 1900, and in some scenarios is likely to exceed 2 degree Celsius (7). Rising temperatures are thought to be correlated with an increase in transmission of enteric diseases due to the impact of ambient temperature on pathogen survival and host behavior (8). In addition to, and as a result of rising temperatures, there has been a marked increase in many extreme weather and climate events, such as droughts, floods, and cyclones, that can impact the frequency and likelihood of disease transmission due to surface and ground water contamination in both developing and industrialized countries (6).

The US National Assessment on the Potential Consequences of Climate Variability and Change has declared this a priority for public health research in the United States (9). A study by Curriero et al (2001), supported by the US Environmental Protection Agency, found a significant association between waterborne disease outbreaks and extreme precipitation across the United States (9). Researchers found that over half of those outbreaks resulted in acute

gastrointestinal illness and approximately 60% of them were attributable to surface water (24%) and groundwater (36%) contamination (9). In developing countries, low rainfall and drought contribute to poor hygiene from a reduction in water supply, and increase malnutrition and disease susceptibility from a reduction in food supply or income; high rainfall allows for pervasive fecal contamination due to excess water runoff and water supply contamination. These conditions will surely increase in variability as climate change and global warming escalates, as will the incidence and associated outcomes of diarrheal disease.

Individual pathogenic agents have been recognized by recent studies from Lanata et al (2013) and Kotloff et al (2013) as the principal causes of diarrhea in low and middle income countries. Enterotoxigenic Escherichia coli (ETEC) and enteropathogenic *E. coli* (EPEC), Shigella spp., rotavirus, norovirus, and *Cryptosporidium* spp are highlighted as highly infective and transmissible, with a wide variety of environmental transmission routes (1, 10, 11). The Global Enteric Multicenter Study (GEMS), the largest study of childhood diarrheal diseases conducted in developing countries, was carried out in seven sites in Africa and Asia. They found *Crypotosporidium* spp., *E. coli* producing heat stable toxin, typical enterpathogenic *E. coli*, rotavirus, and *Shigella* to be the most pathogenic and urged for new and existing intervention methods and improvements (11). For the purposes of this study, we evaluated diarrheagenic *E. coli*, *Cryptosporidium,* and norovirus as marker pathogens of diarrhea caused by bacterial, protozoan, and viral pathogens.

E. coli

In the human intestinal tract, *E. coli* regularly exists without issue. However, pathogenic strains of the bacteria that cause diarrheagenic *E. coli* (DEC) have the potential to cause enteric infection, and in fact are the most common sources of childhood bacterial diarrheal disease in the world (11). Diarrheagenic *E. coli* clusters into six specific strains, namely, EPEC, Shiga toxin-producing *E. coli* (STEC) (also referred to as Verocytotoxin-producing *E. coli* (VTEC) or enterohemorrhagic *E. coli* (EHEC)), ETEC, enteroinvasive *E. coli* (EIEC), enteroaggregative *E. coli* (EAEC or EAggEC), and diffusely adherent *E. coli* (DEAC) (12). *E. coli* bacteria are primarily transmitted through the fecal-oral route from ingestion of or contact with contaminated food or water. Those living in developing countries are put at higher risk for infection due to an overall lack of sanitation and infrastructure. Freeman et al (2009) cites various studies that take note of seasonal peaks of *E. coli* during the summer months, and it is commonly taught that bacterial gastroenteritis generally occurs over the summer season (13, 14).

Cryptosporidium

Cryptosporidium is the causative parasite of cryptosporidiosis, which can cause diarrhea and is responsible for 60% of the world's parasitic waterborne disease outbreaks (11, 15). It is transmitted from person-to-person or through the fecal-oral route from ingestion of contaminated drinking water or recreational water. The microscopic nature of the parasite, in addition to its resistance to chlorine, makes conventional water treatment ineffective and thus environmental

control particularly difficult (16). The presentation of illness can be particularly lengthy and severe for immunocompromised individuals and thus is a common study population for research (17). Furthermore, intervention methods to control the spread of disease remain limited for this population, as well as for the malnourished, the elderly, and children, all of whom are extremely susceptible to infection.

Studies of cryptosporidiosis have found clear seasonal patterns. Temperate climates experience increases during the spring and fall, peaking with increases in temperature, while tropical regions see a rise in cases throughout the warm, rainy season, indicating precipitation as a strong indicator for increases in disease incidence (17, 18). However this is noted to vary by location even within the same geographic region (18)

Norovirus

Norovirus is one of the most important causative agents of enteric infections around the world, and is the most common source of gastroenteritis outbreaks, foodborne disease infections, and community-acquired diarrheal disease for all age groups in the United States (19). The virus is of the Caliciviridae family, and can be classified into five genogroups, GI, GII, GII, GIV, and GV, within approximately 40 genotypes (20). Only the GI, GII, and GII genogroups have been found to infect humans and a certain level of severity and infectivity has been associated with each (21). Noroviruses are estimated to account for over 90% of non-bacterial gastroenteritis epidemics (19). Their highly

infectious nature is a result of environmental resistance and a low dose response for infection (22).

In temperate climates, norovirus infection is most common in the winter months (October-April), though several studies have cited summer peaks as well (23-25). It is postulated that seasonal variations allow for a greater incidence of viral infections in the northern and southern hemisphere, but remain low to moderate in equatorial regions (20, 26). However, the increase in weather variations due to climate change may alter the seasonality patterns of norovirus and instead allow for them to thrive more commonly throughout the year, resulting in a higher incidence of disease and potentially harboring an environment for the emergence of new strains (20).

Research has demonstrated that seasonal patterns of infectious diseases can be substantially affected by climate change (27). This can be seen through a longer period of heightened disease transmission from a higher pathogen survival and reproduction rate, as well as in changing epidemic peaks associated with a pathogen's seasons (17, 27). Jagai et al (2009) calls for a more critical understanding of the environmental factors that affect seasonality of disease patterns as a strategy to understand, predict, and prepare for the lasting effects of climate change. Studies that explore this topic are limited, especially on a large geographic scale, and thus further epidemiological research is required to establish a more definitive causal link between the change in seasonal patterns and occurrence of enteric disease.

METHODS

Hypothesis

The directionality of the relationship between each pathogen (*E. coli*, *Cryptosporidium*, and norovirus) and the associated monthly mean temperature and rainfall estimates varies by pathogenic class – bacteria and protozoa having a positive relationship, and viruses a negative one.

Literature Search

Separate systematic reviews of the literature were carried out for each of the three pathogens to identify studies reporting incidence of diarrheal disease due to norovirus, diarrheagenic *E. coli*, and *Cryptosporidium*. Studies were identified through a U.S. National Library of Medicine PubMed search using Endnote X7 software (28). Search terms included the pathogen name ["*Escherichia coli*" and ("diarrhea" or "diarrheagenic"] or ["norovirus"] or ["cryptosporidiosis" or "*Cryptosporidium*"], and each of the following terms – ["ambient temperature"], ["climate"], ["rain"], ["relative humidity"], ["season"], and ["weather"]. *E. coli* was also searched in combination with the terms ["incidence"], ["surveillance"], and ["rainfall"].

The literature search in its entirety was conducted in two parts. Two independent researchers conducted the first literature search on May 16, 2013. Supplemental searches were completed in which reference lists from all included studies, as well as review articles, were scanned for identification of relevant papers. In addition, if a study reported monthly rates of cases without the total

number of cases per month, the author of the paper was contacted. For cryptosporidiosis specifically, authors were contacted for original data if monthly data was noted as collected but was not presented in the article. Additional data was provided by authors for two studies on *E. coli* (29, 30), one study on norovirus (31), and 11 studies on *Cryptosporidium*(32-42) . There were 17 included studies on *Cryptosporidium* that came from data extracted from a previous search, conducted by Jagai et al (17). Each of the 61 articles included in Jagai et al were reviewed in full, resulting in 17 eligible studies. The second literature search was conducted on November 14, 2016 by two different independent researchers. This search included studies from 2013 on. Supplemental searches were not conducted and authors were not contacted for the second literature search.

As detailed in the PRISMA diagram (Figure 1), records went through a four-step process. The first step was identification of relevant studies through the Endnote PubMed database with the pre-determined search terms, and through any supplemental searches of reference lists or review articles. Studies found through the literature search were passed through to the second step, in which studies were screened for duplicates and were excluded after a review of titles and abstracts using specific inclusion and exclusion criteria. The remaining studies were evaluated in step three, in which the full text was assessed for inclusion using similar criteria as in step two. The last part of the process separated the final list of included studies that would be used for the quantitative synthesis into three categories – seasonality, temperature, and rainfall.

When reviewing abstracts and titles for eligibility, studies had to have followed two general inclusion criteria and six general exclusion criteria. The inclusion criteria stated that the study (i) must have been conducted continuously for at least one year, and (ii) reported monthly data on the number of patients with diarrhea caused by the specific pathogen. The exclusion criteria did not allow for studies that (i) reported outbreak data, (ii) used travelers as study subjects, (iii) used only immunocompromised populations as study subjects, (iv) were laboratory based or used non-human subjects, (v) presented monthly percentages without the total number of cases for each month, or (vi) were cohort by design. In addition to the general inclusion and exclusion criteria detailed above, pathogen specific search criteria were carried out when initially reviewing titles and abstracts: *E. coli* and cryptosporidiosis studies that reported on less than 25 confirmed cases of diarrhea were excluded, *E. coli* studies that included ["traveler(s)"] and/or ["outbreak"] in the title were excluded, only norovirus studies that were conducted after 1997 – when modern PCR based diagnostics for norovirus began widespread use – were included, and cryptosporidiosis case control studies that reported the disease in asymptomatic controls were included. Furthermore, studies that detailed various pathotypes, genotypes, and species of *E. coli*, norovirus, and *Cryptosporidium*, respectively, were included and summed for a total case count.

Once the initial inclusion and exclusion criteria were applied, the remaining studies were reviewed in full and excluded for the other following reasons: (i) there was no data presented, (ii) there was no monthly data presented, (iii) the study used outbreak data, (iv) the data was redundant (i.e.,

multiple publications using the same data), (v) the study population was too specific to assess overall infection for that location, (vi) the study was unrelated to the specific pathogen, (vii) the required data could not be translated if presented in another language, (viii) necessary graphs were unclear, and (ix) only prevalence data was reported.

Outcome Data: Extraction and Conversion

Only monthly incidence (total number of new cases each month) data was utilized to avoid confounding results by changes in the monthly proportion of other pathogens to the total (14). This data was either directly taken from a study's published tables or was extracted from their graphs using Plot Digitizer software (43). Prior to 2014, study authors were contacted to request original data when published data was not presented at a high enough resolution for digital extraction, but was otherwise excluded if the graph was unclear or if the reported total case count was more than 10% different than the Plot Digitizer results.

Several studies reported outcome data in the form of weekly counts or monthly rates. To ensure comparability across studies, weekly cases were summed and converted to monthly data, monthly rates that were reported as a percentage of monthly total cases for that pathogen (and included a monthly denominator) were converted to monthly case counts, and monthly rates reported per a population number (e.g., per 100 or 1000 patients) were converted to monthly incidence counts using the total number of cases reported for the study. If a study reported disease burden (as monthly case counts) separately for

more than one location, then each location was treated as its own unique dataset for analysis purposes.

Independent Variables

Monthly temperature and precipitation were the primary variables of interest for an article's study period and location. Average monthly temperature data was taken from the Hadley Centre CRUTEM4 (version CRUTEM.4.5.0.0) dataset, or if unavailable, from the Global Historical Climatology Network-Monthly (GHCN-M) version 3 (v3.3.0.20170404) (44, 45). The Hadley Centre uses a more robust algorithm for choosing which weather stations to include in their dataset and thus was the preferred source for temperature data, when available. Monthly precipitation data was taken from GHCN-M version 2 (46). Adjusted precipitation data was used when available, otherwise the unadjusted precipitation data was used as reported.

All weather data came with associated station codes for cities, identifiable by name as well as latitude and longitude. If weather data was unavailable for the specific city that the study was conducted in, weather stations within 100 kilometers were used. If weather data was not available from a weather station within 100 kilometers, no weather data was collected for that study and it was excluded from the temperature and/or precipitation analysis. Only studies confined to one geographic location, defined by a single weather station, were included in the weather data analysis; studies that reported case data for large regions or from multiple cities were excluded from the temperature and precipitation analysis but were included in the seasonality analysis. In addition,

studies that reported aggregate monthly case count data in which cases were averaged across months for multiple years were also excluded for the weather data analysis but included in the seasonality analysis.

Each study location included in the quantitative synthesis was described in terms of other covariates. These included latitude, elevation, average monthly temperature, and average monthly precipitation or number of days of annual precipitation (using data from Weatherbase.com), in addition to country specific mortality strata, crude birth rate and population density as recorded by the World Health Organization and the United Nations (47-50). The norovirus dataset also included a variable indicative of a new strain year, i.e., dominated by a new pandemic strain of norovirus. Case data reported from July 2002-June 2003 or July 2006-June 2007 was classified as a pandemic month, while all other months were considered endemic (51).

Seasonality Analysis

Overall seasonality of diarrheagenic *E. coli*, norovirus, and *Cryptosporidium* were compared by plotting the combined pathogen-specific incidence by month (averaged over all study years) and stratified by geographic location. The geographic location was clustered by the northern hemisphere (>23°N), the southern hemisphere (>23°S), and the area bounded by the Tropic of Cancer on the north and the Tropic of Capricorn on the South, also known as the “tropics” (23°N-23°S). Across a study period, the proportion of cases that fell within each calendar month of the study was determined and averaged across all studies for each pathogen. This was done to normalize the case count for all

studies, since the denominator for the monthly proportion of cases differed per study. To visualize a non-pathogen specific year, the same process was carried out irrespective of which pathogen a study belonged to.

The peak month, defined as the highest amount of cases per study, and the season strength, measured by the "peak-to-mean" ratio, was also evaluated. The ratio of the peak to mean values was calculated as the average number of cases in the month with the most cases, divided by the average number of cases per month over the course of the entire study. This was completed for each pathogen, stratified by geographic location.

Statistical Modeling

The relationship between climatic variables and disease incidence for diarrheagenic *E. coli, Cryptosporidium,* and norovirus for each study location was examined using generalized log-linear Poisson regression models in the R Statistical Programming Language (52). For each study within a pathogen specific dataset, monthly case counts were modeled as a function of monthly average temperature (°C), and as a function of monthly average precipitation (cm). A Newey-West regression approach was used to account for serial correlation of monthly data points within studies, a common problem with time-series comparisons (53). A series of forest plots were created using the metan function in Stata (version 10.1) for each pathogen to visualize the variability among studies (54).

All studies for each pathogen specific dataset were pooled together to calculate an overall association between monthly cases and mean monthly

temperature and precipitation using a generalized estimating equation (GEE) model with a Poisson distribution and an autoregressive correlation structure, clustered by study (55). The R geeglm function in the geepack library was used to account for temporal gaps of one or two consecutive months in the weather predictor data through the waves argument (14). The waves argument "names a positive integer-valued variable that is used to identify the order and spacing of observations within groups in a GEE model. This argument is crucial when there are missing values and gaps in the data"(56).

All models included WHO mortality stratum as a binary variable (developed country versus developing country (high-mortality developing or low-mortality developing)) to control for the country's level of development, as well as a 1-month lag variable for both temperature and precipitation data. This lag variable was implemented to assess the effects of temperature or precipitation one month prior to incidence cases of disease. Temperature and precipitation levels were evaluated using a combined multivariate model as a result of several studies missing either temperature or precipitation data. The full model for each pathogen dataset thus included the following covariates: temperature and/or precipitation data, temperature and/or precipitation 1-month lag data, and the WHO mortality stratum binary variable.

Quasi-Akaike information criterion (QAIC) values were used for selecting a final GEE model using the Multi-Model Inference (MuMIn) R package (57). These information criterion scores balance explanatory power of the model with model complexity, and can account for different levels of overdispersion that would potentially occur from a high degree of variation in the outcome data,

specifically if a considerable amount of studies were missing temperature or precipitation data (58). The best model was selected based on the lowest QIC value. Model selection was evaluated using one full model, as well as four reduced models that allowed for different combinations of the four weather covariates while still including the mortality stratum variable in all models. Models with both temperature and temperature lag, or precipitation lag, were excluded from consideration.

RESULTS

Systematic Review

A total of 134 studies (*E. coli*=38, *Cryptosporidium*=47, norovirus=49) with 140 datasets (*E. coli*=39, *Cryptosporidium*=48, norovirus=53) were included in the final analyses (Table 1a-c and Figure 1). Included datasets had study locations in temperate (n=97) and tropical latitudes (n=43) with study periods ranging between 1973 and 2015. Each country was classified as low-mortality developing (LMD) (n=31), high-mortality developing (HMD) (n=42), or developed (n=64) per the WHO annual health report. Studies located in developing countries included 72% of *E. coli* studies, 51% of *Cryptosporidium* studies, and 42% of norovirus studies. Researchers targeted a range of ages within their study population, mostly enrolling either young children or indiscriminately enrolling patients of any age. Broadly classified, study settings included community or out-patient clinics, hospitals or emergency rooms, or data was used from laboratory reports or surveillance systems.

E. coli and norovirus were the only pathogens in which additional disease related information was collected for this study, specifically on pathotypes and new strain year, respectively. Of included *E. coli* studies, most were represented by ETEC, EPEC, and EAEC/EAggEC pathotypes. Among the included norovirus studies, 28 took place over a study period that was classified as a new strain year, based on specific pandemic months.

Seasonality

The distribution of all cases for each pathogen across a 12-month period was evaluated for all study years combined (Figure 2). The northern and southern hemisphere typically have anticipated seasonal patterns, while the tropics tend to have less variation, but do so according to the rainy and warm seasons throughout the year.

E. coli studies were found to have an average ratio of peak to mean values of 3.23 for the northern hemisphere, 3.94 for the southern hemisphere, and 2.73 for the tropics (Table 3). The temperate latitude seasonality plots demonstrate the typical pattern of *E. coli* incidence peaking in the summer months (Figure 2). In the northern hemisphere, 72% of studies peaked between June and August, while 67% of studies peaked between December and February in the southern hemisphere (Table 3).

Norovirus exhibited a typical trend of peaking in the winter and declining in the summer for the northern hemisphere, with a strong peak to mean ratio of 4.45 (Figure 2, Table 3). In the northern hemisphere, only 3% of studies saw June through August as the peak month for cases, while nearly half found cases to peak in December through February (Table 3). The southern hemisphere showed less of a typical seasonal pattern and had a lower peak to mean ratio of 3.46 (Table 3). This, however, could be attributed to the lack of studies in this geographic location, as only 6% of norovirus studies were conducted in the southern hemisphere (Table 2).

Cryptosporidium was found to have a strong season strength in the northern hemisphere with a peak to mean ratio of 6.48, followed by the tropics

with an average peak to mean level of 4.42 and the southern hemisphere at 3.42 (Table 3). Among studies conducted in the northern and southern hemispheres, 53% and 84%, respectively, saw cases peak in the spring (Mar-May for northern; September-November for southern) or fall (September-November for northern; Mar-May for southern) (Table 3). The peak month of cases was relatively evenly distributed across studies in the tropics.

Association with Climate Variables

The majority of studies showed a positive association between the incidence of disease and mean monthly temperature and precipitation (Figures 3-5). Temperature data was available for 21 studies of diarrheagenic *E. coli*; 15 of these studies (71%) showed a statistically significant, positive association with disease incidence and only three (14%) showed a negative association, all with a non-significant relationship. Approximately half of the 18 *E. coli* studies with available precipitation data showed a statistically significant, positive association with disease incidence, while only two (11%) showed a statistically significant, negative association.

Of 23 *Cryptosporidium* studies with available temperature data, 20 studies (87%) showed a positive association between the incidence of infection and temperature – 15 of them (75%) proving to be statistically significant – and 16 of 22 studies (73%) with precipitation data showed a positive association between incidence and rainfall, nine (41%) being statistically significant. A negative correlation existed between *Cryptosporidium* disease incidence and

three temperature studies (13%) and six precipitation studies (27%), with only one of each being statically significant.

Results of the analysis proved to be more varied for norovirus. A negative relationship with disease incidence was found to be more common among both temperature and precipitation studies. Of the 26 studies with available temperature data, 19 of them (73%) had a negative correlation with incidence of infection and all but one were found to be statistically significant. Regarding the association with precipitation, 16 of the 22 studies (73%) with rainfall data resulted in a negative correlation with disease incidence, seven (32%) being significant, and only one of six positively correlated studies was found significant. Although some precipitation results proved to be significant, most exhibited a weak association, evident by the small effect sizes.

Results from the GEE models are shown in Tables 4-5. The best fit model for all pathogens was chosen by the lowest quasi-information criterion (QIC) value outputted with a model that included the WHO mortality strata variable, and did not include both a weather variable (temperature or precipitation) and its associated 1-month lag time (Tables 4a-b). The final, best-fit model for *E. coli* included temperature and precipitation, with estimates of the incidence rate ratios (IRR) of 1.08 (95% CI: 1.05-1.11) and 1.00 (95% CI: 0.99-1.01), respectively. However the only model coefficient that was found to be significant at the $P<0.5$ level was temperature ($P<0.0001$). The best-fit model for *Cryptosporidium* included the 1-month lag temperature variable and precipitation, with estimates of the incidence rate ratios of 1.06 (95% CI: 1.02-1.10) and 1.01 (95% CI: 0.99-1.02), respectively. Results revealed that only the lag

temperature variable was found to be significant (P<0.0033). Similar to the final model of *E. coli*, the norovirus best-fit model included temperature and precipitation. The estimate of the IRR for temperature was 0.96 (95%CI: 0.92-1.00) and 0.99 (0.99-1.00) for precipitation. Norovirus slightly differed from the other two pathogen models by also requiring inclusion of the new strain year variable, in addition to the required WHO mortality strata variable. The incidence rate ratios that were found for each pathogen model represent the relative increase in disease for a 1° C increase in mean temperature or a 1 cm increase in mean rainfall across all studies included in the model.

DISCUSSION

The results presented in this analysis demonstrate a heterogeneous relationship of response to climatic variables amongst the three different pathogens assessed. A positive correlation with *E. coli* and *Cryptosporidium* and their associated weather variables was found evident, while a negative correlation was found between norovirus and its associated weather variables (Table 5). These results were expected based on the general understanding of the seasonal peaks and valleys associated with each pathogen – *E. coli* and *Cryptosporidium* cases typically peak during the summer months, and norovirus cases peak in the winter months, for temperate lateral regions. The quantification of these patterns is beneficial in creating a threshold for past and current seasonal patterns so changes can be assessed in future studies.

In the meta-analysis of each pathogen's pooled dataset across all studies, the best-fit model suggests that, on average, a 1°C increase in mean temperature is associated with an 8% (95% CI: 5%-11%) increase in the incidence of diarrheagenic *E. coli*, controlling for precipitation and country development status. For a 1°C increase in mean 1-month lagged temperature, a 6% (95% CI: 2%-10%) increase in the incidence of *Cryptosporidium* was found, controlling for precipitation and country development status. A 4% (95% CI: 0%-8%) decrease in the incidence of norovirus cases was found to be associated with a 1°C increase in average monthly temperature, controlling for precipitation, country development status, and new strain year. All three temperature-disease relationships were found to be statistically significant at the $P<0.05$ level when the described variables were controlled for. These findings suggest that if other

bacterial diseases are similar to *E. coli* and peak in warmer conditions, then bacteria could potentially represent a larger attributable fraction of diarrheal disease under future warmer climatic conditions.

Other epidemiological studies by comparison have found similar associations between all-cause diarrhea incidence and changes in average temperature. Analyses conducted in Japan (Onozuka et al, 2010), Bangladesh (Hashizume et al, 2007), Peru (Checkley et al, 2000), and Fiji (Singh et al, 2001) found an increase in diarrhea incidence of 3-11% for a 1°C increase in ambient temperature (59-63). Carlton et al further confirmed these regional results in a meta-analysis demonstrating a 7% increase in all-cause diarrhea for a 1°C increase in temperature, with significant heterogeneity across pathogenic class (14, 64). The research from this analysis and from other published studies demonstrate a linear relationship between temperature and diarrhea rates, however other research has shown a non-linear relationship that is dependent upon the locally prevalent pathogens and climatic conditions (63). Checkley et al found that a 5°C increase in temperature in Peru was associated with an increase of diarrhea-related hospital admissions by 77% during the winter months but only by 21% during the summer (61).

This analysis did not reveal a strong relationship between incidence of diarrheal disease and monthly mean precipitation for any pathogen. This could be due to more potential inherent error in the rainfall data than temperature data since rainfall tends to vary more across smaller distances. In addition, average monthly precipitation data may not capture the appropriate effects of rainfall because heavy rainfall during or following wet seasons or extreme precipitation

events are more likely to drive the incidence of diarrhea than average rainfall, based on previous research (14, 60, 63, 65-67). Furthermore, any non-linear effects would not have been captured by the models used in this analysis. Mellor et al recommends using a mechanistic, systems-based approach to address such complexities of modeling diarrheal disease and climate change (63).

A consequence of using the QIC model selection method in this analysis is that explanatory variables that are non-significant at the $P<0.05$ level are still included in the model, as was seen with all model coefficients, except temperature and lagged temperature. The confounding variables overall were restricted due to the ecological structure of the study, and thus data for other potentially significant variables was limited (14). A wide variety of factors can influence the rates of diarrheal disease besides country development status, including other environmental variables such as humidity, specific components related to pathogen growth and transmission, and factors influencing host susceptibility. Quantifying these variables would add complexity to the model and furthermore, not enough data describing such factors for incorporation exists. Additionally, this study did not account for co-infections and the dataset as a whole was limited since the majority of norovirus studies occurred in developed countries, while *E. coli* and *Cryptosporidium* studies mainly occurred in the developing world.

Future Directions

Further modeling should be carried out to predict the relative proportion of diarrheal disease attributable to each of these three pathogens under future

warming scenarios, according to the predictions of the models from this analysis. The data collected for this analysis would allow for modeling the change in pathogen cases for the expected temperature increase for any given region.

These data could also be used to help implement better-timed public health interventions for diarrheal disease. The demonstrated seasonal patterns can be applied to local areas to improve timing of targeted hygiene education campaigns, water treatment efforts, and vaccine distribution. This is important for both the developed and developing world, as studies have shown that the developed world is not impervious to diarrheal disease, particularly outbreaks.

Diarrheal diseases are often cited as one of the major types of negative health outcomes of climate change, but in reality, a large amount of uncertainty exists in the estimates associated with the relationship between climatic drivers and diarrheal disease. Kolstad et al carried out an analysis based on various emission scenarios estimating an increase in the incidence of diarrheal disease by up to 22%-29% by the year 2099, and concluded that a lack of exposure-disease relationship data, followed by non-linearities and potential threshold issues, contribute the greatest amount of uncertainty in predicting future conditions (68). Climate change threatens to undermine the substantial progress we have made in combatting diarrheal disease. Understanding the seasonality of diarrheal disease by gathering empirical data offers insight into the impact of weather on disease patterns, allowing us to anticipate the inevitable effects of climate change and properly prepare for the impact on infectious diseases around the world.

REFERENCES

1. Julian TR. Environmental transmission of diarrheal pathogens in low and middle income countries. *Environ Sci Process Impacts* 2016;18(8):944-55.
2. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388(10053):1459-544.
3. Levine MM, Kotloff KL, Nataro JP, et al. The Global Enteric Multicenter Study (GEMS): impetus, rationale, and genesis. *Clin Infect Dis* 2012;55 Suppl 4:S215-24.
4. Guerrant RL, DeBoer MD, Moore SR, et al. The impoverished gut--a triple burden of diarrhoea, stunting and chronic disease. *Nat Rev Gastroenterol Hepatol* 2013;10(4):220-9.
5. Guerrant RL, Oria RB, Moore SR, et al. Malnutrition as an enteric infectious disease with long-term effects on child development. *Nutr Rev* 2008;66(9):487-505.
6. IPCC. Climate Change 2014: Synthesis Report. Contribution of Working Groups I, II and III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change [Core Writing Team, R.K. Pachauri and L.A. Meyer (eds.)]. 2014:Intergovernmental Panel on Climate Change: Geneva, Switzerland, 151 pp.
7. IPCC, 2013. *Climate Change 2013: The Physical Science Basis Contribution of Working Group I to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change*:[Stocker, T.F., D. Qin, G.-K. Plattner, M. Tignor, S.K. Allen, J. Boschung, A. Nauels, Y. Xia, V. Bex and P.M. Midgley (eds.)]. Cambridge University Press, Cambridge, United Kingdom and New York, NY, USA, 1535 pp.

8. Levy K, Woster AP, Goldstein RS, et al. Untangling the Impacts of Climate Change on Waterborne Diseases: a Systematic Review of Relationships between Diarrheal Diseases and Temperature, Rainfall, Flooding, and Drought. *Environ Sci Technol* 2016;50(10):4905-22.

9. Curriero FC, Patz JA, Rose JB, et al. The association between extreme precipitation and waterborne disease outbreaks in the United States, 1948-1994. *Am J Public Health* 2001;91(8):1194-9.

10. Lanata CF, Fischer-Walker CL, Olascoaga AC, et al. Global causes of diarrheal disease mortality in children <5 years of age: a systematic review. *PLoS One* 2013;8(9):e72788.

11. Kotloff KL, Nataro JP, Blackwelder WC, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet* 2013;382(9888):209-22.

12. Centers for Disease Control and Prevention. *CDC Health Information for International Travel 2016*:New York: Oxford University Press; 2016.

13. Freeman JT, Anderson DJ, Sexton DJ. Seasonal peaks in Escherichia coli infections: possible explanations and implications. *Clin Microbiol Infect* 2009;15(10):951-3.

14. Philipsborn R, Ahmed SM, Brosi BJ, et al. Climatic Drivers of Diarrheagenic Escherichia coli Incidence: A Systematic Review and Meta-analysis. *J Infect Dis* 2016;214(1):6-15.

15. Baldursson S, Karanis P. Waterborne transmission of protozoan parasites: review of worldwide outbreaks - an update 2004-2010. *Water Res* 2011;45(20):6603-14.

16. Wolyniak EA, Hargreaves BR, Jellison KL. Seasonal retention and release of Cryptosporidium parvum oocysts by environmental biofilms in the laboratory. *Appl Environ Microbiol* 2010;76(4):1021-7.

17. Jagai JS, Castronovo DA, Monchak J, et al. Seasonality of cryptosporidiosis: A meta-analysis approach. *Environ Res* 2009;109(4):465-78.

18. Cacciò SMW, G. (ed.). Cryptosporidium: Parasite and Disease. 2014:Springer-Verlag, Wien.

19. Lopman B, Gastanaduy P, Park GW, et al. Environmental transmission of norovirus gastroenteritis. *Curr Opin Virol* 2012;2(1):96-102.

20. Rohayem J. Norovirus seasonality and the potential impact of climate change. *Clin Microbiol Infect* 2009;15(6):524-7.

21. Chan MC, Lee N, Hung TN, et al. Rapid emergence and predominance of a broadly recognizing and fast-evolving norovirus GII.17 variant in late 2014. *Nat Commun* 2015;6:10061.

22. Colas de la Noue A, Estienney M, Aho S, et al. Absolute Humidity Influences the Seasonal Persistence and Infectivity of Human Norovirus. *Appl Environ Microbiol* 2014;80(23):7196-205.

23. Lopman BA, Reacher M, Gallimore C, et al. A summertime peak of "winter vomiting disease": surveillance of noroviruses in England and Wales, 1995 to 2002. *BMC Public Health* 2003;3:13.

24. Lewis DC, Hale A, Jiang X, et al. Epidemiology of Mexico virus, a small round-structured virus in Yorkshire, United Kingdom, between January 1992 and March 1995. *J Infect Dis* 1997;175(4):951-4.

25. Wright PJ, Gunesekere IC, Doultree JC, et al. Small round-structured (Norwalk-like) viruses and classical human caliciviruses in southeastern Australia, 1980-1996. *J Med Virol* 1998;55(4):312-20.

26. Ahmed SM, Lopman BA, Levy K. A systematic review and meta-analysis of the global seasonality of norovirus. *PLoS One* 2013;8(10):e75922.

27. Harvell CD, Mitchell CE, Ward JR, et al. Climate warming and disease risks for terrestrial and marine biota. *Science* 2002;296(5576):2158-62.

28. NCBI Resource Coordinators (2017). Database Resources of the National Center for Biotechnology Information. *Nucleic Acids Research*;45(D1):D12-D7.

29. Klein EJ, Stapp JR, Clausen CR, et al. Shiga toxin-producing Escherichia coli in children with diarrhea: a prospective point-of-care study. *J Pediatr* 2002;141(2):172-7.

30. Samonis G, Maraki S, Christidou A, et al. Bacterial pathogens associated with diarrhoea on the island of Crete. *Eur J Epidemiol* 1997;13(7):831-6.

31. Hulth A, Andersson Y, Hedlund KO, et al. Eye-opening approach to norovirus surveillance. *Emerg Infect Dis* 2010;16(8):1319-21.

32. Ajjampur SS, Liakath FB, Kannan A, et al. Multisite study of cryptosporidiosis in children with diarrhea in India. *J Clin Microbiol* 2010;48(6):2075-81.

33. Bennett A, Epstein LD, Gilman RH, et al. Effects of the 1997-1998 El Nino episode on community rates of diarrhea. *Am J Public Health* 2012;102(7):e63-9.

34. Chai JY, Kim NY, Guk SM, et al. High prevalence and seasonality of cryptosporidiosis in a small rural village occupied predominantly by aged people in the Republic of Korea. *Am J Trop Med Hyg* 2001;65(5):518-22.

35. Huh JW, Moon SG, Lim YH. A survey of intestinal protozoan infections among gastroenteritis patients during a 3-year period (2004-2006) in Gyeonggi-do (province), South Korea. *Korean J Parasitol* 2009;47(3):303-5.

36. Lake IR, Pearce J, Savill M. The seasonality of human cryptosporidiosis in New Zealand. *Epidemiol Infect* 2008;136(10):1383-7.

37. Naumova EN, Chen JT, Griffiths JK, et al. Use of passive surveillance data to study temporal and spatial variation in the incidence of giardiasis and cryptosporidiosis. *Public Health Rep* 2000;115(5):436-47.

38. Perch M, Sodemann M, Jakobsen MS, et al. Seven years' experience with Cryptosporidium parvum in Guinea-Bissau, West Africa. *Ann Trop Paediatr* 2001;21(4):313-8.

39. Pintar KD, Pollari F, Waltner-Toews D, et al. A modified case-control study of cryptosporidiosis (using non-Cryptosporidium-infected enteric cases as controls) in a community setting. *Epidemiol Infect* 2009;137(12):1789-99.

40. Skeels MR, Sokolow R, Hubbard CV, et al. Cryptosporidium infection in Oregon public health clinic patients 1985-88: the value of statewide laboratory surveillance. *Am J Public Health* 1990;80(3):305-8.

41. Terletskaia-Ladwig E, Eggers M, Enders M, et al. [Epidemiological aspects of gastrointestinal infections]. *Dtsch Med Wochenschr* 2011;136(3):69-75.

42. Vrbova L, Johnson K, Whitfield Y, et al. A descriptive study of reportable gastrointestinal illnesses in Ontario, Canada, from 2007 to 2009. *BMC Public Health* 2012;12:970.

43. Huwaldt JA. Plot Digitizer. *In: SourceForgenet*;Boston: Free Software Foundation, 2011.

44. Jones PD, Lister DH, Osborn TJ, et al. Hemispheric and large-scale land-surface air temperature variations: An extensive revision and an update to 2010. *J Geophys Res-Atmos* 2012;117.

45. Lawrimore JH, Menne MJ, Gleason BE, et al. An overview of the Global Historical Climatology Network monthly mean temperature data set, version 3. *J Geophys Res-Atmos* 2011;116.

46. Peterson TC, Vose RS. An overview of the global historical climatology network temperature database. *B Am Meteorol Soc* 1997;78(12):2837-49.

47. Weatherbase. http://www.weatherbase.com.accessed/ March 2017.

48. WHO. The World Health Report 2003: shaping the future.WHO: Geneva, Switzerland.

49. United Nations. Department of Economic and Social Affairs, Population Division (2015). *World Population Prospects: The 2015 Revision - Special Aggregates, DVD Edition*;Crude Birth Rate.

50. United Nations. Department of Economic and Social Affairs, Population Division (2015). *World Population Prospects: The 2015 Revision, DVD Edition*;Population Density.

51. Lopman B, Vennema H, Kohli E, et al. Increase in viral gastroenteritis outbreaks in Europe and epidemic spread of new norovirus variant. *Lancet* 2004;363(9410):682-8.

52. R Core Team (2016). R: A language and environment for statistical computing. *R Foundation for Statistical Computing, Vienna, Austria*;https://www.r-project.org/.

53. Newey WK, West KD. A Simple, Positive Semidefinite, Heteroskedasticity and Autocorrelation Consistent Covariance-Matrix. *Econometrica* 1987;55(3):703-8.

54. StataCorp. Stata Statistical Software: Release 10. *College Station, TX: StataCorp LP* 2007.

55. Liang KY, Zeger SL. Longitudinal Data-Analysis Using Generalized Linear-Models. *Biometrika* 1986;73(1):13-22.

56. Weiss J. Curriculum in Ecology. *University of North Carolina, Chapel Hill* 2011.

57. Barton K. Package "MuMIn: Multi-model inference" for R, R Package Version 1.15.6. (http://cran.r-project.org/package=MuMIn). 2012.

58. Kim HJ, Cavanaugh JE, Dallas TA, et al. Model selection criteria for overdispersed data and their application to the characterization of a host-parasite relationship. *Environ Ecol Stat* 2014;21(2):329-50.

59. Onozuka D, Hashizume M, Hagihara A. Effects of weather variability on infectious gastroenteritis. *Epidemiol Infect* 2010;138(2):236-43.

60. Hashizume M, Wagatsuma Y, Faruque AS, et al. Factors determining vulnerability to diarrhoea during and after severe floods in Bangladesh. *J Water Health* 2008;6(3):323-32.

61. Checkley W, Epstein LD, Gilman RH, et al. Effect of El Nino and ambient temperature on hospital admissions for diarrhoeal diseases in Peruvian children. *Lancet* 2000;355(9202):442-50.

62. Singh RB, Hales S, de Wet N, et al. The influence of climate variation and change on diarrheal disease in the Pacific Islands. *Environ Health Perspect* 2001;109(2):155-9.

63. Mellor JE, Levy K, Zimmerman J, et al. Planning for climate change: The need for mechanistic systems-based approaches to study climate change impacts on diarrheal diseases. *Sci Total Environ* 2016;548-549:82-90.

64. Carlton EJ, Woster AP, DeWitt P, et al. A systematic review and meta-analysis of ambient temperature and diarrhoeal diseases. *Int J Epidemiol* 2016;45(1):117-30.

65. Auld H, MacIver D, Klaassen J. Heavy rainfall and waterborne disease outbreaks: the Walkerton example. *J Toxicol Environ Health A* 2004;67(20-22):1879-87.

66. Alexander KA, Carzolio M, Goodin D, et al. Climate change is likely to worsen the public health threat of diarrheal disease in Botswana. *Int J Environ Res Public Health* 2013;10(4):1202-30.

67. Carlton EJ, Eisenberg JN, Goldstick J, et al. Heavy rainfall events and diarrhea incidence: the role of social and environmental factors. *Am J Epidemiol* 2014;179(3):344-52.

68. Kolstad EW, Johansson KA. Uncertainties associated with quantifying climate change impacts on human health: a case study for diarrhea. *Environ Health Perspect* 2011;119(3):299-305.

69. Alam M, Akhtar YN, Ali SS, et al. Seasonal variation in bacterial pathogens isolated from stool samples in Karachi, Pakistan. *J Pak Med Assoc* 2003;53(3):125-9.

70. Baqui AH, Yunus MD, Zaman K, et al. Surveillance of patients attending a rural diarrhoea treatment centre in Bangladesh. *Trop Geogr Med* 1991;43(1-2):17-22.

71. Black RE, Brown KH, Becker S, et al. Contamination of weaning foods and transmission of enterotoxigenic Escherichia coli diarrhoea in children in rural Bangladesh. *Trans R Soc Trop Med Hyg* 1982;76(2):259-64.

72. Black RE, Brown KH, Becker S, et al. Longitudinal studies of infectious diseases and physical growth of children in rural Bangladesh. I. Patterns of morbidity. *Am J Epidemiol* 1982;115(3):305-14.

73. Buvens G, De Gheldre Y, Dediste A, et al. Incidence and virulence determinants of verocytotoxin-producing Escherichia coli infections in the Brussels-Capital Region, Belgium, in 2008-2010. *J Clin Microbiol* 2012;50(4):1336-45.

74. Cassel-Beraud AM, Morvan J, Coulanges P. [Evaluation of the prevalence of the main enteropathogenic agents in the West Imerina region: Manarintsoa]. *Arch Inst Pasteur Madagascar* 1990;57(1):255-64.

75. Cho SH, Kim JH, Kim JC, et al. Surveillance of bacterial pathogens associated with acute diarrheal disease in the Republic of Korea during one year, 2003. *J Microbiol* 2006;44(3):327-35.

76. Chowdhury F, Rahman MA, Begum YA, et al. Impact of rapid urbanization on the rates of infection by Vibrio cholerae O1 and enterotoxigenic Escherichia coli in Dhaka, Bangladesh. *PLoS Negl Trop Dis* 2011;5(4):e999.

77. Cisse MF, Ouangre RA, Gaye A, et al. Micro-organisms in Infantile Gastroenteritis at Dakar, Senegal. *La Presse Médicale* 1989;18:1827-30.

78. Cohen D, Shoham O, Orr N, et al. An inverse and independent association between Helicobacter pylori infection and the incidence of shigellosis and other diarrheal diseases. *Clin Infect Dis* 2012;54(4):e35-42.

79. Estrada-Garcia T, Lopez-Saucedo C, Thompson-Bonilla R, et al. Association of diarrheagenic Escherichia coli Pathotypes with infection and diarrhea among Mexican children and association of atypical Enteropathogenic E. coli with acute diarrhea. *J Clin Microbiol* 2009;47(1):93-8.

80. Gatti MSV, Ricci LC, Serafim MB, et al. Incidence of Enterotoxigenic Escerichia coli (ETEC), rotavirus and Clostridium perfringens from cases of diarrhea among children, in the region of Campinas, SP, Brazil. *Revista do Instituto de Medicina Tropical de São Paulo* 1989;31(6):392-8.

81. Gonzales L, Joffre E, Rivera R, et al. Prevalence, seasonality and severity of disease caused by pathogenic Escherichia coli in children with diarrhoea in Bolivia. *J Med Microbiol* 2013;62(Pt 11):1697-706.

82. Guerrant RL, Kirchhoff LV, Shields DS, et al. Prospective study of diarrheal illnesses in northeastern Brazil: patterns of disease, nutritional impact, etiologies, and risk factors. *J Infect Dis* 1983;148(6):986-97.

83. Gurwith MJ, Williams TW. Gastroenteritis in children: a two-year review in Manitoba. I. Etiology. *J Infect Dis* 1977;136(2):239-47.

84. Household KC, Mann MD, Bowie MD. Enteropathogens associated with acute infantile diarrhoea in Cape Town. *S Afr Med J* 1988;73(2):83-7.

85. Huang Z, Pan H, Zhang P, et al. Prevalence and Antimicrobial Resistance Patterns of Diarrheagenic Escherichia coli in Shanghai, China. *Pediatr Infect Dis J* 2016;35(8):835-9.

86. Huber HC, Kugler R, Liebl B. [Infections with enterohemorrhagic Escherichia coli (EHEC)--results of an epidemiologic survey in Bavaria for the April 1996 to May 1997 time frame]. *Gesundheitswesen* 1998;60(3):159-65.

87. Khan MU, Eeckels R, Alam AN, et al. Cholera, rotavirus and ETEC diarrhoea: some clinico-epidemiological features. *Trans R Soc Trop Med Hyg* 1988;82(3):485-8.

88. Kim KH, Suh IS, Kim JM, et al. Etiology of childhood diarrhea in Korea. *J Clin Microbiol* 1989;27(6):1192-6.

89. Kim NO, Jung SM, Na HY, et al. Enteric Bacteria Isolated from Diarrheal Patients in Korea in 2014. *Osong Public Health Res Perspect* 2015;6(4):233-40.

90. Mutanda LN. Epidemiology of acute gastroenteritis in early childhood in Kenya. 1. Incidence in hospitals. *J Trop Pediatr* 1980;26(5):172-6.

91. Onanuga A, Igbeneghu O, Lamikanra A. A study of the prevalence of diarrhoeagenic Escherichia coli in children from Gwagwalada, Federal Capital Territory, Nigeria. *Pan Afr Med J* 2014;17:146.

92. Ostroff SM, Kobayashi JM, Lewis JH. Infections with Escherichia coli O157:H7 in Washington State. The first year of statewide disease surveillance. *JAMA* 1989;262(3):355-9.

93. Qadri F, Das SK, Faruque AS, et al. Prevalence of toxin types and colonization factors in enterotoxigenic Escherichia coli isolated during a 2-year period from diarrheal patients in Bangladesh. *J Clin Microbiol* 2000;38(1):27-31.

94. Qadri F, Saha A, Ahmed T, et al. Disease burden due to enterotoxigenic Escherichia coli in the first 2 years of life in an urban community in Bangladesh. *Infect Immun* 2007;75(8):3961-8.

95. Qu M, Lv B, Zhang X, et al. Prevalence and antibiotic resistance of bacterial pathogens isolated from childhood diarrhea in Beijing, China (2010-2014). *Gut Pathog* 2016;8:31.

96. Rao MR, Abu-Elyazeed R, Savarino SJ, et al. High disease burden of diarrhea due to enterotoxigenic Escherichia coli among rural Egyptian infants and young children. *J Clin Microbiol* 2003;41(10):4862-4.

97. Robins-Browne RM. Seasonal and racial incidence of infantile gastroenteritis in South Africa. *Am J Epidemiol* 1984;119(3):350-5.

98. Samal SK, Khuntia HK, Nanda PK, et al. Incidence of bacterial enteropathogens among hospitalized diarrhea patients from Orissa, India. *Jpn J Infect Dis* 2008;61(5):350-5.

99. Santosham M, Sack RB, Reid R, et al. Diarrhoeal diseases in the White Mountain Apaches: epidemiologic studies. *J Diarrhoeal Dis Res* 1995;13(1):18-28.

100. Sinclair MI, Hellard ME, Wolfe R, et al. Pathogens causing community gastroenteritis in Australia. *J Gastroenterol Hepatol* 2005;20(11):1685-90.

101. Stoll BJ, Glass RI, Huq MI, et al. Surveillance of patients attending a diarrhoeal disease hospital in Bangladesh. *Br Med J (Clin Res Ed)* 1982;285(6349):1185-8.

102. Thomas A, Cheasty T, Frost JA, et al. Vero cytotoxin-producing Escherichia coli, particularly serogroup O157, associated with human infections in England and Wales: 1992-4. *Epidemiol Infect* 1996;117(1):1-10.

103. Wierzba TF, Abdel-Messih IA, Abu-Elyazeed R, et al. Clinic-based surveillance for bacterial- and rotavirus-associated diarrhea in Egyptian children. *Am J Trop Med Hyg* 2006;74(1):148-53.

104. Abal-Fabeiro JL, Maside X, Llovo J, et al. Aetiology and epidemiology of human cryptosporidiosis cases in Galicia (NW Spain), 2000-2008. *Epidemiol Infect* 2015;143(14):3022-35.

105. Assadamongkol K, Gracey M, Forbes D, et al. Cryptosporidium in 100 Australian children. *Southeast Asian J Trop Med Public Health* 1992;23(1):132-7.

106. Biggs BA, Megna R, Wickremesinghe S, et al. Human infection with Cryptosporidium spp.: results of a 24-month survey. *Med J Aust* 1987;147(4):175-7.

107. Chalmers RM, Elwin K, Thomas AL, et al. Long-term Cryptosporidium typing reveals the aetiology and species-specific epidemiology of human cryptosporidiosis in England and Wales, 2000 to 2003. *Euro Surveill* 2009;14(2).

108. Corbett-Feeney G. Cryptosporidium among children with acute diarrhoea in the west of Ireland. *J Infect* 1987;14(1):79-84.

109. Daoud AS, Zaki M, Pugh RN, et al. Cryptosporidium gastroenteritis in immunocompetent children from Kuwait. *Trop Geogr Med* 1990;42(2):113-8.

110. Das P, Roy SS, MitraDhar K, et al. Molecular characterization of Cryptosporidium spp. from children in Kolkata, India. *J Clin Microbiol* 2006;44(11):4246-9.

111. Duong TH, Kombila M, Dufillot D, et al. [Role of cryptosporidiosis in infants in Gabon. Results of two prospective studies]. *Bull Soc Pathol Exot* 1991;84(5 Pt 5):635-44.

112. Eibach D, Krumkamp R, Al-Emran HM, et al. Molecular characterization of Cryptosporidium spp. among children in rural Ghana. *PLoS Negl Trop Dis* 2015;9(3):e0003551.

113. El-Badry AA, Al-Antably AS, Hassan MA, et al. Molecular seasonal, age and gender distributions of Cryptosporidium in diarrhoeic Egyptians: distinct endemicity. *Eur J Clin Microbiol Infect Dis* 2015;34(12):2447-53.

114. Fripp PJ, Bothma MT, Crewe-Brown HH. Four years of cryptosporidiosis at GaRankuwa Hospital. *J Infect* 1991;23(1):93-100.

115. Garvey P, McKeown P. Epidemiology of human cryptosporidiosis in Ireland, 2004-2006: analysis of national notification data. *Euro Surveill* 2009;14(8).

116. Goh S, Reacher M, Casemore DP, et al. Sporadic cryptosporidiosis, North Cumbria, England, 1996-2000. *Emerg Infect Dis* 2004;10(6):1007-15.

117. Haider SS, Baqai R, Qureshi FM, et al. Blastocystis spp., Cryptosporidium spp., and Entamoeba histolytica exhibit similar symptomatic and epidemiological patterns in healthcare-seeking patients in Karachi. *Parasitol Res* 2012;111(3):1357-68.

118. Iqbal J, Hira PR, Al-Ali F, et al. Cryptosporidiosis in Kuwaiti children: seasonality and endemicity. *Clin Microbiol Infect* 2001;7(5):261-6.

119. Iyer RN, Rao J, Venkatalakshmi A, et al. Clinical and Microbiology Profile and Outcome of Diarrhea by Coccidian Parasites in Immunocompetent Children. *Pediatr Infect Dis J* 2015;34(9):937-9.

120. Katsumata T, Hosea D, Wasito EB, et al. Cryptosporidiosis in Indonesia: a hospital-based study and a community-based survey. *Am J Trop Med Hyg* 1998;59(4):628-32.

121. Laupland KB, Church DL. Population-based laboratory surveillance for Giardia sp. and Cryptosporidium sp. infections in a large Canadian health region. *BMC Infect Dis* 2005;5:72.

122. Learmonth JJ, Ionas G, Ebbett KA, et al. Genetic characterization and transmission cycles of Cryptosporidium species isolated from humans in New Zealand. *Appl Environ Microbiol* 2004;70(7):3973-8.

123. Mai Nguyen X. Cryptosporidial diarrhoea in children. *Infection* 1987;15(6):444-6.

124. Majowicz SE, Michel P, Aramini JJ, et al. Descriptive analysis of endemic cryptosporidiosis cases reported in Ontario, 1996-1997. *Can J Public Health* 2001;92(1):62-6.

125. Mann ED, Sekla LH, Nayar GP, et al. Infection with Cryptosporidium spp. in humans and cattle in Manitoba. *Can J Vet Res* 1986;50(2):174-8.

126. Miller NM, van den Ende J. Seasonal prevalence of Cryptosporidium associated diarrhoea in young children. *S Afr Med J* 1986;70(10):636-7.

127. Molbak K, Hojlyng N, Gottschau A, et al. Cryptosporidiosis in infancy and childhood mortality in Guinea Bissau, west Africa. *BMJ* 1993;307(6901):417-20.

128. Nacro B, Bonkoungou P, Nagalo K, et al. [Clinical profile of cryptosporidiosis in a pediatric hospital environment in Burkina Faso]. *Med Trop (Mars)* 1998;58(1):47-50.

129. Nel ED, Rabie H, Goodway J, et al. A retrospective study of cryptosporidial diarrhea in a region with high HIV prevalence. *J Trop Pediatr* 2011;57(4):289-92.

130. Network ACN. Laboratory-based surveillance for Cryptosporidium in France, 2006-2009. *Euro Surveill* 2010;15(33):19642.

131. Peng MM, Meshnick SR, Cunliffe NA, et al. Molecular epidemiology of cryptosporidiosis in children in Malawi. *J Eukaryot Microbiol* 2003;50 Suppl:557-9.

132. Shahid NS, Rahman AS, Sanyal SC. Cryptosporidium as a pathogen for diarrhoea in Bangladesh. *Trop Geogr Med* 1987;39(3):265-70.

133. Shepherd RC, Sinha GP, Reed CL, et al. Cryptosporidiosis in the West of Scotland. *Scott Med J* 1988;33(6):365-8.

134. Wolfson JS, Richter JM, Waldron MA, et al. Cryptosporidiosis in immunocompetent patients. *N Engl J Med* 1985;312(20):1278-82.

135. Anestad G, Vainio K, Hungnes O. Interference between outbreaks of epidemic viruses: additional Norwegian observations. *Scand J Infect Dis* 2009;41(5):381-2.

136. Arana A, Cilla G, Montes M, et al. Genotypes, recombinant forms, and variants of norovirus GII.4 in Gipuzkoa (Basque Country, Spain), 2009-2012. *PLoS One* 2014;9(6):e98875.

137. Beersma MF, Schutten M, Vennema H, et al. Norovirus in a Dutch tertiary care hospital (2002-2007): frequent nosocomial transmission and dominance of GIIb strains in young children. *J Hosp Infect* 2009;71(3):199-205.

138. Bicer S, Col D, Erdag GC, et al. A retrospective analysis of acute gastroenteritis agents in children admitted to a university hospital pediatric emergency unit. *Jundishapur J Microbiol* 2014;7(4):e9148.

139. Brown JR, Shah D, Breuer J. Viral gastrointestinal infections and norovirus genotypes in a paediatric UK hospital, 2014-2015. *J Clin Virol* 2016;84:1-6.

140. Chan-It W, Thongprachum A, Okitsu S, et al. Detection and genetic characterization of norovirus infections in children with acute gastroenteritis in Japan, 2007-2009. *Clin Lab* 2011;57(3-4):213-20.

141. Chhabra P, Dhongade RK, Kalrao VR, et al. Epidemiological, clinical, and molecular features of norovirus infections in western India. *J Med Virol* 2009;81(5):922-32.

142. Dai YC, Hu GF, Zhang XF, et al. Molecular epidemiology of norovirus gastroenteritis in children in Jiangmen, China, 2005-2007. *Arch Virol* 2011;156(9):1641-6.

143. Dey SK, Nguyen TA, Phan TG, et al. Molecular and epidemiological trend of norovirus associated gastroenteritis in Dhaka City, Bangladesh. *J Clin Virol* 2007;40(3):218-23.

144. Dey SK, Phan TG, Mizuguchi M, et al. Genetic diversity and emergence of norovirus GII/4-2006b in Japan during 2006-2007. *Clin Lab* 2011;57(3-4):193-9.

145. Dey SK, Phathammavong O, Okitsu S, et al. Seasonal pattern and genotype distribution of norovirus infection in Japan. *Pediatr Infect Dis J* 2010;29(5):e32-4.

146. Dove W, Cunliffe NA, Gondwe JS, et al. Detection and characterization of human caliciviruses in hospitalized children with acute gastroenteritis in Blantyre, Malawi. *J Med Virol* 2005;77(4):522-7.

147. Estevez A, Arvelo W, Hall AJ, et al. Prevalence and genetic diversity of norovirus among patients with acute diarrhea in Guatemala. *J Med Virol* 2013;85(7):1293-8.

148. Galeano ME, Martinez M, Amarilla AA, et al. Molecular epidemiology of norovirus strains in Paraguayan children during 2004-2005: description of a possible new GII.4 cluster. *J Clin Virol* 2013;58(2):378-84.

149. Georgiadis S, Pilger DA, Pereira F, et al. [Molecular evaluation of norovirus in patients with acute gastroenteritis]. *Rev Soc Bras Med Trop* 2010;43(3):277-80.

150. Hansman GS, Doan LT, Kguyen TA, et al. Detection of norovirus and sapovirus infection among children with gastroenteritis in Ho Chi Minh City, Vietnam. *Arch Virol* 2004;149(9):1673-88.

151. Iritani N, Seto Y, Kubo H, et al. Prevalence of Norwalk-like virus infections in cases of viral gastroenteritis among children in Osaka City, Japan. *J Clin Microbiol* 2003;41(4):1756-9.

152. Kim JK, Kim JW. Molecular epidemiologic trends of diarrhea-causing virus infection from clinical specimens in Cheonan, Korea, in 2010-2012. *J Clin Lab Anal* 2014;28(1):47-51.

153. Lee BE, Preiksaitis JK, Chui N, et al. Genetic relatedness of noroviruses identified in sporadic gastroenteritis in children and gastroenteritis outbreaks in northern Alberta. *J Med Virol* 2008;80(2):330-7.

154. Lindell AT, Grillner L, Svensson L, et al. Molecular epidemiology of norovirus infections in Stockholm, Sweden, during the years 2000 to 2003: association of the GGIIb genetic cluster with infection in children. *J Clin Microbiol* 2005;43(3):1086-92.

155. Marshall JA, Hellard ME, Sinclair MI, et al. Incidence and characteristics of endemic Norwalk-like virus-associated gastroenteritis. *J Med Virol* 2003;69(4):568-78.

156. Medici MC, Martinelli M, Arcangeletti MC, et al. Epidemiological aspects of human rotavirus infection in children hospitalized with acute gastroenteritis in an area of northern Italy. *Acta Biomed* 2004;75(2):100-6.

157. Nataraju SM, Pativada M, Chatterjee D, et al. Molecular epidemiology of norovirus infections in children and adults: sequence analysis of region C indicates genetic diversity of NVGII strains in Kolkata, India. *Epidemiol Infect* 2011;139(6):910-8.

158. Nguyen TA, Hoang L, Pham le D, et al. Norovirus and sapovirus infections among children with acute gastroenteritis in Ho Chi Minh City during 2005-2006. *J Trop Pediatr* 2008;54(2):102-13.

159. Nguyen TA, Yagyu F, Okame M, et al. Diversity of viruses associated with acute gastroenteritis in children hospitalized with diarrhea in Ho Chi Minh City, Vietnam. *J Med Virol* 2007;79(5):582-90.

160. Oldak E, Sulik A, Rozkiewicz D, et al. Norovirus infections in children under 5 years of age hospitalized due to the acute viral gastroenteritis in northeastern Poland. *Eur J Clin Microbiol Infect Dis* 2012;31(4):417-22.

161. Onishi N, Hosoya M, Matsumoto A, et al. Molecular epidemiology of norovirus gastroenteritis in Soma, Japan, 2001-2003. *Pediatr Int* 2008;50(1):65-9.

162. Pang XL, Preiksaitis JK, Lee BE. Enhanced enteric virus detection in sporadic gastroenteritis using a multi-target real-time PCR panel: a one-year study. *J Med Virol* 2014;86(9):1594-601.

163. Papaventsis DC, Dove W, Cunliffe NA, et al. Norovirus infection in children with acute gastroenteritis, Madagascar, 2004-2005. *Emerg Infect Dis* 2007;13(6):908-11.

164. Park DJ, Kim JS, Park JY, et al. [Epidemiological analysis of norovirus infection between March 2007 and February 2010]. *Korean J Lab Med* 2010;30(6):647-53.

165. Puustinen L, Blazevic V, Huhti L, et al. Norovirus genotypes in endemic acute gastroenteritis of infants and children in Finland between 1994 and 2007. *Epidemiol Infect* 2012;140(2):268-75.

166. Puustinen L, Blazevic V, Salminen M, et al. Noroviruses as a major cause of acute gastroenteritis in children in Finland, 2009-2010. *Scand J Infect Dis* 2011;43(10):804-8.

167. Rasanen S, Lappalainen S, Salminen M, et al. Noroviruses in children seen in a hospital for acute gastroenteritis in Finland. *Eur J Pediatr* 2011;170(11):1413-8.

168. Sa AC, Gomez MM, Lima IF, et al. Group a rotavirus and norovirus genotypes circulating in the northeastern Brazil in the post-monovalent vaccination era. *J Med Virol* 2015;87(9):1480-90.

169. Siqueira JA, Linhares Ada C, Goncalves Mdos S, et al. Group A rotavirus and norovirus display sharply distinct seasonal profiles in Belem, northern Brazil. *Mem Inst Oswaldo Cruz* 2013;108(5):661-4.

170. Sumi A, Kobayashi N, Ohtomo N. Proportion of sporadic gastroenteritis cases caused by rotavirus, norovirus, adenovirus and bacteria in Japan from January 2000 to December 2003. *Microbiol Immunol* 2005;49(8):745-56.

171. Thongprachum A, Khamrin P, Chan-It W, et al. Emergence of norovirus GII/4 2006a and 2006b variants in hospitalized children with acute gastroenteritis in Thailand. *Clin Lab* 2013;59(3-4):271-6.

172. Thongprachum A, Takanashi S, Kalesaran AF, et al. Four-year study of viruses that cause diarrhea in Japanese pediatric outpatients. *J Med Virol* 2015;87(7):1141-8.

173. Victoria M, Carvalho-Costa FA, Heinemann MB, et al. Prevalence and molecular epidemiology of noroviruses in hospitalized children with acute gastroenteritis in Rio de Janeiro, Brazil, 2004. *Pediatr Infect Dis J* 2007;26(7):602-6.

174. Wilhelm CM, Hanna SL, Welch CA, et al. Viral gastroenteritis in Charleston, West Virginia, in 2007: from birth to 99 years of age. *Infect Control Hosp Epidemiol* 2010;31(8):816-21.

175. Xue Y, Pan H, Hu J, et al. Epidemiology of norovirus infections among diarrhea outpatients in a diarrhea surveillance system in Shanghai, China: a cross-sectional study. *BMC Infect Dis* 2015;15:183.

176. Yoon JS, Lee SG, Hong SK, et al. Molecular epidemiology of norovirus infections in children with acute gastroenteritis in South Korea in November 2005 through November 2006. *J Clin Microbiol* 2008;46(4):1474-7.

177. Zhirakovskaia EV, Tikunov AY, Bodnev SA, et al. Molecular epidemiology of noroviruses associated with sporadic gastroenteritis in children in Novosibirsk, Russia, 2003-2012. *J Med Virol* 2015;87(5):740-53.

178. Zhuge XL, Cui DW, Wu YP, et al. [Detection and typing of caliciviruses from patients with acute diarrhea in Hangzhou area, 2009 - 2010]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2011;32(10):1022-5.

TABLES

Table 1a. Characteristics of Studies Included in the Systematic Review of Climatic Drivers of diarrheagenic *Escherichia coli* incidence [Reference List: (29, 30, 69-103)].

Reference	*E. coli* Pathotype(s)	Location	Latitude	Elevation, m	Yearly Rainfall, mm, Mean	Yearly Temperature, degrees Celcius, Mean	Study Period	Study Duration, mo.	*E. coli* Cases, no.	Subject Age/ Descriptor	Study Setting	Urban/Rural Setting	WHO Mortality Stratum	Temperature [a]	Rainfall [a]	Peak Season [b]
Ahmi et al	EPEC	Karachi, Pakistan	25°N	21	210	26	Jan 1997-Dec 2001	60	662	All	Hospital based (tertiary care facility)	Urban	HMD			summer
Bagal et al	ETEC	Matlab, Bangladesh	23°N[c]	10	2330	25	May 1983-Apr 1984	12	369	All	Diarrhea treatment center	Rural	HMD			hot, dry
Black et al	ETEC	Matlab, Bangladesh	23°N[c]	10	2330	25	Apr 1978-Mar 1979	12	180	<5 y	Community	Rural	HMD			hot
Black et al	ETEC	Matlab, Bangladesh	23°N[c]	10	2330	25	Feb 1977-Jan 1979	24	4184	All	Clinic based	Rural	HMD			hot, dry
Bowen et al	VTEC	Brussels, Belgium	51°N	57	820	10	Apr 20068-Oct 2010	31	226	All	Hospital based and Lab reports	NA	Developed	+ [a]	+	summer
Cassel-Beraud et al	EPEC, ETEC	Antananarivo, Madagascar	18°S[c]	1275	1360	18	Nov 1988-Oct 1989	12	133	<14 y	Hospital based	Urban	HMD	+ [a]	+ [a]	warm and rainy
Cho et al	EAEC, EHEC, ETEC, EIEC, EPEC	South Korea	37°N	86	1351 d	12	Jan 2003-Dec 2003	12	225	All	Clinic based	Urban and Rural	LMD			hot and wet summer months
Chowdury et al	ETEC	Dhaka, Bangladesh	23°N[c]	9	1970	26	Mar 20108-Feb 2011	24	1248	All	Hospital based	Urban	HMD			NA
Cisse et al	EPEC	Dakar, Senegal	14°N[c]	84	412	24	Feb 1982-May 1988	75	92	<15 y	Hospital based	Urban	HMD			cool, dry
Cohen et al	EAEC	Cincinnati (OH), United States	39°N	195	987	13.6	Mar 1999-Feb 2000	12	88	Children	Hospital based	Urban	Developed	—	—	NA
Estrada-Garcia et al	EPEC, ETEC	Mexico City, Mexico	19°N[c]	2239	682	15	Jan 1998-Dec 1998	12	25	<3 y	Community	Peri-urban	LMD	+	+	rainy
Gatti et al	ETEC	Campinas, Brazil	23°S[c]	660	130 d	22	Oct 1982-Sep 1986	12	87	<2 y	Community	Urban	LMD	+ [a]	+ [a]	NA
Gonzales et al	ETEC, EPEC, EAEC	Cochabamba and La Paz, Bolivia	17°S[c]	4022	580	7	Jan 20078-Dec 2010	48	299	<60 mo	Hospital based	NA	HMD			cold, dry season
Guerrant et al	ETEC	Pacatuba, Brazil	4°S[c]	24	1460	27	May 1978-Oct 1980	30	33	<5 y	Community	Poor Urban and Rural	LMD	+ [a]	+	warm and rainy
Gurwith and Williams	EPEC	Winnipeg, Canada	50°N	238	510	2	Dec 1973-Nov 1975	25	120	<16 y	Hospital based	Urban	Developed			summer, fall
Heusebure et al	EPEC	Cape Town, South Africa	34°S	42	112 d	17	Apr 1981-Mar 1982	12	479	<1 y	Hospital based	Urban	HMD	+ [a]	— [a]	warm, dry
Huang et al	EPEC, ETEC, STEC, EIEC	Shaghai, China	31°N	7	1140	16	Jan 2012-Oct 2013	17	736	All	Hospital based	NA	LMD	+ [a]	+ [a]	July-Sept
Huber et al	EHEC	Bavaria, Germany	48°N	518	920	8	April 1996-May 1997	12	300	All	Case reports	NA	Developed			NA
Khan et al	ETEC	Dhaka, Bangladesh	23°N[c]	9	1970	26	Jan 1983-Dec 1984	24	472	All	Hospital based	Urban	HMD			spring, autumn
Kim et al	ETEC	Seoul, South Korea	37°N	86	1351 d	12	Feb 1984-Mar 1985	14	52	<15 y	Hospital based and Outpatient	Urban	LMD	—	—	cool, dry
Kim et al	EHEC, ETEC, EAEC, EPEC, EIEC	South Korea	37°N	70	1040	12	Jan 2014-Dec 2014	12	777	all	Lab reports	Urban and Rural	LMD			May, peak at June/July

Klein et al	STEC	Seattle (WA), United States	47°N	37	860	11	Nov 1998-Oct 2001	36	39	children	Hospital based and Private practice	Urban	Developed			summer, fall
Mutanda et al	EPEC	Nairobi, Kenya	1°S[d]	1623	750	19	May 1975-Apr 1976	12	28	children	Hospital based	Urban	HMD	—	—	NA
Onanuga et al	ETEC, EPEC, STEC, EAEC	Gwagwalada, Nigeria	9°N[d]	360	1156	23	April 2008-March 2009	12	61	0-24 mo	Hospital based	Urban	HMD	+	NA	dry season
Ostroff et al	O157:H7	Washington, United States	47°N	37	860	11	Jan 1987-Dec 1987	12	93	all	Case reports	Urban and Rural	Developed			June-Sept
Pai et al	VTEC	Calgary, Canada	51°N	1083	420	4.1	Jul 1984-Jun 1986	24	166	All	Hospital based	Urban	Developed	+*	+*	summer
Qadri et al (2000)	ETEC	Dhaka, Bangladesh	23°N[d]	9	1970	26	Apr 2002-Oct 2004	30	242	<2 y	Community	Urban	HMD			spring
Qadri et al (2007)	ETEC	Dhaka, Bangladesh	23°N[d]	9	1970	26	Sep 1996-Aug 1998	24	662	All	Hospital based	Urban	HMD	+*	+*	hot
Qu et al	EPEC, EAEC, ETEC, EIEC, STEC	Bejing, China	40°N	54	650	12	Apr 2010-Dec 2014	57	118	0-5 y	Outpatient	NA	LMD	+*	+*	summer (Jun-Aug)
Rao et al	ETEC	Abu Homos, Egypt	31°N	5	44 d	20	Mar 1995-Feb 1998	36	933	<3 y	Community	Rural	LMD	+*	NA	warm
Robins-Browne et al	EPEC	Johannesburg, South Africa	26°S	1699	720	16	Oct 1974-Sep 1975	12	55	<2 y	Hospital based	Urban	HMD	+*	+*	hot
Samal et al	EPEC, ETEC, EAggEC	Bhubaneswar, India	20°N[d]	44	1554	27	Jan 2004-Dec 2006	36	669	all	Hospital based	Urban	HMD			NA
Samonis et al	EPEC	Heraklion, Greece	35°N	39	483	18.7	Jan 1992-Apr 1994	28	139	<2 y	Hospital based	30% Urban; 60% Rural	Developed			NA
Santosham et al	ETEC	Whiteriver (AZ), United States	33°N	1588	458 d	12.7	Jan 1982-Dec 1984	36	28	<3 y	Community	Rural	Developed	+*	—	warm
Sinclair et al	EAggEC, EPEC, ETEC, EHEC	Melbourne, Australia	37°S	131	560	14	Sep 1997-Feb 1999	18	53	All	Community	Urban	Developed	+*	—*	NA
Stoll et al	ETEC	Dhaka, Bangladesh	23°N[d]	9	1970	26	Dec 1979-Nov 1980	12	624	All	Hospital based	Urban	HMD	+*	+*	hot, dry
Thomas et al	VTEC	United Kingdom	51°N	61	750	10.3	Jan 1989-Dec 1991	36	1275	All	Lab reports	NA	Developed			summer months
Wierzba et al	ETEC	Abu Homos, Egypt	31°N	5	44 d	20	May 2000-May 2002	25	148	<5 y	Clinic based	Rural	LMD	+*	NA	warm
Wierzba et al	ETEC	Benha, Egypt	31°N	15	20	21	May 2000-May 2002	25	111	<5 y	Clinic based	Peri-urban	LMD	+	—	warm

Abbreviations: EHEC, enterohemorrhagic E. coli; EPEC, enteropathogenic E. coli; ETEC, enterotoxigenic E. coli; EAEC/EAggEC, enteroaggregative E. coli; STEC, shiga-like toxin producing E. coli; VTEC, verotoxin-producing E. coli.
HMD, high-mortality developing country; LMD, low-mortality developing country; NA, not available.

[a] Data denote the sign of the coefficient from generalized linear models performed to determine the relationship between monthly incidence of Norovirus and monthly temperature or monthly rainfall in studies for which these data were available.

[b] Data denote the peak season of cases and reflect the authors' terminology.

[c] Statistically significant (P<.05).

[d] Tropical latitude.

Table 1b. Characteristics of Studies Included in the Systematic Review of Climatic Drivers of *Cryptosporidium* incidence [Reference List: (32-42, 104-134)].

Reference	Location	Latitude	Elevation, m	Yearly Rainfall, mm, Mean	Yearly Temperature, degrees Celcius, Mean	Study Period	Study Duration, mo.	Crypto Cases, no.	Subject Age/ Descriptor	Study Setting	Urban/Rural Setting	WHO Mortality Stratum	Temperature[b]	Rainfall[b]	Peak Season[c]
Abal-Fabeiro et al	Santiago de Compostela (Galicia), Spain	43°N	370	1886	12.6	Jan 2000-Dec 2008	108	822	All	Primary care and Hospital based	Urban and Rural	Developed	+*	+*	summer and autumn
Ajampur et al	Delhi, India	28°N	215	700	25.2	Dec 2005-Dec 2008	37	34	<5 y	Hospital based	NA	HMD	+*	+	NA
Ajampur et al	Trichy, India	11°N[a]	78	886.4	26.9	Dec 2005-Dec 2008	37	16	<5 y	Hospital based	NA	HMD			NA
Ajampur et al	Vellore, India	13°N[a]	252	945	26.3	Dec 2005-Dec 2008	37	20	<5 y	Hospital based	NA	HMD			NA
The ANOFEL Cryptosporidium National Network	France	48°N	96	637.4	12.4	Jan 2006-Dec 2009	48	407	All	Country level surveillance	Urban and Rural	Developed			mid/late summer-autumn
Ansdnrenghel et al	Perth, Australia	32°S	20	800	18	Jan 1986-Dec 1988	35	100	<5 y	Hospital based	NA	Developed	+*	—	summer and wet season
Bennett et al	Lima, Peru	12°S[a]	13	82.1	20	Jan 1995-Aug 1998	39	133	<12 y	Community based	Peri-urban	HMD	+*	NA	spring trimester (Oct-Dec)
Bops et al	Melbourne, Australia	38°S	33	680	14	Nov 1984-Oct 1986	24	55	All	Community based	NA	Developed	+	—	warm, dry months
Chai et al	Hwaseong-gun, South Korea	36°N	74	1477	12	Nov 1996-Oct 1997	12	77	All	Community based	Rural	LMD			spring and autumn
Chalmers et al	United Kingdom	52°N	61	750	10.3	Jan 2000-Dec 2026	84	12,008	All	Country level surveillance	Urban and Rural	Developed			autumn
Corbett-Feeney et al	Ireland	53°N	85	798	9.8	Feb 1983-Feb 1984	12	41	<12 y	Lab based study	Rural	Developed			April and May
Daood et al	Kuwait City, Kuwait	29°N	54	46.6	26	Jan 1988-Jan 1989	18	35	<6 y	Hospital based	Urban	LMD	—	+	March and April
Das et al	Kolkata, India	22°N[a]	12	1586.7	26.7	Jan 2003-Dec 2004	24	40	<5 y	Hospital based	Urban slums	HMD	+*	+*	rainy season and summer
Duong et al	Libreville, Gabon	0.23°N[a]	14	2150	26	Oct 1989-Sep 1990	12	70	<2 y	Community based	Urban and Suburban	HMD	NA	+*	wet season
Efstath et al	Ayago, Ghana	7°N[a]	393	1410.7	25.8	May 2007-Sep 2008	17	116	<14 y	Hospital based	Rural	HMD	NA	—	Apr-Jul
El-Badry et al	Cairo, Egypt	30°N				Jan 2013-Dec 2013	12	168	All	Hospital based	Urban and Peri-urban	LMD			summer and spring
Fripp et al	Pretoria, South Africa	25°S	1399	700	18	Oct 1985-Sep 1989	48	389	All	Hospital based	NA	HMD	+*	+*	monsoon season (June-Sep)
Garvey et al	Ireland	53°N	85	798	9.8	Jan 2004-Dec 2026	36	5569	All	Country level surveillance	rural	Developed			spring and autumn
Goh et al	Allerdale and Copeland (North Cumbria), England	54°N	81	1521	9.4	Mar 1996-Feb 2000	48	132	All	Community based	NA	Developed	+*	—*	spring and autumn
Haider et al	Karachi, Pakistan	25°N	21	210	26	Jan 2007-Dec 2007	12	37	All	Lab based	Urban and Rural	HMD	+*	+*	rainy summer months
Health Protection Scotland	Scotland	56°N	7	901.7	9.6	Jan 2006-Dec 2010	60	378	All	Country level surveillance	NA	Developed			NA

Hah et al	Gyeonggi-do Province, South Korea	37°N	71	111	12	Jan 2004-Dec 2006	36	29	All	Hospital based	NA	Developed			summer and autumn
Iqbal et al	Kuwait City, Kuwait	29°N	54	46 d	26	Sep 1995-Aug 1997	24	51	3 mo - 13 y	Hospital based	Urban and Semi-urban	LMD	— *	+*	Jan-April
Iyer et al	Hyderabad, India	17°N[d]	544	790	26.4	Jan 2009-Dec 2012	48	56	<15 y	Hospital based	NA	HMD			August and September (monsoon season)
Katsumata et al	Surabaya, Indonesia	7°S[d]	3	1470	28	Aug 1992-Jul 1993	12	41	<5 y	Hospital and Community based	NA	LMD	—	NA	March (rainy season)
Lake (ESR data substituted)	New Zealand	37°S	6	1150	15.5	Jan 1996-Dec 2012	187	13310	All	Country level surveillance	Urban	Developed			spring and autumn
Laupland et al	Calgary Health Region, Canada	51°N	1083	418.8	4.4	May 1999-Apr 2002	36	173	All	Lab based	Urban and Rural	Developed			late summer to early fall
Learmonth et al	New Zealand	41°N	128	1220	12.9	Aug 2000-Aug 2003	91	6856	All	Lab based	Urban and Rural	Developed			spring and autumn
Mai Nguyen et al	Bern, Switzerland	47°N	509	1028	7.9	Jan 1986-Dec 1986	12	31	All	Hospital based	NA	Developed	+*	NA	August and September
Majowicz et al	Ontario, Canada	43°N	172	852.9	7.7	Jan 1996-Dec 1997	24	451	All	Province level surveillance	Urban and Rural	Developed			August
Mann et al	Winnipeg (Manitoba), Canada	50°N	238	510	2	Oct 1983-Oct 1984	13	39	All	Lab based	Urban and Rural	Developed	+*	+	late summer to early fall
Miller et al	Durban, South Africa	30°N	7	1050	21	Aug 1985-Jul 1986	12	29	<2 y	Hospital based	NA	Developed	+	+	summer to early autumn
Molbak et al	Bissau, Guinea Bissau	12°N[d]	35	53 d	27	Apr 1987-Mar 1990	36	239	<4 y	Community based	Semi-urban	HMD	+*	+*	rainy season
Nacro et al	Bobo Dioulasso, Burkina Faso	11°N[d]	459	1088	27	Jan 1995-Dec 1995	12	72	<3 y	Hospital based	NA	HMD	+*	+*	beginning of the rainy season
Naumova et al	Boston (MA), United States	42°N	1	1071	10.7	Jan 1993-Dec 2002	120	102	All	State level surveillance	Urban	HMD	+*	+	summer to early fall
Naumova et al	Lowell (MA), United States	42°N	33	1101	9.4	Jan 1993-Dec 2002	120	18	All	State level surveillance	Urban	HMD			summer to early fall
Naumova et al	Worchester (MA), United States	42°N	299	1061	8.9	Jan 1993-Dec 2002	120	58	All	State level surveillance	Urban	HMD	+*	+	summer to early fall
Nel et al	Cape Town, South Africa	34°N	42	580	17	Jan 2004-May 2005	12	63	<18 y	Hospital based	NA	HMD	+	—	warm months; lowest rainfall
Peng et al	Blantyre, Malawi	15°S[d]	777	880	22	Aug 1997-Mar 1999	20	69	<2.5 y	Hospital based	NA	HMD	+	—	rainy season (Oct-Mar)
Perch et al	Bissau, Guinea Bissau	12°N[d]	35	53 d	27	Jan 1991-Dec 1997	84	351	<5 y	Community based	Peri-urban	HMD	+*	+*	beginning of or just before the rainy seasons (May-Jul)
Pintar et al	Waterloo region (Ontario), Canada	43°N	328	940	161.6 d	Apr 2005-Dec 2007	30	36	All	Region level surveillance	Urban and Rural	Developed			autumn
Shahid et al	Dhaka, Bangladesh	24°N	9	2148	26.1	Jan 1984-Dec 1984	12	71	All	Hospital Based	NA	HMD	+*	+*	hot, humid weather (Apr-Jul)
Shepherd et al	Paisley, Scotland	56°N	8	1165	7.8	Jan 1986-Dec 1987	24	83	All	Lab based	NA	Developed			spring and autumn
Shouls et al	Oregon, United States	45°N	6	914.4	12.5	Jan 1985-Dec 19888	42	32	All	Lab based	NA	Developed			summer and early autumn
Terletskaia et al (RKI data substituted)	Germany	52°N	47	586	9	Jan 2001-Dec 2006	72	9044	All	Country level surveillance	NA	Developed			late summer to early autumn
Vrbova et al	Ontario, Canada	43°N	172	852.9	7.7	Jan 2007-Dec 2012	60	473	All	Province level surveillance	NA	Developed			summer months
Wolffson et al	Boston (MA), United States	42°N	1	6.4	10.7	Feb 1983-Jan 1984	12	43	All	Lab based	Urban	Developed	+	+	summer and fall

Abbreviations: HMD, high-mortality developing country; LMD, low-mortality developing country; NA, not available.

[a] Data denote the sign of the coefficient from generalized linear models performed to determine the relationship between monthly incidence of Norovirus and monthly temperature or monthly rainfall in studies for which these data were available.

[b] Data denote the peak season of cases and reflect the authors' terminology.

[c] Statistically significant ($P<.05$).

[d] Tropical latitude.

Table 1c. Characteristics of Studies Included in the Systematic Review of Climatic Drivers of norovirus incidence [Reference List: (31, 41, 51, 135-178)].

Reference	New Strain Year, Y/N [a]	Location	Latitude	Elevation, m	Yearly Rainfall, mm, Mean	Yearly Temperature, degrees Celcius, Mean	Study Period	Study Duration, mo.	Norovirus Cases, No.	Subject Age/ Descriptor	Study Setting	Urban/Rural Setting	WHO Mortality Stratum	Temperature [b]	Rainfall [b]	Peak Season [c]
Ansstad et al	Y	Norway	59°N	17	760	6	Jan 2001-June 2008	90	5274	NA	Lab reports	NA	Developed			winter
Arana et al	N	Gipuzkoa (Basque Country), Spain	43°N	7	1565	13.2	Jan 2009-Dec 2012	48	592	<15 y	Hospital and Clinic based	Urban	Developed	—[e]	+[e]	cold months (fall-winter)
Bonsma et al	Y	Rotterdam, Netherlands	51°N	3	802	10	Jul 2002-Jan 2007	66	221	All	Hospital based and Outpatient	NA	Developed	—[e]	+	NA
Bicer et al	N	Istanbul, Turkey	41°N	36	640	14	Jan 2009-Dec 2009	12	51	Children	Hospital based	Urban	Developed	+	—	winter-spring period
Brown et al	N	London, United Kingdom	51°N	61	750	10.3	Jul 2014-Jan 2015	12	144	0-18 y	Hospital based	Urban	Developed			NA
Chan-It et al	N	Tokyo, Sapporo, Saga, Osaka, and Mainuru, Japan	35°N	7	1520	15	Jul 2007-Jan 2009	24	254	2 mo-15 y	Pediatric clinics	NA	Developed			winter months
Chhabra, et al	Y	Pune, Nagpur, Aurangabad, India	18°N[d]	559	704	24	Jul 2005-Jan 2007	24	89	≤7 y	Hospital based and Outpatient	NA	HMD			summer months
Dai et al	Y	Jiangsu, China	22°N[d]	14	1797.1	22.3	Sep 2005-Aug 2007	24	113	<5 y	Outpatient	NA	LMD	—[e]	—[e]	autumn/winter seasons
Dey et al (2007)	N	Dhaka, Bangladesh	23°N[d]	9	2148	26.1	Oct 2004-Sep 2005	12	41	infants and children	NA	NA	HMD			late autumn/winter seasons
Dey et al (2010)	Y	Sapporo, Tokyo, Mainuru, Osaka, Saga, Kagawa, and	35°N	7	1520	15	Jul 1995-Jun 2007	144	779	<15 y	NA	Urban and Rural	Developed			winter season
Dey et al (2011)	Y	Mainuru, Tokyo, Sapporo, Saga, and Osaka, Japan	35°N	7	1520	15	Jul 2006-Jun 2007	12	99	<14 y	NA	NA	Developed			winter seasons
Dove et al	N	Blantyre, Malawi	15°S[d]	777	880	22	Jul 1998-Jun 1999	12	26	1-54 mo	Hospital based	Urban	HMD	+	+	rainy season (March)
Esteves et al	N	Santa Rosa, Guatemala	14°N[d]	1498	1218	19	Oct 2007-Aug 2010	35	341	All	Hospital based and Ambulatory clinics	35% Urban, 65% Rural	HMD			winter months, following rainy season
Galante et al	N	Asunción, Paraguay	25°S	100	1370	23	Jan 2004-Dec 2005	24	161	≤5 y	Hospital based	Urban	LMD	+	+	no seasonal pattern
Georgiadis et al	Y	Porto Alegre, Brazil	30°S	3	123 d	19.5	Oct 2006-Oct 2007	13	48	NA	Lab reports	NA	LMD	+	—	southern hemisphere spring
Hansman et al	N	Ho Chi Minh City, Vietnam	11°N[d]	18	1930	28	Dec 1999-Nov 2000	12	72	1 mo-15 y	Hospital based	Urban	LMD			end of rainy season, first half of dry season
Hjelt et al	Y	Sweden	59°N	60	539	6	Jul 2005-Dec 2010	54	22895	NA	Lab reports	NA	Developed			NA
Iritani et al	N	Osaka City, Japan	34°N	14	1340	16	Apr 1996-Mar 2000	48	185	<12 y	Pediatric clinics	NA	Developed	—[e]	—[e]	late autumn-winter
Kim et al	N	Cheonan, South Korea	36°N	25	1193	11	Jul 2010-Oct 2012	28	136	<10 y	Hospital based	Urban	LMD			winter and early spring
Lee et al	Y	Alberta, Canada	51°N	1083	418.8	4.4	Jan 2003-Apr 2004	16	141	<7 y	Lab reports	Urban	Developed	—[e]	NA	Nov-Mar
Lindell et al	Y	Stockholm, Sweden	59°N	60	539	6	Aug 2000-Jun 2003	35	859	All	Hospital based and Lab reports	Urban	Developed	—[e]	—[e]	Jan-Mar
Lopman et al	Y	Denmark	55°N	4	640	8	Jan 1995-Dec 2002	84	1896	NA	Lab reports	NA	Developed			NA
Lopman et al	Y	Finland	60°N	56	630	5	Jan 1995-Dec 2002	84	1629	NA	Lab reports	NA	Developed			spring
Lopman et al	Y	Slovenia	46°N	361	620	8	Jan 1995-Dec 2002	84	888	NA	Lab reports	NA	Developed			NA
Lopman et al	Y	Sweden	59°N	60	539	6	Jan 1995-Dec 2002	84	3213	NA	Lab reports	NA	Developed			NA

Marshall et al	N	Melbourne, Australia	37°S	131	560	14	Sep 1997-Feb 1999	18	73	All	Community	Urban	Developed	+*	+	late spring/early summer
Medici et al	Y	Parma, Italy	44°N	57	781	11	Jan 2000-Dec 2002	36	62	Children	Hospital based	Urban	Developed	— *	NA	Sep-Jan (Nov peak)
Nataraju et al	N	Kolkata, India	22°N[d]	12	1585.7	26.7	Nov 2007-Oct 2009	24	78	All	Hospital based	Urban and Rural	HMD	+*	—	NA
Nguyen et al (2007)	Y	Ho Chi Minh, Vietnam	11°N[d]	18	1950	28	Oct 2002-Sep 2003	12	56	37 d-9 y	Hospital based	Urban and Rural	LMD			rainy season (May-Oct)
Nguyen et al (2008)	Y	Ho Chi Minh, Vietnam	11°N[d]	18	1950	28	Dec 2005-Nov 2006	12	32	children	Hospital based and Outpatient	Urban and Rural	LMD			rainy season (May-Oct)
Oldak et al	N	Bialystok, Poland	53°N	150	580	6	Jul 2009-Jun 2010	12	40	<5 y	Hospital based	NA	Developed	— *	— *	autumn months (Sep-Nov, Jan-Mar)
Oishi et al	Y	Sona, Japan	37°N	67	1230	12	Sep 2001-Aug 2003	24	66	children	Hospital based	Rural	Developed	— *	—	autumn-winter
Pang et al	N	Alberta, Canada	51°N	1083	418.8	4.4	Jul 2008-Jul 2009	13	437	All	Hospital based, Community clinics,	Urban and Rural	Developed	— *	NA	winter
Papaventsis et al	N	Antananarivo, Madagascar	18°S[d]	1275	1360	18	May 2004-May 2005	13	14	≤16 y	Hospital based and Rehydration clinics	NA	HMD			November and December
Park et al	Y	Seoul, South Korea	37°N	86	135 d	12	Mar 2007-Feb 2010	36	1379	All	Hospital based	NA	LMD	— *	— *	autumn and winter
Puustinen et al (2011)	N	Tampere, Finland	61°N	92	590	3	Sep 2009-Aug 2010	12	49	<15 y	Hospital based and Outpatient	NA	Developed	— *	—	NA
Puustinen et al (2011)	Y	Finland	61°N	92	590	3	Jul 1997-Jun 2007	180	1172	<3 y	Community	NA	Developed			NA
Rasanen et al	Y	Tampere, Finland	61°N	92	590	3	Sep 2006-Aug 2008	24	196	≤15 y	Hospital based and Outpatient	Urban	Developed	— *	—	Jan/Feb-Apr
Sa et al	N	Fortaleza (Ceara state), Brazil	3°S[d]	24	1425.3	26.6	May 2008-April 2009	12	34	1 mo-10 y	Hospital based	NA	LMD	— *	+	NA
Siqueira, J. A. et al	N	Belem (State of Para), Brazil	1°S[d]	16	2790	25.9	May 2008-April 2011	36	171	<5 y	Hospital based	NA	LMD	+	—	Sep, Oct, and Feb
Sumi et al	Y	Japan	35°N	7	1520	15	Jan 2000-Dec 2003	36	3413	Young children	Pediatric clinics	NA	Developed			early winter
Terletskaia-Ladwig et al	Y	Germany	48°N	418	730	8	Jan 2002-Dec 2008	84	682562	All	NA	NA	Developed			Sep-Apr
Thongprachum et al (2013)	Y	Chiang Mai, Thailand	18°N[d]	313	1200	26	Jan 2006-Dec 2006	12	32	<5 y	Hospital based	NA	LMD	— *	—	rainy and winter seasons
Thongprachum et al (2015)	N	Hokkaido, Tokyo, Shizuoka, Kyoto, Osaka, and Saga, Japan	33°N	4	1631	15	Jul 2009-Jun 2013	48	938	≤15y	Pediatric clinics	NA	Developed			winter
UK Data	Y	England/Wales	51°N	61	750	10.3	Jan 1997-Dec 2009	156	47109	All	NA	NA	Developed			NA
Victoria et al	N	Rio de Janeiro, Brazil	22°S[d]	6	1090	24.2	Jan 2004-Dec 2004	12	65	Children	Hospital based	NA	LMD			autumn and spring seasons (dry periods)
Wilhelm et al	Y	Charleston (WV), USA	38°N	228	1104	12.9	Jan 2007-Dec 2007	12	972	All	Hospital based	NA	Developed	—	—	Jan-Jul
Xue et al	N	Shanghai, China	31°N	7	1140	16	May 2012-April 2014	24	903	All	Hospital sentinels	Urban	LMD	— *	— *	winter or cold seasons
Yoon et al	Y	Seoul, South Korea	37°N	86	135 d	12	Nov 2005-Nov 2006	13	114	<5 y	Hospital based	NA	LMD			winter (GI) and spring/fall (GII)
Zhirakovskaia et al	Y	Novosibirsk, Russia	55°N	177	448	1.8	Jun 2003-Dec 2012	102	1291	<3 y	Hospital based	Urban and Rural	Developed	— *	NA	Dec-Mar
Zhuge	N	Hangzhou, China	30°N	42	1440	16	Jul 2009-Aug 2010	14	195	NA	NA	NA	LMD	— *	— *	NA

Abbreviations: HMD, high-mortality developing country; LMD, low-mortality developing country; NA, not available

[a] Data denote the emergence of a variant strain between July 2002-June 2003 or July 2006-2007.

[b] Data denote the sign of the coefficient from generalized linear models performed to determine the relationship between monthly incidence of Norovirus and monthly temperature or monthly rainfall in studies for which these data were available.

[c] Data denote the peak season of cases and reflect the authors' terminology.

[d] Tropical latitude.

* Statistically significant (P<.05).

Table 2. Summary of Studies Included in the Final Analyses

Pathogen	Seasonality Analysis (No. datasets)	Temperature Models (No. datasets)	Precipitation Models (No. datasets)	Northern Hemisphere [a] No. (%)	Southern Hemisphere [b] No. (%)	Tropics [c] No. (%)
E. coli	39	21	18	19 (48.72)	3 (7.69)	17 (43.59)
Cryptosporidium	48	24	23	29 (60.42)	7 (14.58)	12 (25.00)
Norovirus	53	26	21	36 (67.92)	3 (5.66)	14 (26.42)

[a] Northern Hemisphere: (>23°N)
[b] Southern Hemisphere: (>23°S)
[c] Tropics: (23°N-23°S)

Table 3. Summary of Seasonal Peaks of Incidence Cases Reported by Studies, by Geographic Location

Pathogen	Location	Peak Month, Studies, No. (%) [a]				Ratio of Peak to Mean Values, Mean [b]
		Dec-Feb	Mar-May	Jun-Aug	Sep-Nov	
E. coli						
	North hemisphere	0 (0)	2 (11)	13 (72)	3 (17)	3.23
	South hemisphere	2 (67)	1 (33)	0 (0)	0 (0)	3.94
	Tropics	0 (0)	12 (71)	5 (29)	0 (0)	2.73
Cryptosporidium						
	North hemisphere	2 (7)	6 (21)	11 (39)	9 (32)	6.48
	South hemisphere	1 (17)	4 (67)	0 (0)	1 (17)	3.42
	Tropics	2 (17)	3 (25)	5 (42)	2 (17)	4.42
Norovirus						
	North hemisphere	17 (47)	7 (19)	1 (3)	11 (31)	4.45
	South hemisphere	1 (33)	0 (0)	0 (0)	2 (67)	3.46
	Tropics	3 (21)	5 (36)	2 (14)	4 (29)	3.08

[a] Peak month reflects the single calendar month averaged over all years of the study with the highest pathogen case load.
[b] Calculated as the mean number of cases in the month with the most cases, divided by the mean number of cases per month over the course of the entire study.
The ratio reported here reflects the ratio of peak to mean values by geographic location.

Tables 4a-c: Comparison of the Best-Fit Generalized Estimating Equation Models with Poisson Distribution, Controlling for Serial Correlation and Clustering by Study

Table 4a: *E. coli* Model Selection

Model	Temp.	Temp. 1-mo Lag	Precip.	Precip. 1-mo Lag	Developed vs Developing [a]	QIC [b]	Delta [c]
Temperature + Precipitation [d]	0.07525	NA	0.00273	NA	0.67136	-9235	0
Temperature Lag + Precipitation	NA	0.06916	-0.00158	NA	1.02316	-9104	131
Temperature + Precipitation Lag	0.07821	NA	NA	-0.00151	0.73965	-9139	96
Temperature Lag + Precipitation Lag	NA	0.066903	NA	0.000286	0.984727	-8999	236

[a] WHO mortality strata classification, grouped as developed or developing (high- and low-mortality developing).
[b] Quasi-information criterion (QIC) values shown for each model, based on running all pathogen-specific models in a common dataset.
[c] Delta values denote the difference in QIC values, based on the best fit model.
[d] Best fit model, as evaluated by lowest quasi-information criterion (QIC) value.

Table 4b: *Cryptosporidium* Model Selection

Model	Temp.	Temp. 1-mo Lag	Precip.	Precip. 1-mo Lag	Developed vs Developing [a]	QIC [b]	Delta [c]
Temperature + Precipitation	0.05201	NA	0.00782	NA	-0.38431	-1242	69
Temperature Lag + Precipitation [d]	NA	0.05783	0.00639	NA	-0.58277	-1311	0
Temperature + Precipitation Lag	0.0493	NA	NA	-0.00844	-0.38641	-1037	274
Temperature Lag + Precipitation Lag	NA	0.05492	NA	-0.00888	-0.59813	-1127	184

[a] WHO mortality strata classification, grouped as developed or developing (high- and low-mortality developing).
[b] Quasi-information criterion (QIC) values shown for each model, based on running all pathogen-specific models in a common dataset.
[c] Delta values denote the difference in QIC values, based on the best fit model.
[d] Best fit model, as evaluated by lowest quasi-information criterion (QIC) value.

Table 4c: Norovirus Model Selection

Model	Temp.	Temp. 1-mo Lag	Precip.	Precip. 1-mo Lag	Developed vs Developing [a]	New Strain Year [b]	QIC [c]	Delta [d]
Temperature + Precipitation [e]	-0.0411	NA	-0.00146	NA	0.72894	0.17157	-19515	0
Temperature Lag + Precipitation	NA	-0.04156	-0.00115	NA	0.24468	0.15922	-19020	495
Temperature + Precipitation Lag	-0.0386	NA	NA	-0.0136	0.5508	0.1992	-19499	16
Temperature Lag + Precipitation Lag	NA	-0.03772	NA	-0.01308	0.22574	0.16399	-18950	565

[a] WHO mortality strata classification, grouped as developed or developing (high- and low-mortality developing).
[b] Emergence of a variant strain between July 2002-June 2003 or July 2006-2007.
[c] Quasi-information criterion (QIC) values shown for each model, based on running all pathogen-specific models.
[d] Delta values denote the difference in QIC values, based on the best fit model.
[e] Best fit model, as evaluated by lowest quasi-information criterion (QIC) value.

Table 5. Results of Best-Fit Generalized Estimating Equation Models with Poisson Distribution, Controlling for Serial Correlation and Clustering by Study

	Model	IRR (95% CI) [a]	P-value	Studies, No.	Months, No.	QIC [b]
E. coli	temperature, precipitation			18	329	-9235
	temperature	1.08 (1.05-1.11)	<0.0001			
	precipitation	1.00 (0.99-1.01)	0.41			
	developing vs developed	1.96 (0.41-9.38)	0.40			
Cryptosporidium	temperature lag, precipitation			21	718	-1311
	temperature 1-mo lag	1.06 (1.02-1.10)	0.00			
	precipitation	1.01 (0.99-1.02)	0.17			
	developing vs developed	0.56 (0.17-1.91)	0.35			
Norovirus	temperature, precipitation			21	464	-19515
	temperature	0.96 (0.92-1.00)	0.05			
	precipitation	0.99 (0.99-1.00)	0.65			
	developing vs developed	2.07 (0.75-5.72)	0.16			
	new strain year	1.19 (0.65-2.17)	0.58			

[a] Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) are shown for a 1°C change in temperature and a 1 cm change in rainfall.
[b] Quasi-information criterion (QIC) values are shown for each model, based on running all pathogen-specific models in a common dataset.

FIGURES

Figure 1. PRISMA diagram of the study selection process.

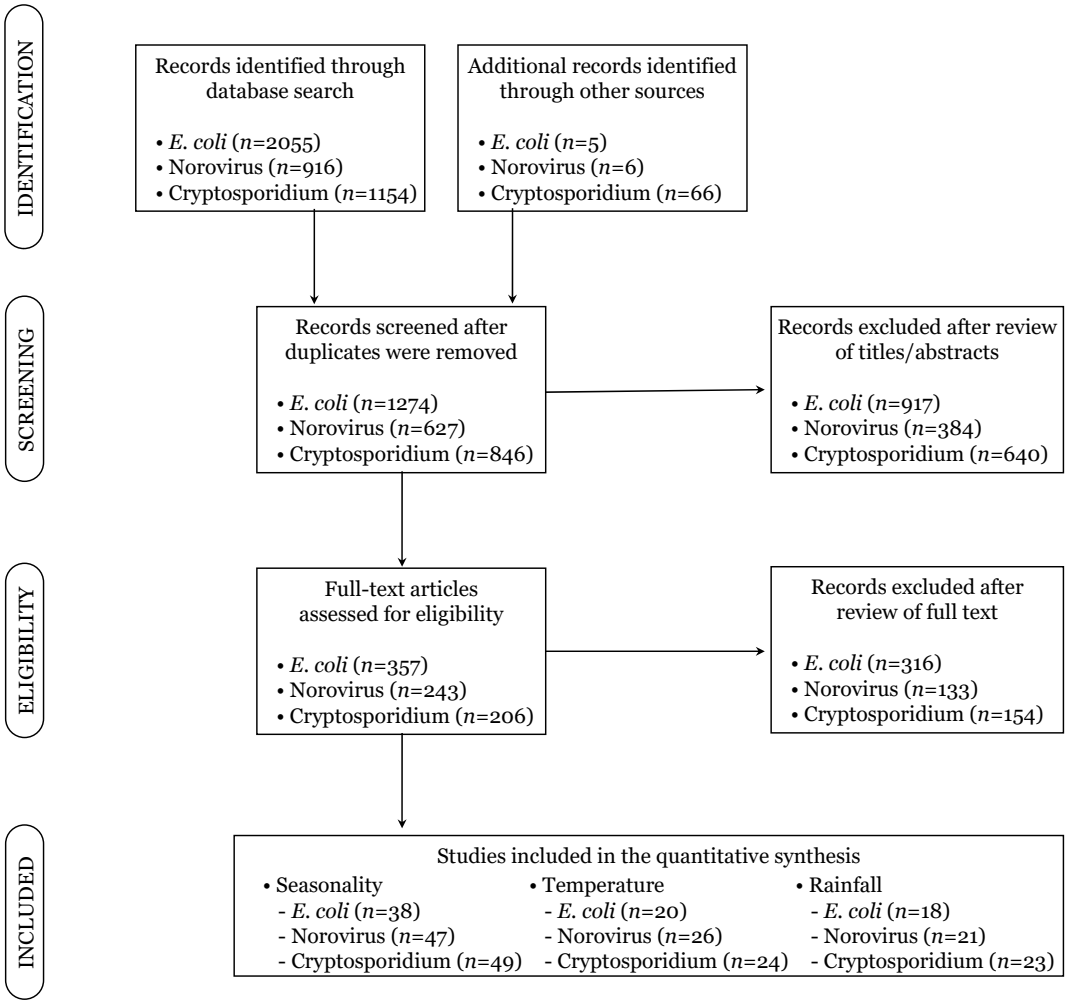
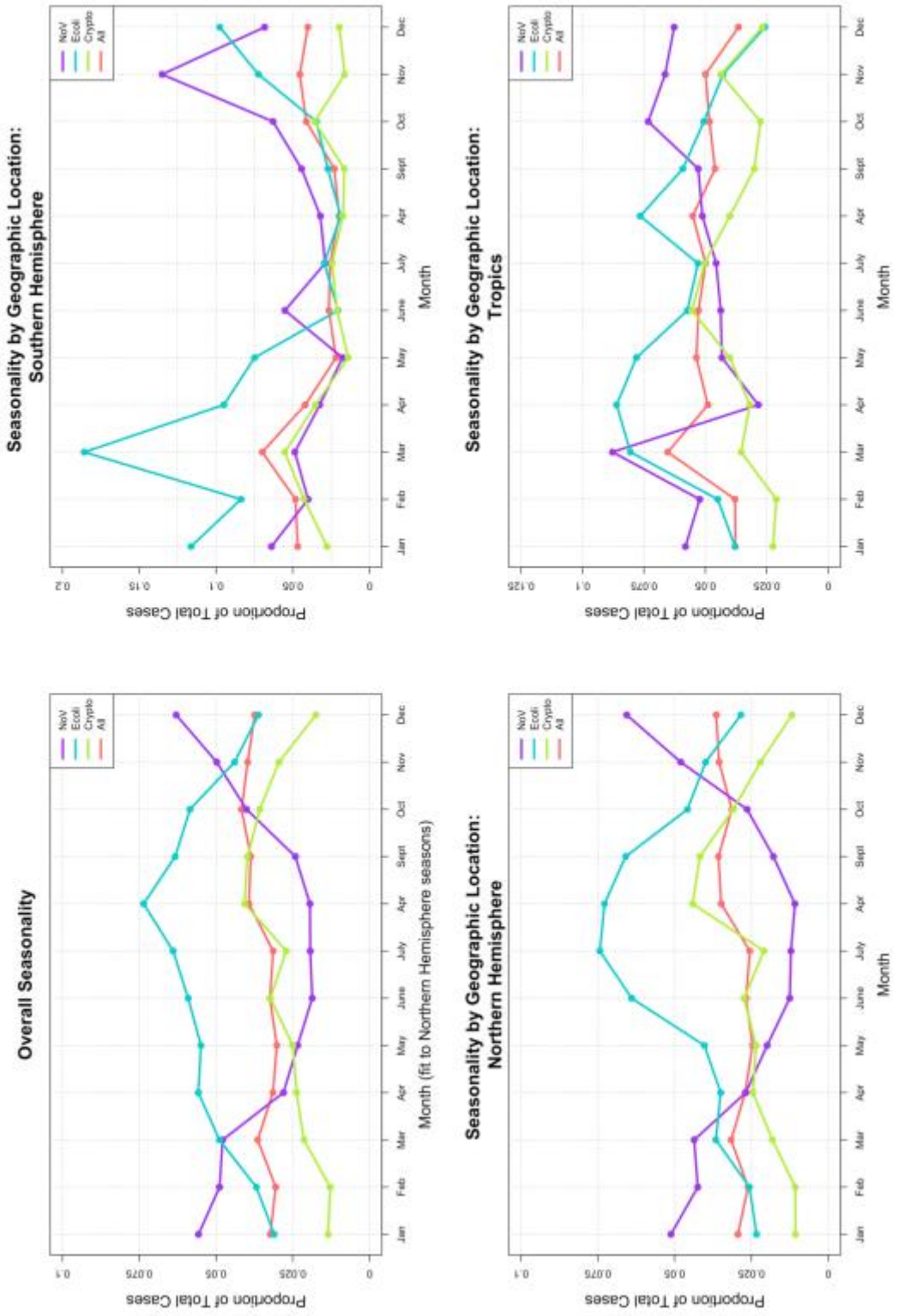


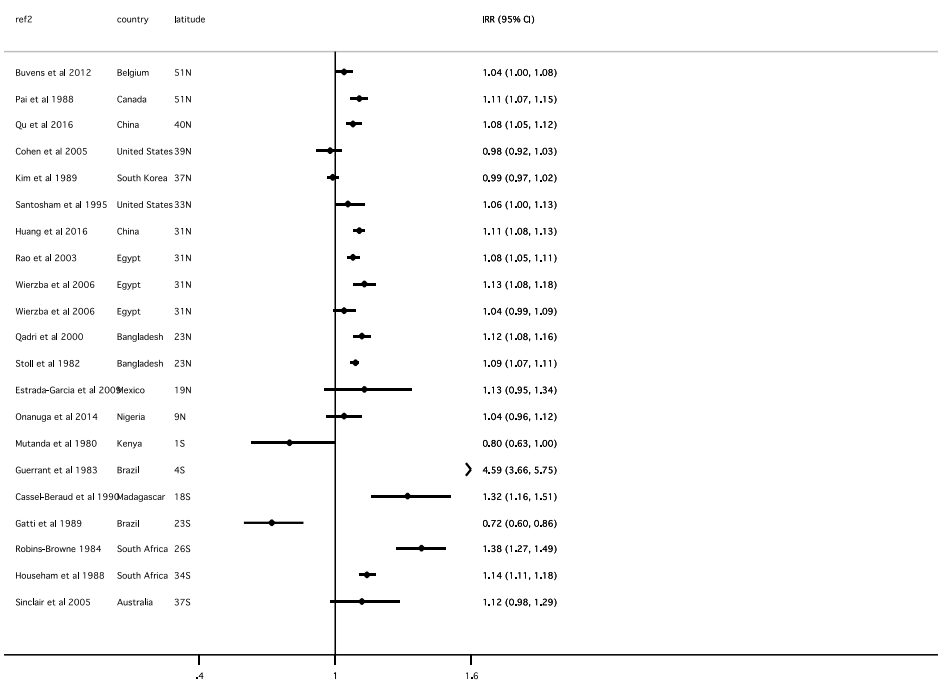
Figure 2: Seasonality patterns of each pathogen over 12-months for all studies, clustered by geographic location.



Figures 3-5: Forest plots show incidence rate ratios (IRR) and 95% confidence intervals (CI), calculated with generalized log-linear Poisson regression models and using Newey-West standard errors, for the relationship between pathogen incidence and (A) monthly mean temperature (°C) and (B) rainfall (cm) for each study.

Figure 3: Forest plots of the relationship between diarrheagenic *E. coli* incidence and monthly mean temperature (°C) and (B) rainfall (cm) for each study.

A



B

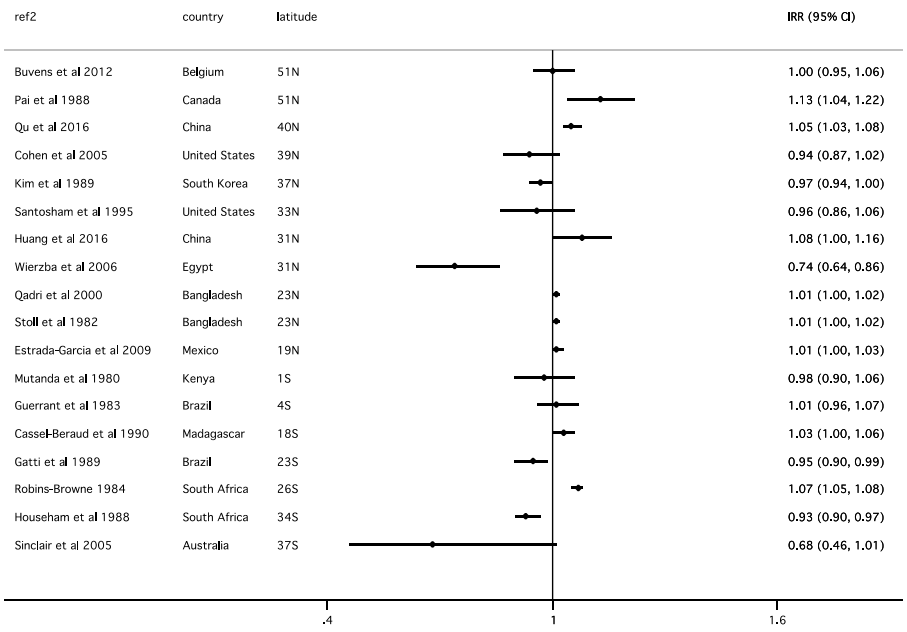
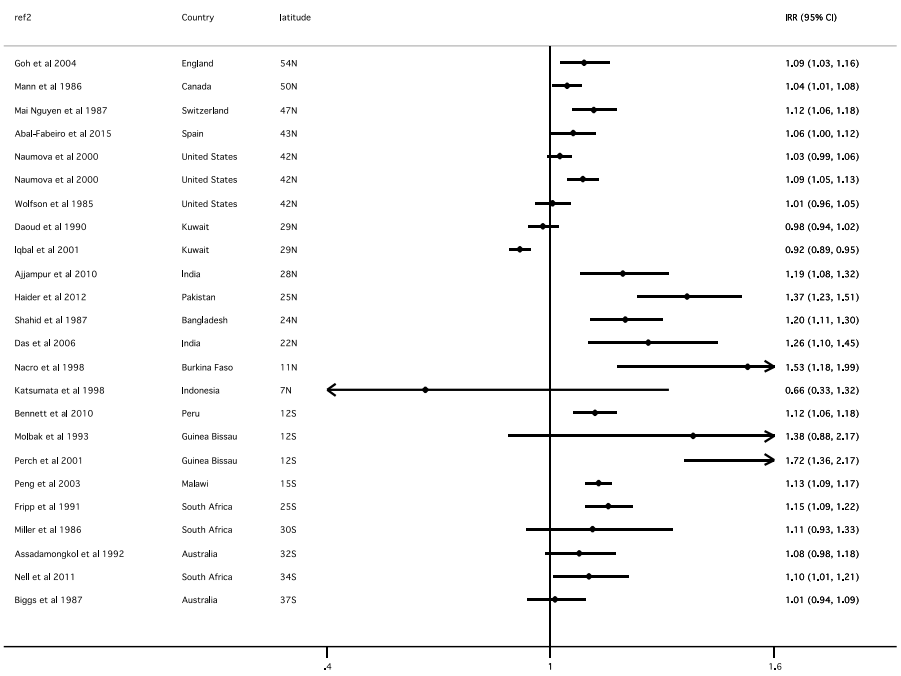


Figure 4: Forest plots of the relationship between *Cryptosporidium* incidence and monthly mean temperature (°C) and (B) rainfall (cm) for each study.

A



B

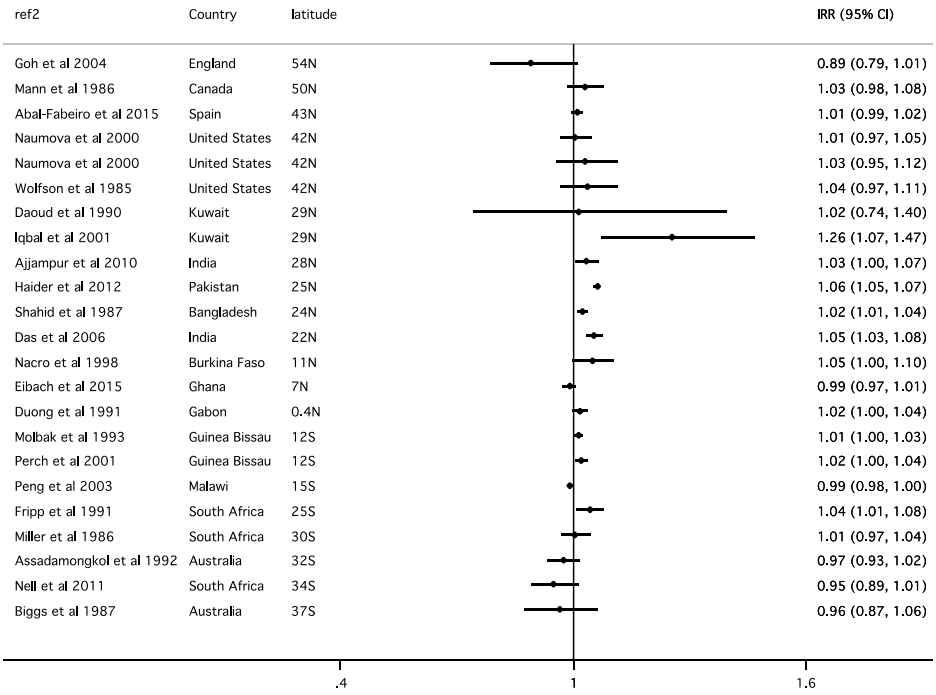
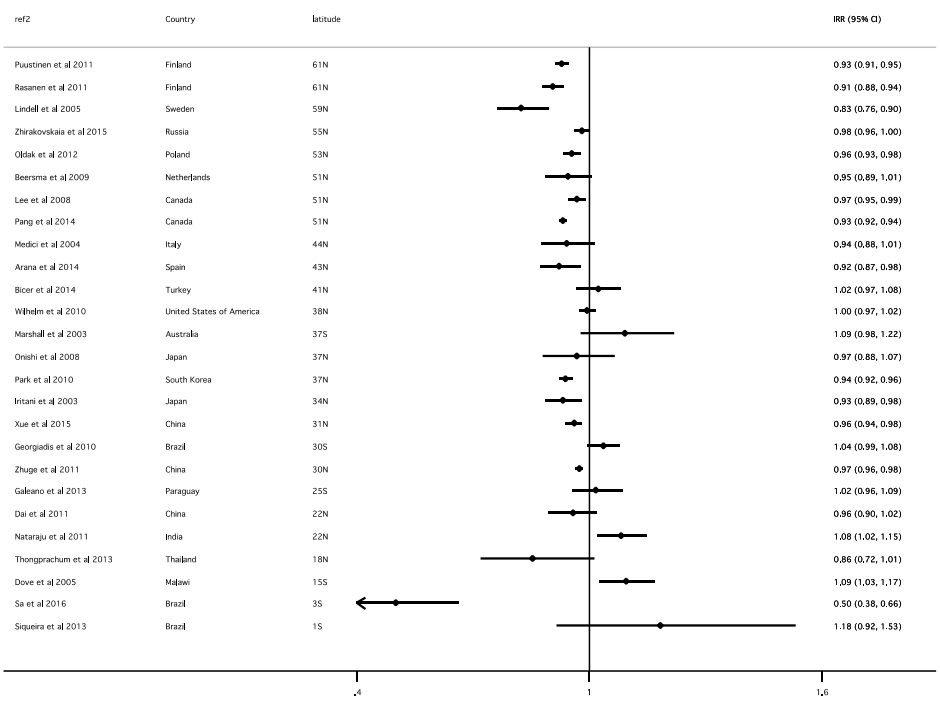


Figure 5: Forest plots of the relationship between norovirus incidence and monthly mean temperature (°C) and (B) rainfall (cm) for each study.

A



B