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Association of Temperature, Precipitation, and Humidity with Incidence of Infectious Diarrheal Disease in the Sichuan Province of China from 2005 to 2016

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By

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B.A.
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2018

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Abstract

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Infectious diarrhea is a major cause of morbidity and mortality globally, causing 1.6 million deaths and 49.8 million disability-adjusted life years lost in 2016. Diarrheal disease often has distinct seasonality, with viral cases more often occurring in the colder, drier winter months and bacterial cases more often in the warmer, wetter summer months. In Sichuan, China, and the capital city of Chengdu, while there has been an overall decreasing trend in diarrheal disease, seasonal patterns have shifted from annual to biannual peaks, beginning in January 2012. This study utilized China's National Infectious Disease Reporting System to investigate the relationship between meteorological factors and diarrheal disease and how the shift in disease seasonality modified the impact of temperature, humidity, and precipitation on the incidence of 'other infectious diarrhea' in Chengdu. A negative binomial generalized linear model was fit to estimate the effects of extreme precipitation, relative humidity, and temperature on diarrheal disease, while controlling for season and autocorrelation. Relative humidity lagged 1 week was associated with diarrheal disease (IRR, 95% CI: 0.995 (0.990, 0.999) for each 1% increase in relative humidity). After the shift, for every 1% increase in non-lagged humidity, the rate of diarrheal disease decreased by 0.01 (IRR and 95% CI: 0.990 (0.983, 0.997)). No significant relationships were found between all other meteorological terms and diarrheal disease either before or after the shift to biannual peaks. The weekly rate of diarrheal disease after the shift in 2012 was 3.5 times higher than the rate beforehand (IRR, 95% CI: 3.547 (1.237, 10.170)). The significance of the diarrheal disease autocorrelation terms, the log of the count of cases lagged at 1-4 weeks and at 8 weeks, indicates that disease prevalence is more strongly associated with transmission of diarrheal disease in Chengdu than meteorological factors (IRR, 95% CI: 1-week lag: 1.198 (1.125,1.256); 2-week lag: 1.164 (1.091, 1.241); 3-week lag: 1.106 (1.037, 1.181); 4-week lag: 1.088 (1.020, 1.160); 8-week lag: (IRR, 95% CI: 0.927 (0.866, 0.991) for each additional case). Further research that includes both infectious disease dynamics and meteorological factors is needed to identify other drivers may have contributed to the shift in seasonality of diarrheal disease cases.

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1. Introduction

Infectious Diarrhea

Infectious diarrheal disease is a major cause of morbidity and mortality globally. Diarrheal disease is the eighth leading cause of death among all ages, causing about 1.6 million deaths in 2016, and among the top five leading causes of death in the world among children under 5 years old (1, 2). Globally in 2015, almost 500,000 deaths were among children under 5 years old, making up 8.6% of all deaths in this age group (3). In addition to deaths, diarrheal disease caused 49.8 million disability-adjusted life years lost in 2016 (2). Deaths attributable to diarrheal disease have decreased among children younger than 5 years, in part due to increased availability of interventions such as oral rehydration solution therapy (ORS) and health care access. Over all ages, rates of diarrheal disease have decreased, but mortality due to diarrheal disease has decreased more quickly than morbidity due to chronic low exposure to enteric pathogens, with higher rates of decrease among children younger than 5 years of age as compared to people of all ages (3). Diarrheal disease is associated with acute gastroenteritis, characterized by acute symptoms including loose stools, vomiting, fever, or abdominal cramps (4), as well as with longer-term negative health effects such as reduced immune response, growth faltering, impaired cognitive development, and increased risk for certain chronic diseases (5).

There are various etiologies of diarrheal disease, including viral, bacterial, and protozoan pathogens. The Global Enteric Multicenter Study (GEMS) found that most infectious moderate to severe diarrhea in children under 5 globally can be attributed to four different enteric pathogens: rotavirus, *Cryptosporidium*, enterotoxigenic *Escherichia coli* producing heat-stable toxin (ST-ETEC), and *Shigella* (6). The Etiology, Risk Factors, and

Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health Study (MAL-ED) found that viral infectious diarrhea was most common, with *Shigella*, rotavirus, Sapovirus, adenovirus and ETEC with the highest attributable incidence among children in 7 study sites worldwide (7). Across settings and populations, most cases of infectious diarrhea are viral in etiology, with rotavirus as the number one cause of diarrheal deaths and severe disease in children and norovirus representing dominant causes of gastrointestinal illness across all age groups (8, 9).

Transmission Pathways of Diarrheal Disease

Enteric pathogens are transmitted via the fecal-oral route which includes many different transmission pathways, though the primary route of exposure varies by pathogen, population, and setting. The various environmental pathways for fecal-oral transmission are described in what is often called the F-diagram, and include fluids (i.e., water, for drinking, recreational, or for other uses), fingers (hands), food, fields (soil), fomites, and flies (10, 11). Enteric pathogens, primarily bacterial pathogens, are often found in environmental reservoirs and are transmitted through insufficient water and sanitation infrastructure. In some high-income countries, the burden of bacterial diarrheal disease has decreased dramatically with improvements to this infrastructure (11). In the case of viral enteric pathogens, such as norovirus and rotavirus, person-to-person transmission through close contact with infected persons is the dominant pathway in most settings, though transmission can also occur by other routes, including food, water, and other environmental pathways (8, 9, 12, 13).

Seasonality of Diarrheal Disease

Diarrheal disease is characterized by distinct seasonality, though seasonal patterns can vary by place, pathogen, and population. In temperate regions, rotavirus and norovirus are often more prevalent in the colder, drier, winter months, while bacterial enteric pathogens typically peak during the warmer, wetter, summer months (9, 14-16). However, these patterns are not consistent everywhere; for example, in Kenya, rotavirus infections were detected more commonly in the warm, dry months (17). Additionally, changes in climate could potentially contribute to shifts in the seasonal patterns of enteric diseases because weather factors such as temperature, humidity, and precipitation can affect the dynamics of enteric pathogen prevalence (18). Seasonal patterns of diarrheal disease also differ by age. Children under 5 years of age experience increased incidence of diarrheal disease in the fall or winter, while older children and adults experience increased incidence in the summer (19). This could be due to a higher burden among young children of viral diarrheal disease that typically peaks in the winter and a higher burden of bacterial diarrheal disease among older children and adults that typically peaks in the summer.

Climate, Weather, and Infectious Diarrhea

There is a large body of evidence suggesting that the changes in temperature, humidity and precipitation due to climate change have the potential to alter incidence of diarrheal diseases, with estimates of increased relative risk by 2039 ranging from 8-11% (20-22). As the effects of climate change have become more pronounced, this burden has likely become larger (21). Temperature, rainfall, and other meteorological factors can influence human behavior which could modify diarrheal disease risk; for example, higher temperatures could encourage more outdoor activities involving food which may lead to higher rates of foodborne diarrheal disease, or lower rainfall could push people with limited water supply to use unimproved drinking water and decrease hand hygiene (22). The impact of meteorological and climatic changes on diarrheal disease is complex and may also have varying effects by age, behaviors, infrastructure, and other cultural, political, and social factors (23-25).

Climate change has the potential to change the dynamics of diarrheal diseases as many are transmitted through mechanisms related to unsafe water and sanitation which may be exacerbated by climate change. The estimated 829,000 deaths attributed to diarrheal disease from inadequate water, sanitation, and hygiene in 2016 will likely increase as climate change continues to negatively impact WASH systems in part because of less predictability in temperature, rainfall, and extreme weather events (2).

Temperature

Most evidence supports a positive association between temperature and bacterial diarrhea and a negative association between temperature and viral diarrhea (26, 27). Temperature can be defined in various ways, including diurnal temperature range, minimum temperature, maximum temperature, and average temperature (28, 29). In China, high temperature has been shown to be positively associated with bacterial dysentery, with even higher incidence of bacterial dysentery when relative humidity and/or precipitation was also elevated (30). Additionally, maximum temperature was found to be positively associated with the incidence of all-cause and bacterial diarrhea, but was negatively associated with the incidence of viral diarrhea (26, 28, 31-33). Using maximum, minimum, and average temperature as exposures, each was positively associated with the risk of bacterial infectious diarrhea in urban areas of China (34, 35). Diurnal variation in temperature has also been demonstrated to be positively associated with all-cause childhood diarrhea (36). As the climate warms, temperature increases may contribute to improved survival of enteric pathogens, particularly bacterial pathogens, in the environment, resulting in higher risks for transmission.

Precipitation

Precipitation has also been hypothesized to impact incidence of infectious diarrheal diseases, considering the effects of various representations of precipitation, including heavy rainfall events, flooding, and drought. Heavy rainfall events are associated with diarrhea, but the effects may be influenced by recent precipitation (26, 37). Heavy rainfall events caused the highest risk of diarrheal transmission when following a period of low rainfall (26, 38), while heavy rainfall after a wet period was protective against diarrhea (26). However, there have been conflicting results showing no association between rainfall and rotavirus (39) and a negative association between both total and extreme precipitation and diarrhea (40-42).

It is also possible that other factors influence how rainfall influences diarrheal incidence. For example, heavy rainfall events increased the risk of infectious diarrhea the most among communities in Ecuador where treatment of drinking water was rare, but in Rwanda, high runoff after heavy rainfall events was protective against diarrheal disease among those with access to unimproved toilets (38, 40). These differences were likely due to varying infrastructure and development levels, including access to sanitation and drinking water treatment.

Climate change is expected to have differing impacts on water availability by region, which results in differing impacts on enteric pathogen transmission pathways. Increased water availability may be more common in some regions as the climate changes. Flooding, increased rainfall, or more frequent heavy rainfall events could result in reduced water quality, depending on regional factors (43). Higher rainfall may cause more runoff of accumulated fecal matter and pathogens into the drinking water supply, reducing water quality (44). Alternatively, higher levels of water may dilute contaminated water which can improve water quality (40, 43).

In areas with predicted decreases in water availability, transmission of enteric pathogens via contaminated hands and surfaces may increase. (43). Areas with reduced availability of water may also see longer travel times to collect water, which has been associated with drinking water re-contamination in storage (45). In other regions, a decrease in availability of water may increase the risk of diarrheal disease through changes in handwashing behavior, soap usage, compromised improved water sources, or increased use of informal and potentially lower quality water sources (43, 46, 47).

Relative Humidity

Relative humidity has the potential to impact transmission of diarrheal disease due to improved pathogen survival, growth, and person-to-person transmission associated with higher humidity for some pathogens (23). However, certain viruses such as influenza, rotavirus, and adenovirus may survive better at low humidity (48-50).

Humidity may also be a useful indicator of potential impacts associated with rainfall. Because humidity is often a predictor of rainfall, very low humidity caused by a drought could have negative implications for the quality of water and sanitation infrastructure, while high humidity is likely associated with high rainfall and could improve transmission of some enteric pathogens (23).

Relative humidity has weaker evidence supporting its association with infectious diarrhea. Some studies have found no association between humidity and dysentery in a

Chinese county with a subtropical monsoon climate (30, 39). Significant positive associations of humidity and morbidity due to infectious diarrhea have been demonstrated in both urban China and rural Bangladesh (51, 52), with one study finding the highest risk of infectious diarrhea at an average relative humidity of 67-78% (23). However, other studies have found negative associations between relative humidity and diarrheal disease incidence (32, 53). Shifting seasonality of disease has also been observed in China, with increased diarrheal disease incidence earlier in the year in areas with average relative humidity below 69.5% (54). Additionally, the impact of humidity on infectious diarrhea can be modified by temperature, such that with higher temperatures in addition to higher humidity, diarrheal disease incidence may increase (30). These differences could be due to different populations, geographies, or different primary pathogens responsible for the diarrheal disease.

Diarrheal Disease Dynamics

Meteorological factors interact with population-level factors such as population immunity, making it difficult to detect a direct relationship between weather and disease. Infectious disease models such as the SIR (Susceptible, Infectious, Recovered) model may oversimplify transmission dynamics, not accounting for factors such as clusters or differences in infectiousness by geography or by host, and they also do not take extrinsic factors including weather into account (55). As demonstrated by Dushoff et al, small changes in influenza transmission caused by meteorological factors can be amplified by population immunity to cause seasonal patterns to emerge (56). Temperature can change the probability of transmission of rotavirus (39); however, although these meteorological factors affect transmission, we can only observe cases of disease. This relationship between transmission and cases of disease is complex, depending on various population factors including population immunity and contact rates between people, making it difficult to detect a direct relationship between meteorological factors and disease, even if they do impact transmission.

Weather and Diarrhea in Urban Settings

Diarrhea is widespread in both urban and rural settings. With increased urbanization globally, more people are moving to cities, including in the Sichuan province (57). One study shows an increased risk of diarrheal disease in urban areas in Senegal (57), while a study in China demonstrated higher enteric pathogen prevalence in rural areas (58).

Impervious surfaces in China from 1980 to 2017 have dramatically increased because of rapid urbanization and growth, changing the city environments to create more runoff and flooding (59) that could lead to increased diarrheal disease transmission by flushing accumulated pathogens into drinking water. Rapid growth in cities can contribute to water resource scarcity, which can impact ability to maintain hygiene, particularly soap usage and handwashing behavior, and could promote the use of unsafe water sources (60). Additionally, urban areas can become heat islands, creating warm areas that are ideal for pathogen growth (61). However, urban areas are more likely to have better coverage and access to water and sanitation infrastructure as compared to rural areas (62). These factors all indicate that the patterns of diarrheal disease in urban areas may be different from those in rural areas, where most research on meteorological factors and diarrheal disease has been conducted.

Sichuan Province and Chengdu City

Sichuan province is in western China, bordering Tibet to the west, with diverse weather and geographic features. It is the second largest province in China geographically and fourth largest by population with 81 million people (63). The north and west parts of the province are rural, mountainous, and sparsely populated, contrasting with the lower-lying, more densely populated central and eastern regions, centered around the capital city of Chengdu (63). In recent years, Chengdu has experienced drastic urbanization, with a population in 2014 of about 14 million people, and with that, developments in infrastructure (64). Figure 1 shows a map of the metro area of Chengdu made up of 20 districts (Jinjiang, Qingyang, Jinniu, Wuhou, Chenghua, Pengzhou, Dujiangyan, Pidu, Xindu, Qingbaijiang, Jintang, Jianyang, Longquanyi, Shuangliu, Wenjiang, Chongzhou, Dayi, Qionglai, Pujiang, Xinjin) within the Sichuan province of China.

There is a substantial burden of diarrheal disease in China, including in the Sichuan province, though there has been a general decline in associated morbidity and mortality due to diarrheal disease globally and in China between 2007 and 2017 (1, 3). Consistent with global trends, the rates of diarrheal disease in China are highest for children under 5 years old (65). Diarrheal disease is generally more common in rural areas, including in the Sichuan province of western China, where in 2008, there were 2.3 (1.9, 2.8) diarrheal disease deaths per 100,000 population (3). The availability of water and sanitation infrastructure such as piped water and sanitation facilities varies widely from higher access in urban areas such as Chendgu to low access in poorer and rural areas to the west of the Sichuan province (62).

The geographic distribution of enteric pathogens varies, such that *Shigella* and adenovirus are more common in rural areas and diarrheagenic *E. coli* is more common in urban areas (15, 65). Among diarrheal diseases, rotavirus, norovirus, and adenovirus were the most common viral etiologies of diarrheal disease, affecting more commonly children under 2 years of age. Among the elderly, norovirus was also the most prevalent pathogen (15). Diarrheagenic *Escherichia coli*, *Salmonella,* and *Shigella* were the most common bacterial etiologies of diarrheal disease and increased in prevalence with age (9, 15). (15)

In China, the National Infectious Disease Reporting System (NIDRS) records several mandatory reportable diseases through real-time passive surveillance from health facilities (54, 66). The category “Other infectious diarrhea” includes diarrheal disease of various unidentified bacterial and viral etiologies, excluding cholera, bacillary dysentery, typhoid, and paratyphoid.

Historically, diarrheal disease in the Sichuan province has shown distinct summer seasonality, with a broad annual peak in diarrheal disease incidence across the summer months. However, a recent analysis NIDRS other infectious diarrhea data in Sichuan province from 2005 to 2018 demonstrated an overall downward trend in diarrheal cases and a shift in seasonality, from annual summer peaks to biannual peaks in summer and winter, demarcated by a changepoint beginning in January 2012 (67). We suspect that the shifting seasonality may be due to changing etiology of most of the cases of ‘Other infectious diarrhea’, explained by either a decline in bacterial cases that is unmasking a consistent viral peak in winter or by an increase in viral diarrhea while bacterial diarrhea decreases. From 2013 to 2016, Gong et al noted winter peaks of diarrheal disease that were mainly of viral etiology and summer peaks of primarily bacterial etiology among adults in Shanghai, China, an etiological season pattern we suspect is also occurring in Sichuan (68). In the case of shifting etiology associated with the shift in seasonal patterns, we may expect changing relationships between diarrheal disease and meteorological factors, as viral and bacterial enteric pathogens are often differentially impacted by temperature, rainfall, and relative humidity. Notably, this phenomenon of shifting seasonality and decreasing diarrheal disease incidence was observed in the Sichuan province overall, though the shifting seasonal trend has been conserved in urban areas, particularly, the urban center of Chengdu.

This study utilized China's NIDRS infectious disease reporting system to investigate the relationship between meteorological factors and diarrheal disease and how the shift in disease seasonality beginning in January 2012 modified the impact of temperature, humidity, and precipitation on the incidence of 'other infectious diarrhea' in the city of Chengdu.

2. Methods

Diarrheal disease case data

The National Infectious Disease Reporting System (NIDRS) is a passive surveillance system that provides disease data from across China. This system collects real-time surveillance data for 39 legally notifiable infectious diseases, including diarrheal diseases categorized as typhoid, bacillary dysentery, Hepatitis A, amoebic dysentery, and ‘Other Infectious Diarrhea’ (54, 66). ‘Other Infectious Diarrhea’, referred to from now on as diarrheal disease, is defined as any infectious diarrhea not including cholera, dysentery, typhoid, and paratyphoid. Daily case reports of diarrheal disease from 2005 to 2016 in the city of Chengdu in Sichuan Province of China were obtained from the Chinese Centers for Disease Control (CDC). Case-specific demographic information, including sex, date of birth, age, location of residence, and occupation, were also included in the dataset. NIDRS data were used courtesy of the Remais lab at the University of California – Berkeley.

Meteorological data

Meteorological data were obtained from the Global Surface Summary of the Day (GSOD) from the National Centers for Environmental Information under the National Oceanic and Atmospheric Administration. Daily precipitation (inches), minimum, maximum, and average temperature (degrees Fahrenheit), and average dew point (degrees Fahrenheit) were obtained for the Wenjiang weather station, located within the Chengdu metro area, 16 km west of the city center, from September 1, 2004 to January 1, 2019. Relative humidity was calculated from dewpoint and temperature using the August-Roche-Magnus approximation (69).

Daily meteorological values were aggregated to weekly averages for temperature and relative humidity. Previous research has indicated that extreme precipitation may be a more important predictor of diarrheal disease than total precipitation (38, 44). In this case, extreme precipitation was measured as a dichotomous variable, such that any week having at least 1 day of precipitation over the 80th percentile of daily precipitation over the study period was considered to have extreme precipitation (38, 44).

Statistical analyses

This paper evaluates whether a relationship exists between meteorological factors and cases of diarrheal disease and whether this relationship changed after a shift in seasonality of diarrheal disease cases from annual peaks to biannual peaks that began in January 2012. The meteorological factors considered include extreme precipitation, average weekly relative humidity, and average weekly temperature. An indicator variable was created for pre- and post-seasonality shift.

Spearman correlation coefficients were obtained for the pairwise associations of the meteorological factors and diarrheal disease case counts. To prevent multicollinearity from multiple meteorological variables, only pairs with pairwise correlation coefficients less than 0.8 were used in the model (70).

The diarrheal disease case count data were overdispersed, so a negative binomial generalized linear model was fit to estimate the effects of extreme precipitation, relative humidity, and temperature on diarrheal disease, while controlling for season and autocorrelation. The reference season was designated as spring because this season consistently had the lowest case count. Interaction terms of the seasonality shift indicator variable and each season indicator variable were included. In contrast to Sichuan province overall, in Chengdu, there was only a slight long-term, secular decrease in cases from 2005 to 2016, though the seasonal changes persist, so a term controlling for year was not included in the model (67). Interaction between each term and the indicator of pre- and post-seasonality shift were included to evaluate the impact of seasonality shift on the association between meteorological factors and diarrheal disease. To account for delayed impacts of weather events, lag terms for each of the weather variables were added to the model, as were interaction terms of each lagged weather variable with the indicator of pre- and post-seasonality shift. To control for autocorrelation with prior diarrheal cases, lag terms for the log of diarrheal disease cases were also added to the model.

To select our final model, we compared models using different definitions of precipitation and number lag terms based on AIC, R-squared, and using likelihood ratio tests. We compared models using total precipitation and 2 definitions of extreme precipitation, defined as dichotomous variables, such that any week having at least 1 day of precipitation over the 80th or 90th percentile of daily precipitation over the study period was considered to have extreme precipitation. Extreme precipitation defined by the 80th percentile cutoff was selected because of previous research indicating that heavy rainfall was an important predictor of diarrheal disease (38, 44) For all meteorological terms, we tested an increasing number of lag terms, starting from a 1 week-lag term, and added more lag terms until the likelihood ratio test was insignificant, indicating that the term no longer improved the model. Based on this method, 11 lags for each meteorological variable were included. We also added the 11 lagged log diarrheal disease counts to control for autocorrelation.

The final model used extreme precipitation at the 80th percentile cut-off and included 11 lagged meteorological terms and 11 lagged terms to control for autocorrelation. This model had the lowest AIC and highest R-squared value compared to other tested models. The final model is written out below:

$$
\begin{aligned}
\log(\mathit{diarrheal\ disease\ cases}) \\
&= \beta_0 + \beta_1 * winter + \beta_2 * summer + \beta_3 * fall + \beta_4 * prepost \\
&+ \beta_{5-15} * loglagcount1 - 11wks + \beta_{16-27} * tavglag0 - 11wks \\
&+ \beta_{28-39} * rhavglag0 - 11wks + \beta_{40-51} * prcp80lag0 - 11wks \\
&+ \beta_{52-63} * (prepost * tavglag0 - 11wks) + \beta_{64-75} \\
&* (prepost * rhavglag0 - 11wks) + \beta_{76-87} \\
&* (prepost * prcp80lag0 - 10wks) + \beta_{88} * (prepost * winter) + \beta_{89} \\
&* (prepost * summer) + \beta_{90} * (prepost * fall) \ \dagger
\end{aligned}
$$

† Winter, summer, and fall refer to dummy variables for season, with spring as the reference group. Prepost refers to an indicator variable for pre- and post-seasonality shift beginning in January 2012 of diarrheal disease cases. Loglagcount1-11wks are the log of the lagged diarrheal cases in the prior 11 weeks. Tavglag0-11wks refers to 12 variables of the average weekly temperature from 0 to 11 lagged weeks. Rhavglag0-11wks refers to 12 variables of the average relative humidity from 0 to 11 lagged weeks. Prcp80lag0-11wks refers to 12 variables of extreme precipitation, such that a week was considered to have had extreme precipitation if at least 1 day within the week had precipitation over the 80th percentile, from 0 to 11 lagged weeks. Parameters from β_{52-90} are interaction terms with the prepost variable.

Results are presented as incidence rate ratios for diarrheal disease cases associated with a one-unit change in the predictor variable.

3. Results

Description of diarrheal disease cases

The descriptive statistics for daily diarrheal disease cases from 2005 to 2016 in Chengdu city in the Sichuan Province are in Table 1. Within this time period, 79,633 cases of diarrheal disease were reported. Of these cases, 56.5% occurred in males, with 43.55% in females. These cases were primarily in children, with 49.66% of the cases in children under 2 years of age, and 60.57% in children under 5 years of age.

From 2005 to 2016, the average annual number of cases was relatively consistent though decreasing slightly, with an overall mean of 6,636 cases per year. However, the annual pattern of diarrheal disease cases began to shift from one peak per year in the summer to two distinct peaks per year, in summer and winter, starting in January of 2012 which is consistent with the pattern over the Sichuan province (Figure 2) (67).

Description of meteorological data

The average weekly temperature (Figure 3a) has consistent annual variation with no apparent changes over time. Average relative humidity from 2005 to 2016 hovers mostly between 60 and 80% humidity and does not change appreciably over the years (Figure 3b). Total weekly precipitation is typically below 2 inches per week, with a few weeks in the middle of each year where there is higher precipitation, but there is no long-term change (Figure 3c). The number of weeks with extreme precipitation per year does not change over time and has an average of about 30 from 2005 to 2016 (Figure 3d). The fit lines in blue show that there is no difference in temperature and total precipitation over the years, and there is a slight increase in relative humidity. Seasonality of weather is consistent over time in Chengdu from 2005 to 2016. For each week, the temperature increased by 0.0004 degrees F ($p = 0.01$), relative humidity increased by 0.002% (p

<0.001) and total precipitation increased by 0.00009 inches (p = 0.03). The number of weeks per year with at least 1 day of precipitation over the 80th percentile did not change from 2005 to 2016 (p = 0.61) (Figure 3).

The meteorological variables illustrate the distinct and consistent annual seasonal patterns, shown as the average over all years from 2005 to 2016 (Figure 4 (a, b, c)). Average weekly temperature reaches an annual high in the summer, around weeks 27 to 33 or July and August, of 80 degrees F, and an annual low in the winter of about 40 degrees F (Figure 4a). The average relative humidity per week over all years remains between 55% and 80% but is typically lowest around week 20, in May (Figure 4b). Precipitation is low, hovering around 0 inches, for the dry season in the winter, then peaks at an average of more than 3 inches weekly in the summer, from May to September (Figure 4c).

Spearman correlations between meteorological factors and diarrheal disease case counts

Each meteorological factor is significantly correlated with the diarrheal disease case count, except for relative humidity. Each meteorological factor is significantly correlated with each other, though the pairwise correlation coefficients were each below 0.8, which is the typical threshold for multicollinearity.

Negative binomial generalized linear model

The weekly rate of diarrheal disease after the shift beginning in January 2012 to biannual peaks was about 3 times higher than the weekly rate when there were annual peaks (IRR and 95% CI: 3.547 (1.237, 10.170) – Table A in Appendix). None of the indicator variables for season, nor their interaction terms with the pre-/post-seasonality term were significantly associated with diarrheal disease (Figure 5 and Table A in Appendix). The autocorrelation terms to adjust for prior diarrheal disease cases up to 4 weeks lagged were positively associated with cases (IRRs, 95% CI: 1-week lag: 1.198 (1.125,1.256); 2-week lag: 1.164 (1.091, 1.241); 3-week lag: 1.106 (1.037, 1.181); 4-week lag: 1.088 (1.020, 1.160) for each additional case – Table A in Appendix). The rest of the autocorrelation terms were not associated with diarrheal disease except when lagged 8 weeks, there was a negative association, indicating that more diarrheal disease cases 8 weeks earlier is associated in lower cases in the present (IRR, 95% CI: 0.927 (0.866, 0.991).

Average weekly temperature was not significantly associated at any lag time with diarrheal disease. Average relative humidity lagged 1 week was associated with diarrheal disease (IRR, 95% CI: 0.995 (0.990, 0.999) for each 1% increase in relative humidity), and while all other terms for relative humidity were not significant, all the IRRs hovered around 1. The effects of extreme precipitation on diarrheal disease had more variation that the other meteorological factors but had no relationship with diarrheal disease.

The interaction between seasonality shift and meteorological factors were largely insignificant (Figure 5 and Table A in Appendix). Only the interaction term between the seasonality shift term and non-lagged relative humidity was significant (IRR and 95% CI: 0.989 (0.982, 0.996)), indicating that after the shift, for every 1% increase in humidity, the rate of diarrheal disease decreases by 0.011. There was no evident trend in interaction terms over lag times, demonstrating that this model did not capture a difference in the relationship between meteorological factors and diarrheal disease cases before and after the seasonality shift beginning in January 2012.

4. Discussion

This study aimed to evaluate the association of meteorological factors with diarrheal disease incidence before and after a shift in disease seasonality beginning in January 2012 in the city of Chengdu in the Sichuan province of China from 2005 to 2016. The rigorous analysis conducted in this study used weekly meteorological and case data from over a 12-year period, creating many data points. While some studies have been conducted in urban settings in China, the majority have evaluated diarrheal disease in rural areas. This study builds upon existing evidence as it evaluated the relationship of weather and diarrheal disease in an urban, developed context in China. Based on this analysis, the most predictive factors of diarrheal disease incidence were whether the cases occurred after January 2012 and the number of cases in the previous 4 weeks as well as 8 weeks prior. Meteorological factors were not related to diarrheal disease in Chengdu regardless of lag time, and this was not modified by the shift in seasonality.

There was a small secular decline in cases from 2005 to 2016 in addition to the shift in seasonality beginning in January 2012 from annual to biannual peaks of diarrheal disease cases. Because of the lack of major changes in meteorological factors over time, this long-term trend in cases drives the indicator variable for the seasonality shift towards the null, so we would expect it to have an even larger effect if the slightly negative secular trend was controlled for.

The significance of the diarrheal disease autocorrelation term, the log of the count of cases lagged at 1 to 11 weeks, to control for autocorrelation, indicates that disease prevalence is an important predictor of transmission of diarrheal disease in Chengdu, more identifiable than meteorological factors. This is expected because diarrheal disease is infectious, so more cases in the community are associated with higher levels of transmission and infection rates are influenced by the population-level immunity and susceptibility, which is impacted by the number of cases in the community (71). There is a significantly positive but decreasing association between the log of diarrheal disease counts and diarrheal disease over 4 weeks of lag until there is no association after 4 weeks. This suggests that up until 4 weeks later, more cases in the community will be associated with higher levels of transmission, while after that this association is null except for week 8 where the association becomes negative, possibly indicating that there is some population-level immunity.

In the literature, temperature was most often positively associated with bacterial disease, but negatively associated with viral diarrheal disease (26-28, 31-35, 58). However, in pooled estimates, Carlton et al found positive associations between temperature and all-cause and bacterial diarrhea, but no relationship with viral diarrhea, indicating that all-cause diarrhea in their study could have been mostly of a bacterial etiology (31). The impact of precipitation on diarrheal disease has varied widely depending on factors such as recent precipitation and common treatment of drinking water (26, 37-41). The impact of relative humidity on diarrheal disease in the literature is less consistent, with studies showing positive, negative, or null associations (23, 30, 32, 36, 51-53). It is possible that, since the ‘Other infectious diarrhea’ bin captures diarrheal disease of varying etiologies that may have opposite associations with meteorological factors, the combination of both viral and bacterial etiologies obscured these effects on overall diarrheal disease cases, particularly if there were a shift towards viral diarrhea in Chengdu.

Many prior studies evaluating diarrheal disease and its relationship to meteorological factors have been conducted in rural or less-developed urban settings. Although prior studies in developed urban settings have shown a modest positive relationship of temperature with all-cause infectious diarrheal disease (34, 35), there have been some results showing smaller effect sizes comparing urban to rural areas (57) and comparing high-income to low-income countries (31). Chengdu is a developed city in western China, with rapid growth in jobs and in wages in recent years (67). It is possible that the lack of relationship of meteorological factors to diarrheal disease is explained in part by the more developed urban context of Chengdu and by high access to adequate water and sanitation facilities.

There was no difference in the effects of meteorological factors on diarrheal disease before and after the shift. Based on this analysis, meteorological factors are not drivers of diarrheal disease in Chengdu and this relationship does not change, even with shifting seasonality. This may indicate that shifting etiologies of disease obscure the relationship between meteorological variables and seasonality of disease. It could be that the etiology of the diarrheal disease has shifted from primarily bacterial infections to both bacterial and viral infections, or that there is an emergence of viral diarrheal disease. Alternatively, it is possible that the primary transmission pathways for diarrheal disease in Chengdu are not influenced by meteorological variables, even if these pathways are shifting and changing the seasonality and etiology of diarrheal disease. Improvements in water and sanitation infrastructure that come with rapid development in China (3) could contribute to decreased transmission of bacterial diarrheal disease, while allowing for person-to-person viral diarrheal disease transmission to continue.

Although many papers have shown associations between meteorological factors and diarrheal disease, some show null results. For example, Atchinson et al found no association between either precipitation or humidity and rotavirus, and Liu et al found no association of humidity with diarrheal disease (30, 39) The results from this study also indicate that temperature, extreme precipitation, and relative humidity were not important predictors of diarrheal disease in Chengdu from 2005 to 2016.

Limitations

The negative binomial generalized linear model assumed a linear relationships between meteorological factors and diarrheal disease cases, but it is possible that the relationships are not linear, as demonstrated in a similar study with a U-shaped relationship in Jiangsu province, China (23); other possibilities were not evaluated. We did not test for age-specific effects, which were shown to impact the effect of meteorological factors on diarrheal disease in other studies (23). Additionally, based on available population data, the population was constant over the study period, so it was not included in the model. However, these population statistics may not include transient population changes driven by migrant workers or other factors. As mentioned previously, the diarrheal disease cases used as outcomes included all cases reported in NIDRS as 'Other Infectious Diarrhea' which includes diarrheal diseases of various etiologies. Since the etiologies of the cases were not known, it is possible that the mix of viral, bacterial, and protozoan infections obscured the relationship with meteorological factors.

Lastly, it is well documented that assessing the impact of climate and environmental factors on infectious diseases such as diarrheal disease is challenging because of other factors influencing the pattern of disease (72, 73). These include population level dynamics such as population-level immunity and transmission, as well as human behavior that could modify how the infectious disease spreads throughout the population. Drivers of seasonality of infectious disease are also challenging to identify. Meteorological factors do not directly cause diarrheal disease, but it is possible that they can affect transmission in multiple ways that we are unable to directly observe. The variables controlling for 11 weeks of autocorrelation of cases were significant and positively associated with diarrheal disease cases, supporting the hypothesis that there are other non-meteorological factors influencing disease patterns. The model in this study focused on only the meteorological factors and did not account for these other factors that likely influence transmission and incidence of diarrheal disease. Mechanistic or compartmental models, such as SIR (susceptible-infected-recovered) models, which directly model transmission, rather than relying on statistical relationships, can be more appropriate to capture infectious disease dynamics and how weather may influence them.

Public Health Implications

Unlike many previously published papers in which meteorological factors have been associated with diarrheal disease (30, 39), in Chengdu, China we did not find an association regardless of whether it was before or after the seasonality shift beginning in January 2012. This lack of association and that the effect size was large for cases in the previous 4 weeks indicate transmission is primarily driven by prevalence. Further research will be needed to incorporate meteorological and other environmental factors into mechanistic or compartmental models or to encourage the use of other statistical methods that aim to understand the mechanisms behind the relationship of weather and diarrheal disease (72). Additionally, it could be possible that because of the context of

Chengdu, a large, developed city, the influence of weather on diarrheal disease incidence is not as important as it is in rural areas or less-developed cities.

Conclusion

In Chengdu, China from 2005 to 2016, there was no association of average temperature, extreme precipitation, or relative humidity with diarrheal disease cases, regardless of whether it was before or after the shift in seasonality that began in January 2012. Further research that includes both infectious disease dynamics and meteorological factors is needed to identify other drivers may have contributed to the shift in seasonality of diarrheal disease cases.

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Figures and Tables

Figure 1. Map of Chengdu metro area (bright red), within Sichuan province (blue) in China (inset).

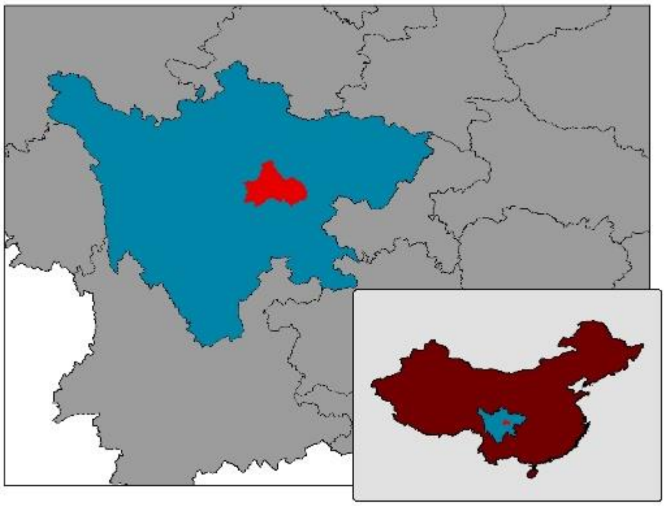


Table 1. Descriptive Statistics for Diarrheal Disease Cases from 2005-2018 in Chengdu, Sichuan Province

	n	**%**
Total Cases	79,633	---
Sex		
Male	44,952	56.5%
Female	34,681	43.6%
Age		
0-1	39,545	49.7%
2-4	8,527	10.7%
5-14	7,796	9.8%
15-24	3,978	5.0%
25-34	3,751	4.7%
35-44	4,079	5.1%
45-54	3,408	4.3%
55-64	3,564	4.5%
65+	4,985	6.3%

Figure 2. Plot of weekly cases of diarrheal disease in Chengdu from 2005 to 2016

This plot shows the number of weekly cases of diarrheal disease in Chengdu from 2005 to the end of 2016. There is a slight negative secular trend decreases 0.0097 cases per week ($p < 0.001$).

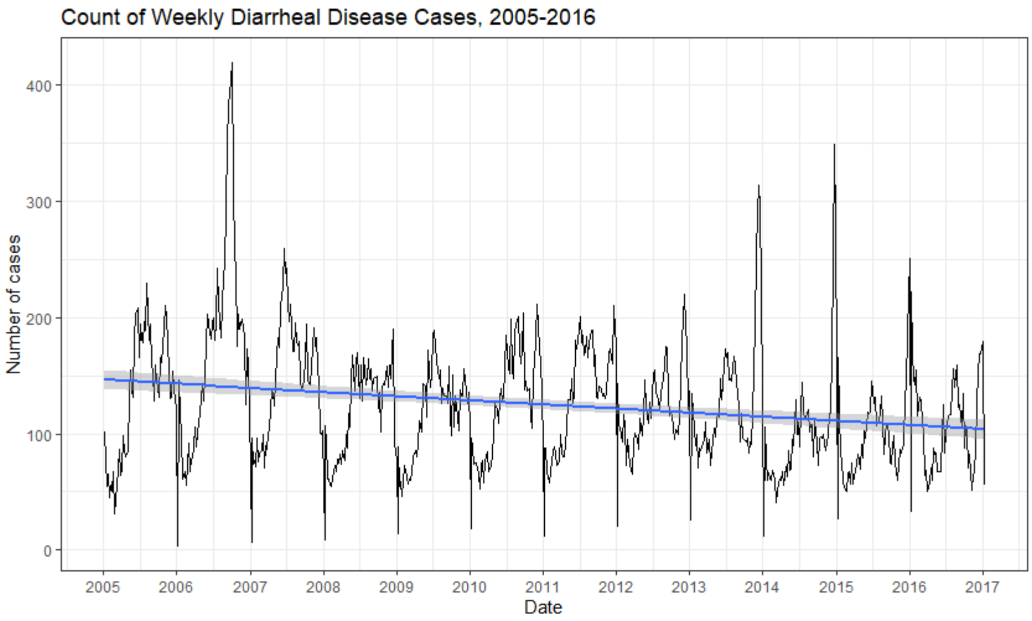
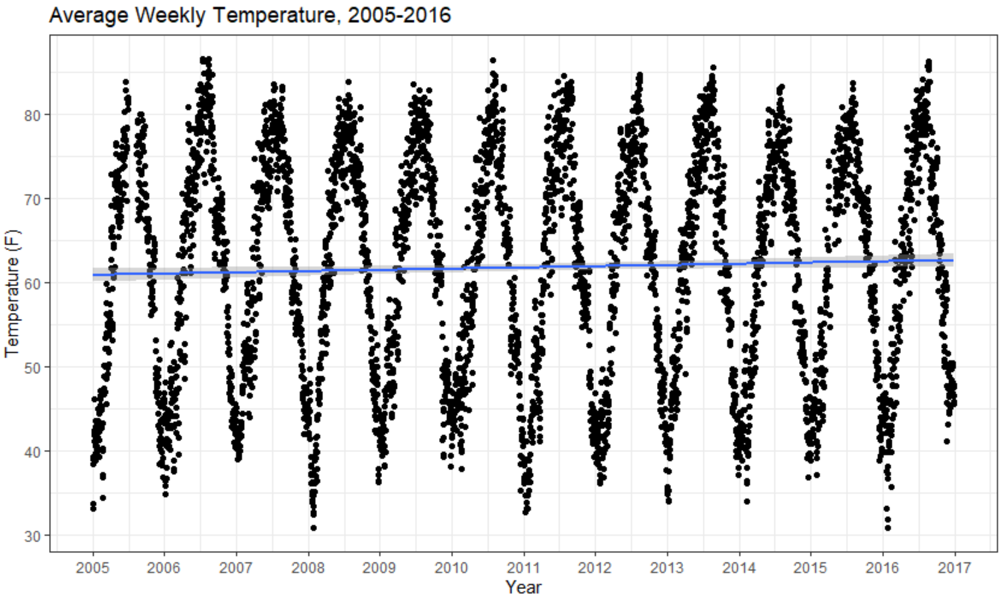
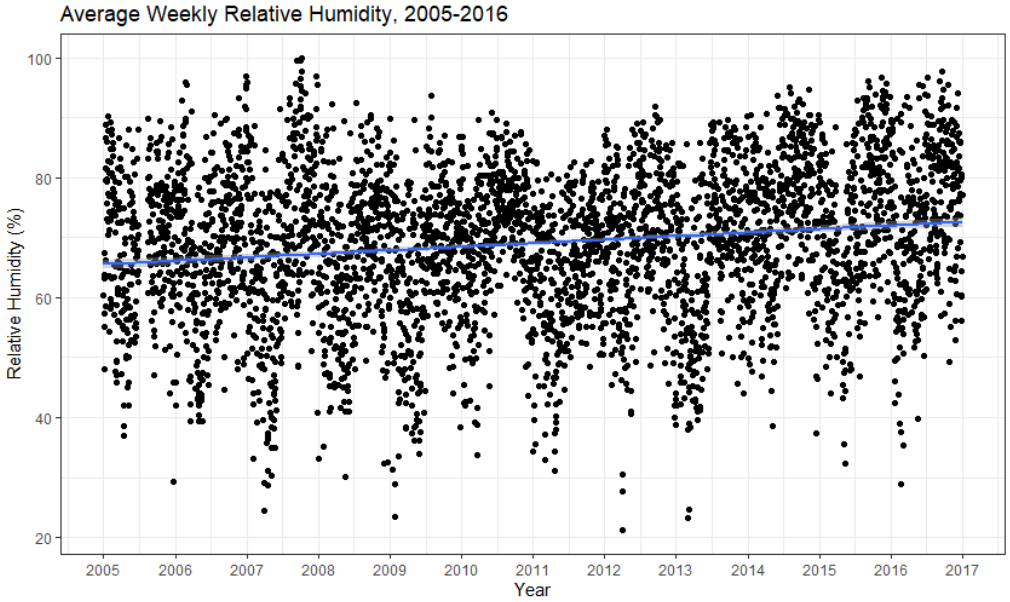


Figure 3 (a, b, c, d).

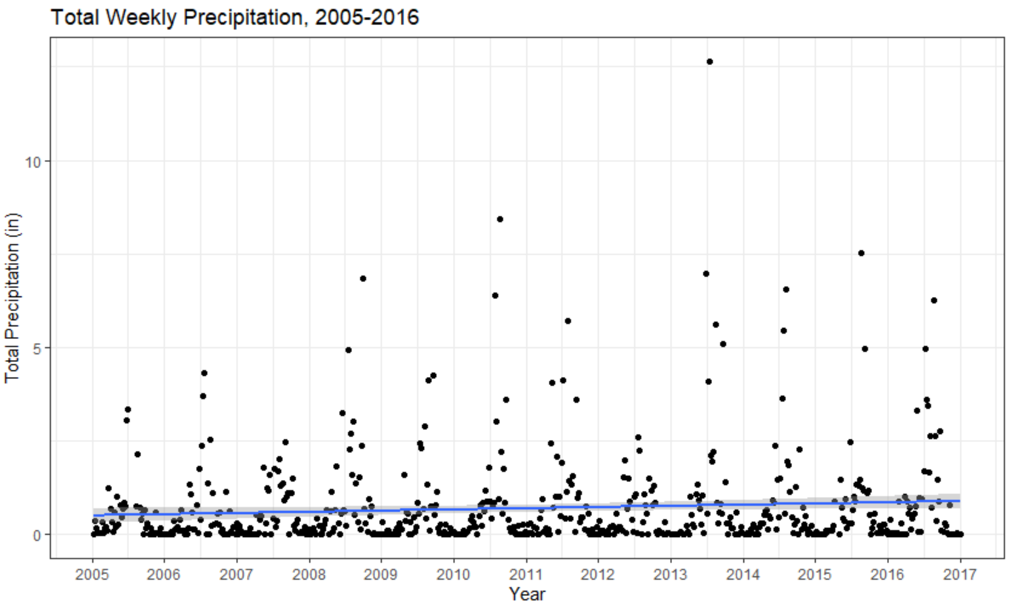
For each week, the temperature increased by 0.0004 degrees F (p = 0.01), relative humidity increased by 0.002% (p <0.001) and total precipitation increased by 0.00009 inches (p = 0.03). The number of weeks per year with at least 1 day of precipitation over the 80th percentile did not change from 2005 to 2016 (p = 0.61).



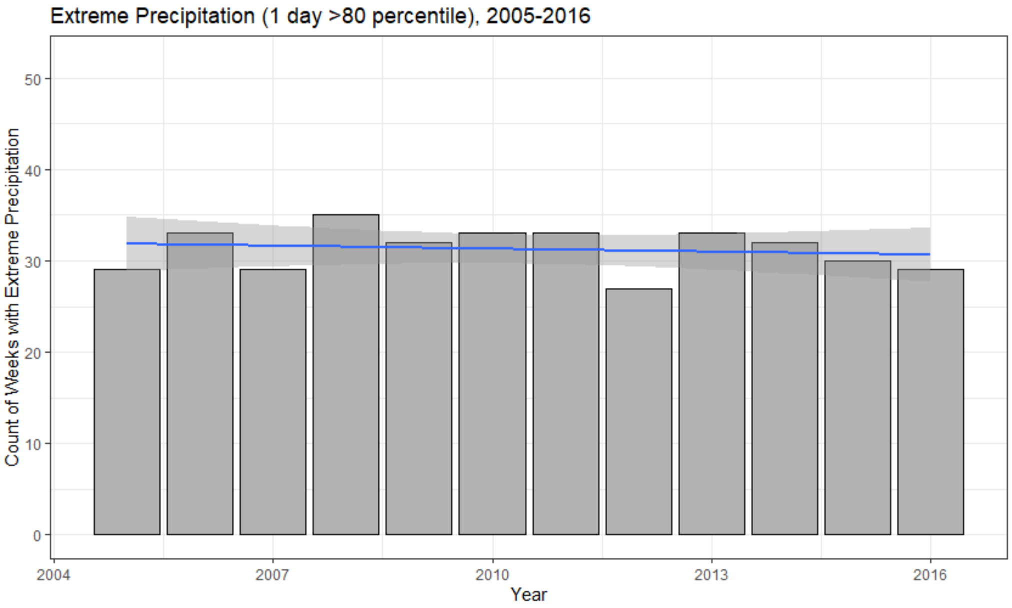
a.



b.


Total Weekly Precipitation, 2005-2016
Total Precipitation (in)
0
5
10
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year

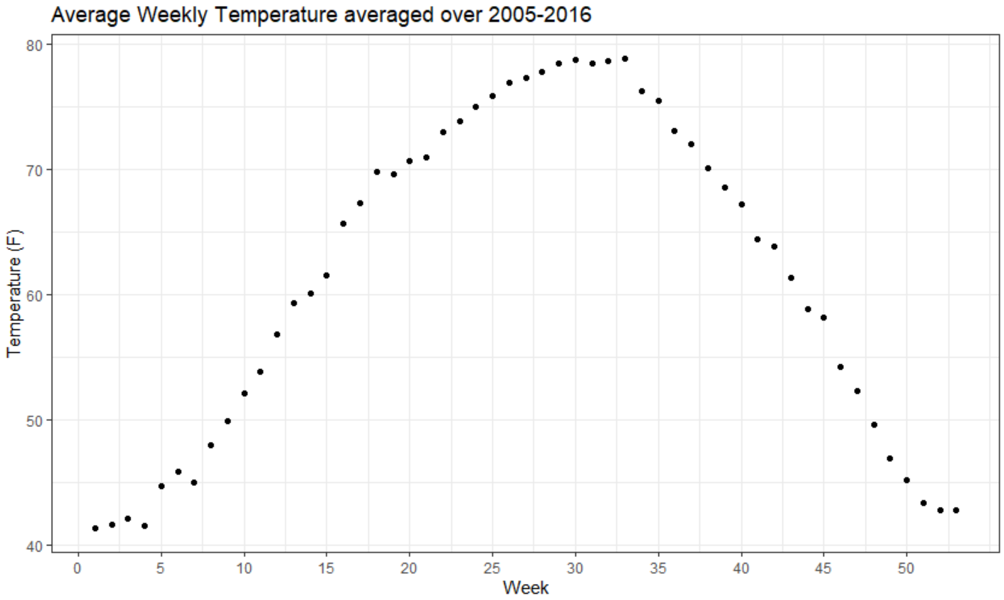
c.


Extreme Precipitation (1 day >80 percentile), 2005-2016
Count of Weeks with Extreme Precipitation
0
10
20
30
40
50
2004
2007
2010
2013
2016
Year

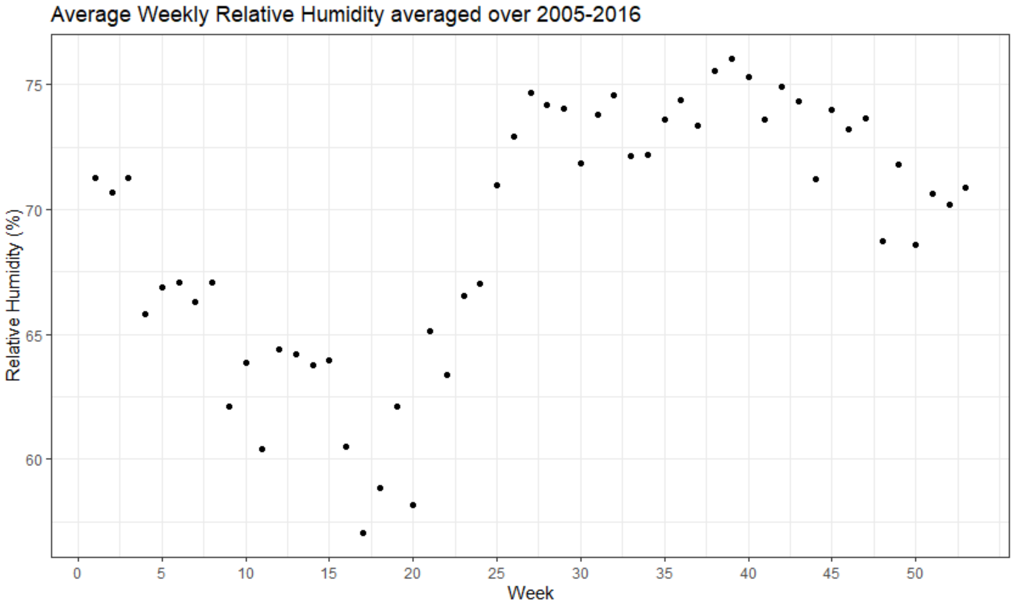
d.

Figure 4 (a, b, c).

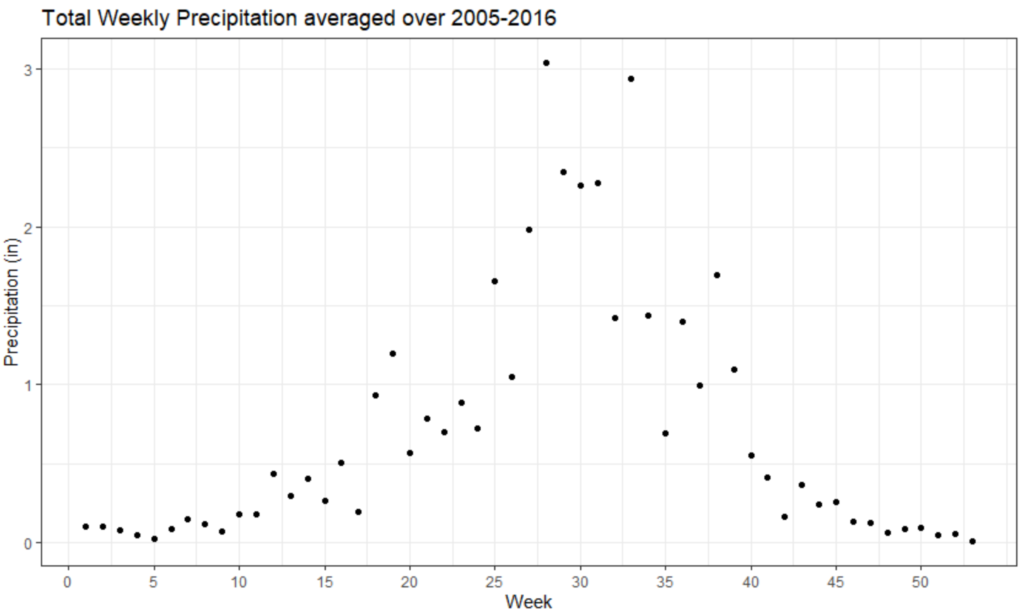
These plots show the distinct seasonality of weekly temperature, relative humidity, and total precipitation averaged over the years from 2005 to 2016. Average weekly temperature peaks in the summer months around 80 degrees F and is lowest in the winter months around 40 degrees F. Relative humidity is lowest around weeks 15-20, during late spring, and is highest in the summer months, around 75% humidity. Total weekly precipitation peaks in the summer months, around weeks 25-35 at a maximum of about 3 inches weekly.



a.



b.



c.

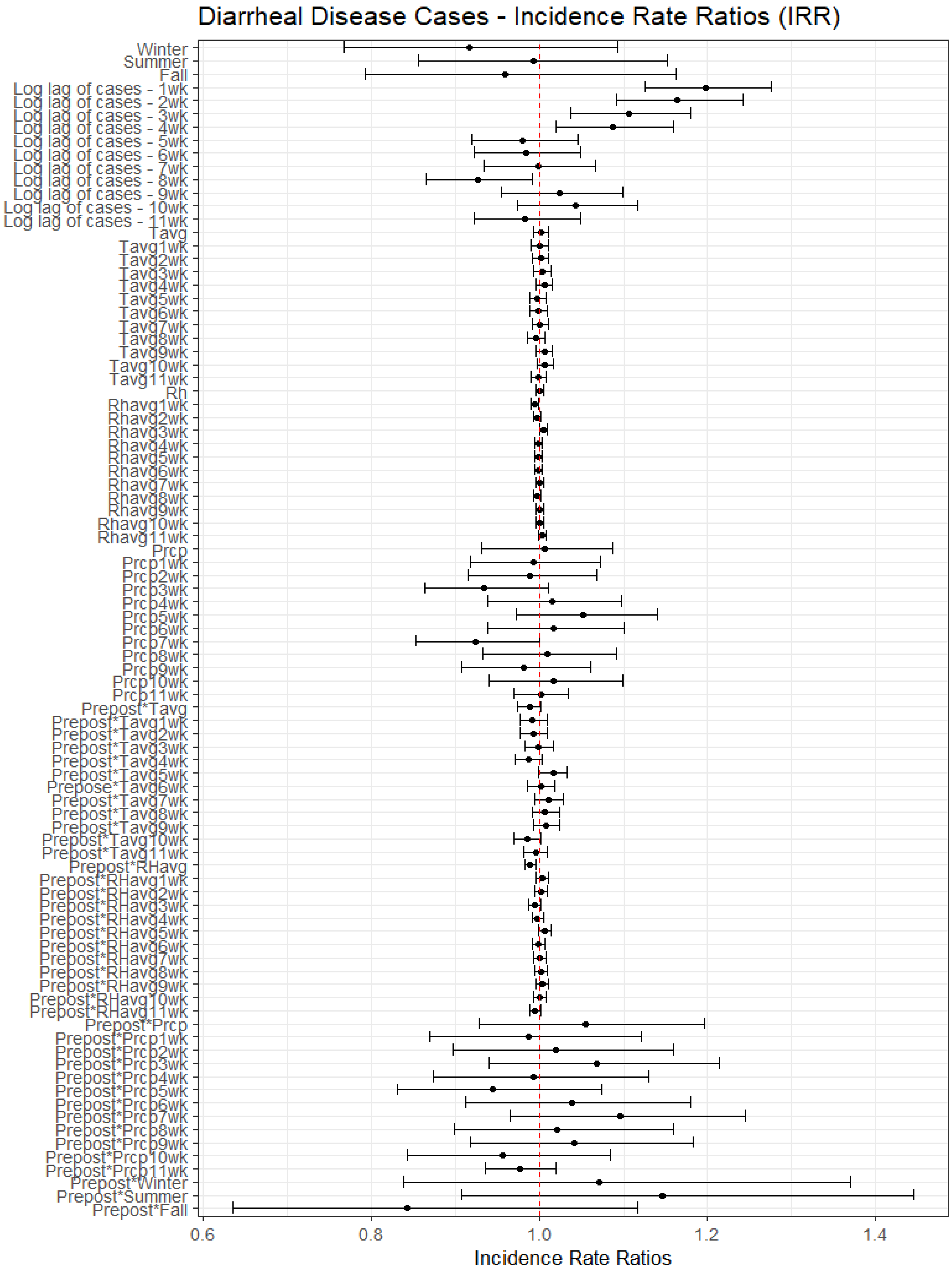
Table 2. Spearman Correlation Coefficients between meteorological factors and diarrheal disease cases.

	Case Count	Avg Temp	Avg RH
Avg Temp	0.12*	1	
Avg RH	0.01	-0.17*	1
80th Prcp	0.14*	0.51*	0.11*

* p-value < 0.05. Temp refers to average weekly temperature, RH refers to average weekly relative humidity, 80th Prcp refers to at least 1 day of precipitation over the 80th percentile during a week.

Figure 5. Incidence Rate Ratios and 95% Confidence Intervals

The red dotted line is an IRR of 1.0, indicating a null effect. The black dots are the incidence rate ratio estimates and the lines are the confidence intervals.



Appendix.

Appendix A. Incidence Rate Ratios and 95% Confidence Intervals

Variables	Incidence Rate Ratios	Lower Confidence Limit	Upper Confidence Limit
Intercept	4.734***	1.967	11.396
Winter	0.916	0.767	1.093
Summer	0.993	0.856	1.153
Fall	0.959	0.792	1.162
Prepost	3.547*	1.237	10.170
Log lag of cases - 1wk	1.198***	1.125	1.276
Log lag of cases - 2wk	1.164***	1.091	1.241
Log lag of cases - 3wk	1.106**	1.037	1.181
Log lag of cases - 4wk	1.088*	1.020	1.160
Log lag of cases - 5wk	0.980	0.919	1.045
Log lag of cases - 6wk	0.984	0.922	1.050
Log lag of cases - 7wk	0.998	0.934	1.067
Log lag of cases - 8wk	0.927*	0.865	0.992
Log lag of cases - 9wk	1.024	0.955	1.099
Log lag of cases - 10wk	1.043	0.974	1.117
Log lag of cases - 11wk	0.983	0.922	1.049
Tavg	1.001	0.993	1.010
Tavg1wk	1.000	0.990	1.010
Tavg2wk	1.001	0.991	1.011
Tavg3wk	1.003	0.993	1.013
Tavg4wk	1.006	0.996	1.016
Tavg5wk	0.998	0.988	1.008
Tavg6wk	0.999	0.989	1.009
Tavg7wk	1.001	0.991	1.011
Tavg8wk	0.996	0.986	1.006
Tavg9wk	1.006	0.996	1.016
Tavg10wk	1.006	0.997	1.016
Tavg11wk	0.999	0.990	1.008
Rh	1.000	0.996	1.005
Rhavg1wk	0.995*	0.990	0.999
Rhavg2wk	0.998	0.993	1.002
Rhavg3wk	1.004	1.000	1.009
Rhavg4wk	0.999	0.994	1.003
Rhavg5wk	0.998	0.994	1.003
Rhavg6wk	0.999	0.995	1.004
Rhavg7wk	1.000	0.996	1.005
Rhavg8wk	0.997	0.993	1.002
Rhavg9wk	1.000	0.996	1.005
Rhavg10wk	1.001	0.996	1.005
Rhavg11wk	1.004	0.999	1.008
Prcp	1.006	0.931	1.087
Prcp1wk	0.992	0.919	1.072
Prcp2wk	0.989	0.915	1.069
Prcp3wk	0.934	0.863	1.011
Prcp4wk	1.015	0.938	1.098
Prcp5wk	1.053	0.972	1.140
Prcp6wk	1.016	0.939	1.100
Prcp7wk	0.924	0.854	1.000
Prcp8wk	1.009	0.932	1.091
Prcp9wk	0.982	0.908	1.061
Prcp10wk	1.017	0.941	1.099
Prcp11wk	1.001	0.970	1.034
Prepost*Tavg	0.988	0.974	1.002
Prepost* Tavg1wk	0.992	0.976	1.009
Prepost* Tavg2wk	0.993	0.977	1.009
Prepost* Tavg3wk	0.999	0.983	1.016
Prepost* Tavg4wk	0.987	0.971	1.004
Prepost* Tavg5wk	1.016	0.999	1.033
Prepose* Tavg6wk	1.002	0.986	1.019
Prepost* Tavg7wk	1.011	0.995	1.028
Prepost* Tavg8wk	1.007	0.991	1.023
Prepost* Tavg9wk	1.008	0.993	1.025
Prepost* Tavg10wk	0.986	0.970	1.002
Prepost* Tavg11wk	0.996	0.981	1.010
Prepost* RHavg	0.989**	0.982	0.996

Prepost* RHavg1wk	1.004	0.996	1.011
Prepost* RHavg2wk	1.002	0.995	1.010
Prepost* RHavg3wk	0.994	0.987	1.001
Prepost* RHavg4wk	0.998	0.991	1.005
Prepost* RHavg5wk	1.007	1.000	1.014
Prepost* RHavg6wk	0.998	0.991	1.006
Prepost* RHavg7wk	1.000	0.993	1.007
Prepost* RHavg8wk	1.002	0.995	1.009
Prepost* RHavg9wk	1.003	0.996	1.010
Prepost* RHavg10wk	1.000	0.993	1.007
Prepost*RHavg 11wk	0.995	0.988	1.002
Prepost*Prcp	1.054	0.929	1.197
Prepost* Prcp1wk	0.987	0.869	1.121
Prepost* Prcp2wk	1.020	0.897	1.159
Prepost* Prcp3wk	1.068	0.941	1.214
Prepost* Prcp4wk	0.994	0.874	1.130
Prepost* Prcp5wk	0.945	0.831	1.074
Prepost* Prcp6wk	1.038	0.913	1.181
Prepost* Prcp7wk	1.096	0.965	1.245
Prepost* Prcp8wk	1.020	0.898	1.159
Prepost* Prcp9wk	1.042	0.918	1.183

*Indicates p-value less than 0.05. ** indicates p-value less than 0.01. *** indicates p-value less than 0.001.