Precipitation Associated with Increased Diarrheal Disease in Mozambique; A Time Series Analysis

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ABSTRACT

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Background

Diarrheal diseases are a leading cause of morbidity and mortality in Africa. Though research has shown diarrheal diseases to be impacted by weather, there is limited evidence of this association in sub-Saharan Africa and no studies conducted in Mozambique. Our study aimed to determine if variation in diarrheal disease counts was associated with precipitation in Mozambique. Estimating this association is the first step in an effort to determine whether the relationship is robust enough to support developing an early warning system to improve health system preparedness and response, and to project future burdens of diarrheal disease associated with climate change.

Methods

Weekly diarrheal disease data were available for 1997-2014 from the Mozambique Ministry of Health (n = 7,324,661). We estimated the association between cases of disease and precipitation, defined as the number of wet days (precipitation > 1mm) per week, in each of Mozambique's four regions, comprising a total of 141 districts. Time series analyses were conducted using a distributed lag Poisson regression model. Models were adjusted for time, maximum temperature, and district.

Results

Using a four-week lag, chosen *a priori*, we found that precipitation was associated with diarrheal disease in adjusted models. One additional wet day in a week was associated with a 1.86% (95% CI: 1.05-2.67%), 1.37% (95% CI: 0.70-2.04%), 2.09% (95% CI: 1.01-3.18%), and 0.63% (95% CI: 0.11-1.14%) increase in diarrheal disease in Mozambique's northern, central, southern, and coastal regions, respectively.

Conclusions

Our study indicates a strong association between diarrheal disease and weather. Additional diarrheal prevention efforts should be targeted to areas with increased rainfall. As climate change increases the number of wet days and heavy precipitation, the burden of diarrheal disease in Mozambique may increase unless additional health system interventions are undertaken.

INTRODUCTION

Sub-Saharan Africa is projected to be highly affected by climate change (Vance et al. 2013). Climate variability and change present current and future risks to human health in this region where many countries have high exposure to climate-related hazards as well as low capacity to manage the associated risks (WHO). Increases in precipitation are one possible consequence of climate change. Changes in precipitation and temperature not only alter the geographic range, pathogenicity, seasonality, and survival of disease causing pathogens, but may also increase human exposure and jeopardize the infrastructure necessary to prevent disease transmission (Carlton et al. 2016). Diarrheal diseases are amongst a wide range of health outcomes sensitive to weather and climate and are already of significant concern in sub-Saharan Africa. Kolstad and Johansson (2011) estimated that by the end of the 21st century, climate change might increase the relative risk of diarrhea in Southern Africa by more than 20 percent.

Transmission pathways through which precipitation operates to increase diarrheal disease are broad and complex and rainfall variability can influence diarrheal disease in many ways. Flooding, often due to heavy precipitation, is linked to increased diarrheal disease prevalence (IPCC 2007). Rainfall runoff and flooding can lead to human exposure to pathogens by flushing pathogens from environmental reservoirs or fecal matter into freshwater supplies (Hashizume et al. 2007, Vance et al. 2013, Singh et al. 2001, and Tornevi et al. 2015). In contrast, water scarcity can necessitate consumption of unsafe water as well as decrease hygienic practices, increasing diarrheal disease (Bandyopadhyay et al. 2011).

Owing to these impacts of rainfall variability, studies have found an increased numbers of cases associated with both high and low rainfall, the dry and wet seasons, below average rainfall, heavy rains, and rainfall shocks (deviations from the long-term average) (Vance et al. 2013; Carlton et al. 2016; Rabassa et al. 2014; Tornheim et al. 2010).

Although diarrheal diseases are considered a leading cause of morbidity and mortality in Africa, the quantity of evidence examining the association between climate and these diseases in sub-Saharan Africa is low (Amegah et al. 2016; Smith et al. 2014). No studies have examined the association between precipitation and diarrheal disease in Mozambique, a country with over seven million cases of diarrheal disease reported between 1997 and 2014 (IHME). Diarrheal disease was the country's fifth leading cause of death as well as fourth leading cause of death and disability combined in 2015 (IHME). In 2013, diarrheal disease was responsible for 13 percent of the country's under-five deaths (WHO).

This study sought to better understand the role that precipitation plays in diarrheal disease in Mozambique using 18-years of data at a weekly resolution with confounders measured over that same time scale. Specifically, our study seeks to understand the short-term association between precipitation and diarrheal disease at the weekly timescale. Understanding this association will allow for improved policies and programs to support prevention of diarrheal disease, an important cause of mortality. Specifically, developing an early warning system for extreme precipitation events may improve health system preparedness and response with the goal of reducing the burden of diarrheal diseases in Mozambique and other nations.

METHODS

We used an ecologic study to better understand the role that precipitation plays in diarrheal disease in Mozambique. We conducted a time series analysis using weekly district-level precipitation estimates and weekly district-level total cases reported in Mozambique from 1997 through 2014.

The study was conducted in Mozambique, a country comprised of four regions, ten provinces, and more than 141[1] administrative districts (Figure 1A). Districts do not cross regional boundaries.

Though disease data collection began in 1989, years prior to 1997 were excluded due to incomplete reporting. Districts that did not report cases for a given week were considered missing. This study included the years 1997-2014 when on average, disease counts were reported by the districts more than 90 percent of all possible weeks (Figure 2A). Individual districts were included in the analysis if their reporting exceeded 85 percent during all the weeks of follow-up; as a result, four districts were excluded from the analysis.

Diarrheal disease counts are weekly aggregates of reported cases by each of the districts to the Mozambique Ministry of Heath reportable disease registry. Healthcare providers are required to track the number of patients seeking care for clinical diarrheal illness, routinely defined as the passing of three or more loose or liquid stools per day. These visits are tallied weekly at the clinic level and reported to the district for aggregation with other clinics, yielding a weekly total.

Precipitation was defined as the number days it rained, or 'wet days,' in a week. Wet days were defined as days for which precipitation met or exceeded one millimeter (mm), one of 27 indices developed by the World Meteorological Organization (WMO) Commission for Climatology and

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[1] The number of districts varied over the 18 years of follow-up, several districts were abolished, two split and more than 10 were formed.

the Expert Team on Climate Change Detection and Indices (ETCCDI) (CSAG 2016). Precipitation data come from the Climate Hazards Group InfraRed Precipitation with Stations (CHIRPS) dataset, which spans nearly worldwide with collection beginning in 1981 (Funk et. al). The CHIRPS dataset contains of daily rainfall data derived from a combination of satellite derived precipitation estimates or merged satellite data, model re-analysis data for large areas, and weather station rainfall data gridded to 0.05 x 0.05 degree spatial resolution. CHIRPS data are available daily for the period 1981-2014 and aggregated to the weekly level by the Climate System Analysis Group (CSAG).

Temperature data come from the Climate Research Unit (CRU), which utilizes more than 4,000 global weather stations (Harris et al., 2014). The data consist of weekly time series estimates of multiple temperature variables as far back as 1979, and are also gridded to 0.05 x 0.05 degree spatial resolution.

Time (year), temperature (degrees Celsius), and region/district were covariates included in the analysis.

The weather-diarrheal disease association of interest also varies temporally across weeks by season (medium-term trends) and years (long-term trends). According to the United States Agency for International Development (USAID) Technical Report on Climate Change and Health Systems in Mozambique, one such secular trend is that the country experienced higher rainfall intensity in more recent years compared with earlier years.

Temperature confounds the association as it often varies concurrently with precipitation and has been shown to influence diarrheal disease rates (Carlton et al. 2015).

Diarrheal disease counts vary from region to region. Further, each region has a different climate profile. There’s strong evidence that rainfall intensity varies spatially in Mozambique. The northern parts of the country receive appreciably more annual precipitation that the southern parts and the driest parts of the country are in the southwest (CSAG 2016).

Rate ratios (RR) and 95% confidence intervals (CI) were calculated to estimate short-term (i.e. less than seasonal, or weekly) associations between weekly case counts of diarrheal disease and number of wet days (precipitation > 1mm) per week. We conducted a time series analysis and fit a generalized linear model (GLM) assuming a Poisson distribution in diarrheal disease counts and allowing for overdispersion (Gasparrini et al. 2010; Zhou et al. 2011). The RR values are exponentiated coefficients that represent the difference in the log of the expected counts comparing a one unit higher values (one additional wet day) to a one unit lower value. We can therefore interpret the RR as a percent difference.

Our *a priori* decision to lag the wet day variable by four weeks was informed by prior research (Alexander et al. 2013 and Tornheim et al. 2010). Using 30 years of diarrheal and climate data in Botswana and a stepwise variable selection procedure that included rainfall, Alexander and colleagues' (2013) found that climatic variables most accurately predicted diarrheal disease at a one-month lag. Our lag was incorporated using an unconstrained distributed lag model with all lagged wet day variables from zero to four weeks in the model simultaneously (Bhaskaran et al. 2013).

We fit one model at the national level to estimate a countrywide association. This model adjusts for time, temperature, and region. Owing to the country's spatial variation in precipitation and disease burden, we fit separate models for all four regions of Mozambique. This region-stratified model controlled for time, temperature, and district. Inclusion of district as an indicator variable allows control of additional heterogeneity and unmeasured factors such as other environmental, economic and social conditions.

Each model included a cubic smoothing spline for time (4 knots/year * 18 years = 72 degrees of freedom) to control for seasonality and long-term trends. Temperature was similarly controlled for using a cubic spline with a knot was placed every 5˚C (temperature minimum and maximum was 14˚C and 42˚C, respectively) and was not lagged (Hashizume et al. 2007, D'Souza et al. 2004, Naumova et al. 2006).

Sensitivity analyses for the degree of control/smoothing in both the time and temperature splines were conducted by halving and doubling the number of knots in each spline used in the main analysis. Our main analysis time spline contains four knots per year to allow for seasonal changes, so we fit the national model with a two-knot per year and eight-knot per year spline. Our temperature spline had a knot for each five degree Celsius difference, therefore we fit the national model with a temperature spline with knots every 2.5 and ten degrees Celsius.

Exploratory analyses were conducted to investigate the strongest lag (between 0-8 weeks) for the association between diarrheal disease and both precipitation and maximum temperature. Owing to associations found in prior literature, we fit a model to explore the association between temperature, defined as the week's highest maximum single day temperature, and diarrheal disease.

RESULTS

Country-wide descriptive statistics

Weekly observations for 18 years and 141 administrative districts resulted in 126,056 observations (4.5% of weeks missing). Diarrheal disease cases were reported on average in 50 (out of 52) weeks each year of follow-up. There were 7,324,661 reported cases of diarrheal disease between 1997-2014. Weekly diarrhea case counts reveal marked seasonality (Figure 1). Diarrheal disease peaks both nationally and in all four regions were observed during the wet season when tropical cyclones and the heaviest rainfall typically occur (CSAG 2016).

The highest weekly diarrhea case count in the dataset was 2,033, observed in the tenth week of the year, which is commonly when disease count peaked. The lowest weekly value of zero cases occurred in weeks when a given district reported no diarrhea cases for treatment. Counts of zero occur more frequently in the years prior to 2000.

There was an increasing trend of total diarrhea cases reported weekly over time. The mean weekly number of cases reported in 1997 was 24, whereas the mean weekly cases reported in 2014 is 63, however, case counts peaked in 2009 with an average of 85 cases reported each week.

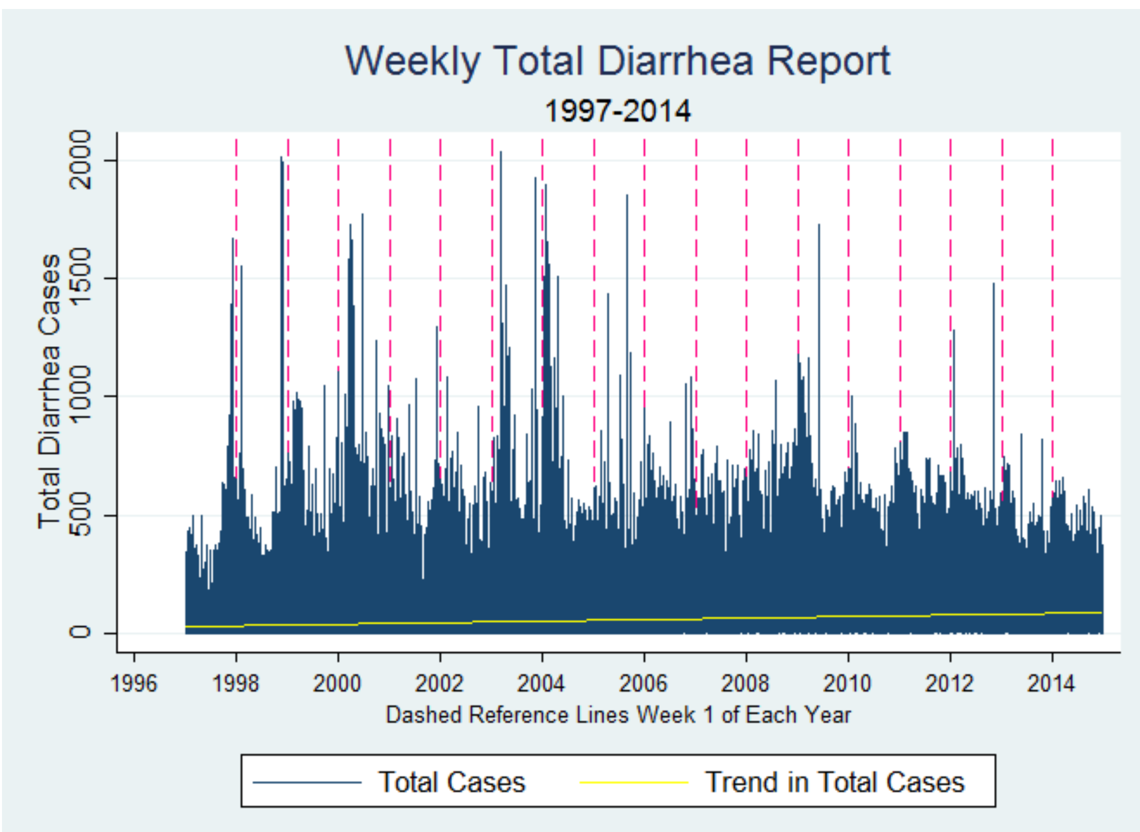

Figure 1. Time series graph of the total number of weekly reported diarrhea cases during the 18-year follow-up (x-axis). Pink lines indicate the first week of each year. The yellow line is the trend in case counts over time.

Temperature and precipitation also display pronounced seasonality (Figure 2). The average number of wet days per week in the country was 1.23 (sd 1.91), with on average 3.31 during the rainy season and nearly zero during the dry season[2]. Of note on the bottom graph of Figure 2 is the average maximum temperature that differs noticeably from the prominent pattern. These lower observations are from the Inhambane province in the southern region, which has minimum average maximum temperatures more than 3˚C lower than the other nine provinces. Descriptive statistics of diarrheal disease, precipitation and temperature are shown in Table 1.

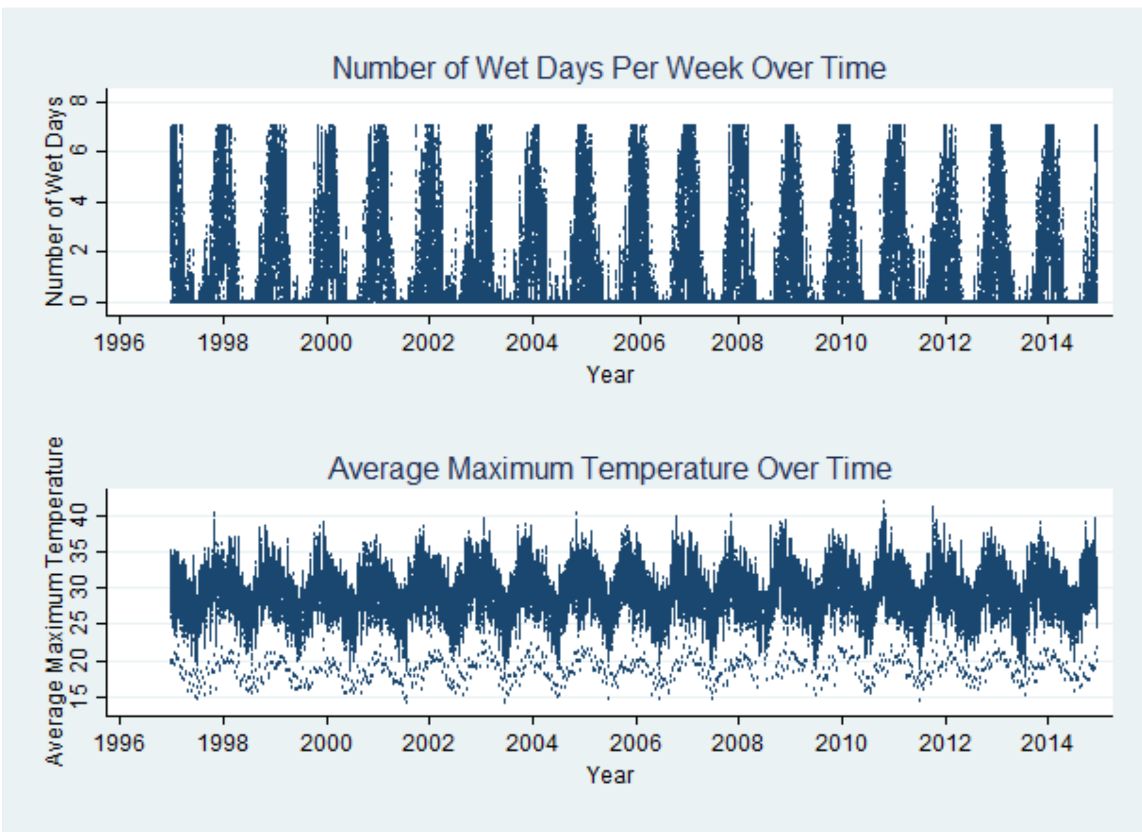

Figure 2. Time series data from 1997-2014. Top graph: Number of wet days per week over follow-up. Bottom graph: Average maximum temperature over time.

[2] Rainy season calculated as weeks 1-8 and 49-52 of the year, to approximate the wettest months of December, January, and February. The dry season was calculated as weeks 26-37 to approximate June, July, and August.

Table 1: Univariate descriptive statistics of weekly reported values during 1989-2014.

	N	Min	Max	Mean	SD
Total diarrhea Cases	126,118	0	2033	59	81
Number of Wet Days	126,118	0	7	1	2
Maximum Temperature ˚C	126,056	15.05	45.25	32.50	3.45

Regional descriptive statistics

While all regions appeared to have their largest annual disease peaks around late February and early March, which marks the end of the summer months (December, January, and February), and some of the warmest temperatures of the year occur, the seasonality of disease varied by region (Figure 3).

The northern and central regions exhibited strong seasonality, with bimodal disease peaks occurring around February and October of each year. The coastal region had a single pronounced disease peak in late February/early March and a less prominent, if any, increase in disease later in the year towards October, November, and December. Lastly, the southern region showed little seasonality with a slight disease increase around March and April, but less variability throughout the year.

All four regions appeared to have their lowest mean disease counts in the middle of the year, corresponding with the cooler, dry winter months of June, July, and August, when the monthly mean temperature often drops below 20°C. The northern region appeared to have the earliest trough beginning in May, while the other regions appeared to have their lowest disease burdens a month or two later in June and July.

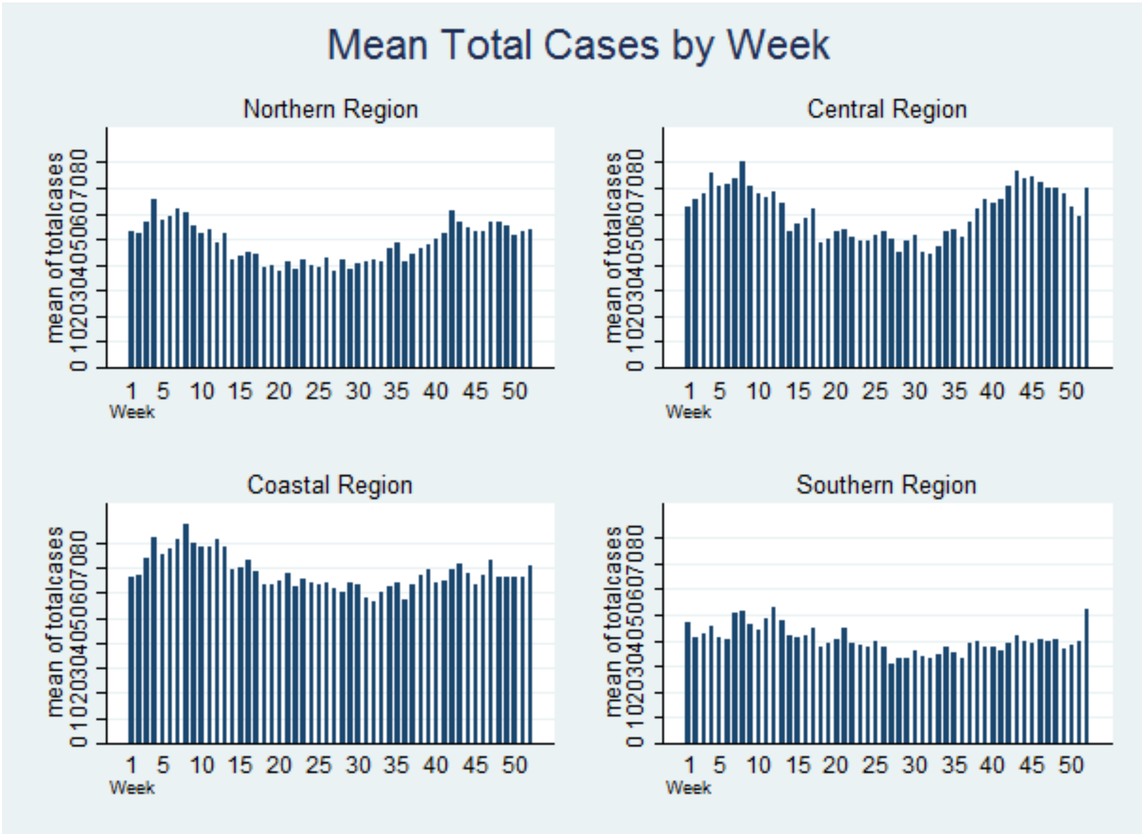

Figure 3. Seasonality of diarrheal disease in Mozambique. Mean diarrheal disease cases by week of year and region.

There was precipitation heterogeneity across regions as well (Table 2). The northern region was the wettest, with an average of 1.62 days per week and a mean weekly precipitation of 20.87mm. The southern region was the driest region across all precipitation indicators. Seasonality of the number of wet days by region is shown in Figure 4. During the wet season, the northern region experienced weeks that averaged more than 5 wet days throughout all 18 years of follow-up. The central region followed with more than 4 wet days during the wettest weeks. The coastal and southern regions wettest weeks experienced between 2 and 3 wet days per week during the wettest weeks. All regions averaged less than one wet day per week in the dry summer months.

Table 2. Regional summary statistics of weekly reported precipitation values in each of Mozambique's four regions.

	Number of Wet Days	Wettest Day (mm)	Total Precipitation (mm)
	mean (SD)	*mean (SD)*	*mean (SD)*
Northern	1.62 (2.29)	8.50 (12.52)	20.87 (33.50)
Central	1.29 (1.98)	8.58 (14.17)	18.63 (34.30)
Coastal	1.01 (1.62)	8.74 (16.15)	16.18 (32.99)
Southern	0.82 (1.26)	7.10 (12.88)	11.39 (23.39)

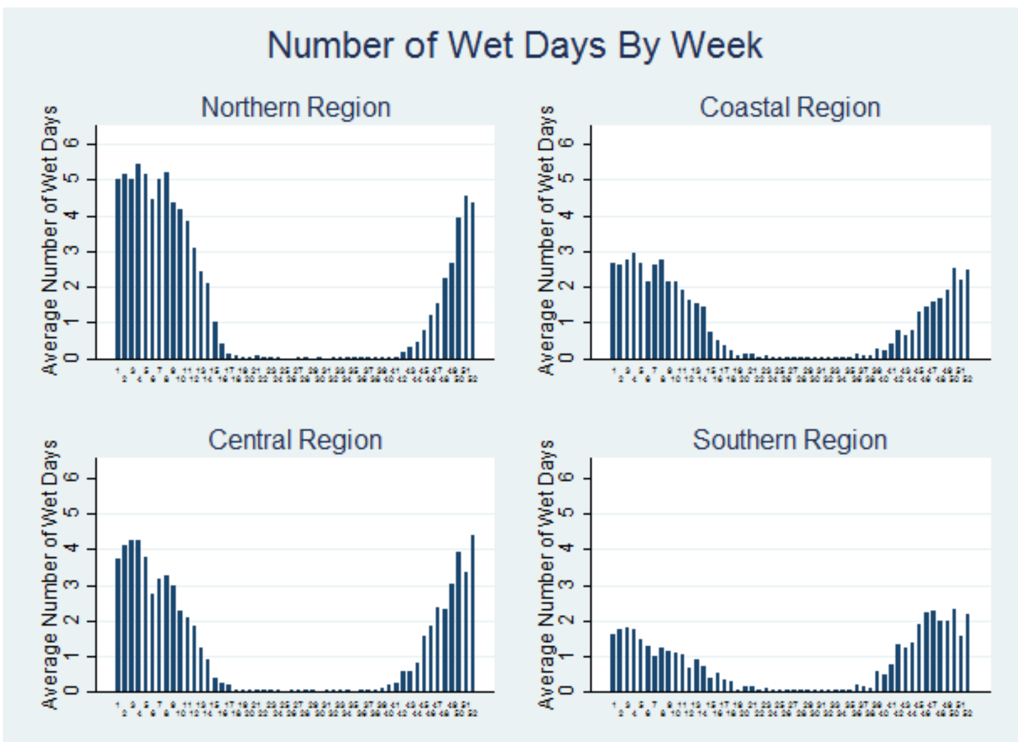

Figure 4. Average number of wet days by week number, 0-52 (x-axis) in Mozambique's 4 regions.

Regression Models

Our national model estimates that each additional wet day in a given week is statistically significantly associated with diarrheal disease, controlling for time, average high temperature, and the region. We estimated a 1.04% increase (RR = 1. 0104) in diarrheal disease counts for each additional wet day (Table 3 and Figure 5).

This national estimate masks, and arguably insufficiently controls for, the considerable heterogeneity in both diarrheal disease burden and precipitation across Mozambique. As such, we fit our regional model and found evidence of a larger association between wet days and diarrheal disease in the northern, central, and southern regions. One additional wet day was statistically significantly associated with a 1.86%, 1.37% and 2.09% increase in diarrheal disease in the northern, central and southern regions, respectively. In the coastal region, one additional wet day was associated with a 0.63% increase in diarrheal disease.

Table 3. National and regions rate ratios (RR) estimates. Estimating the association between number of wet days (precipitation>1mm)† and weekly total cases of diarrheal disease reported in Mozambique, 1997 – 2014

	RR	95% CI LL	95% CI UL
National*			
	1.0104	1.0042	1.0166
Regionalˆ			
Northern	1.0186	1.0105	1.0267
Central	1.0137	1.0070	1.0204
Coastal	1.0063	1.0011	1.0114
Southern	1.0209	1.0101	1.0318

CI = 95% confidence interval; LL = lower limit; UL = upper limit
*Controlling for time, average high temperature and region
ˆControlling for time, average high temperature and district
†Four-week lagged association with zero to four weeks in the model simultaneously

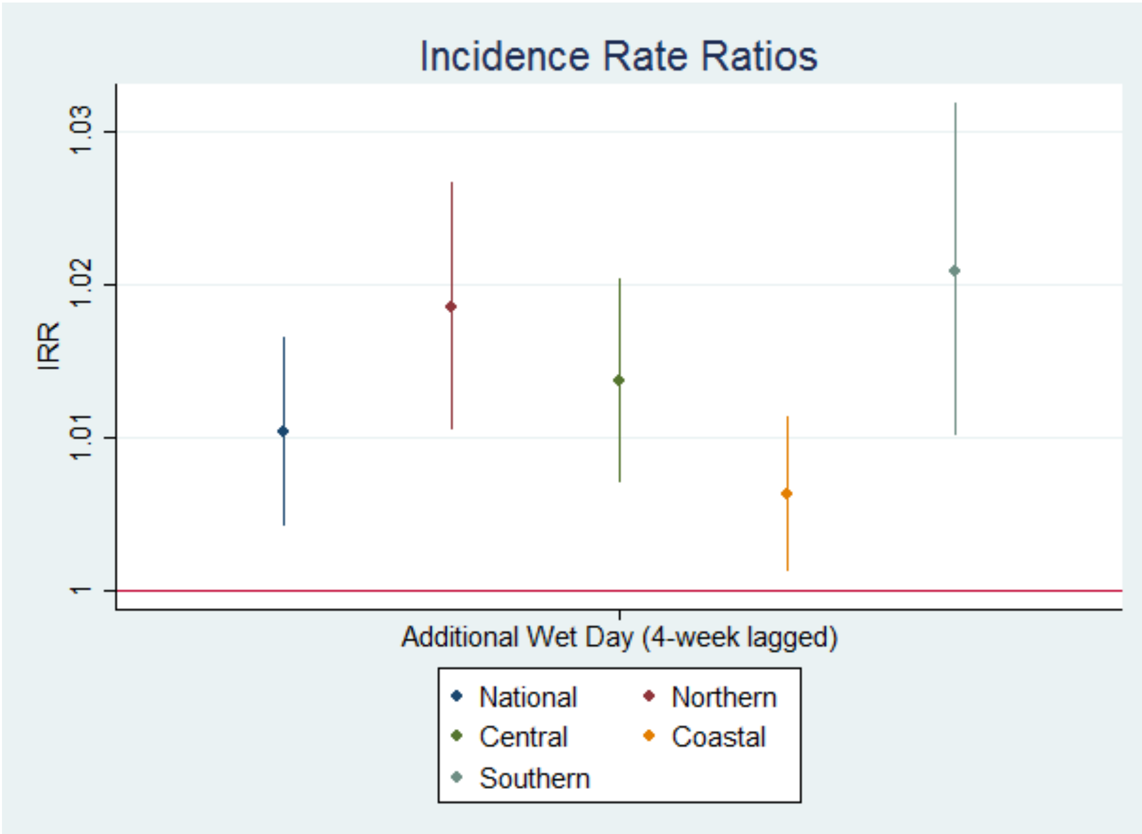

Figure 5. Rate Ratios of diarrheal disease associated with precipitation, lagged four weeks. Lines extend to 95% confidence interval for each estimate. Results are shown for each additional wet day in a model adjusted for time, temperature, and district.

Sensitivity Analyses

To determine if our results were robust to choices made in model fitting at the national level, we performed two sensitivity analyses by changing the way time and temperature splines were modeled. Model estimates were robust to both halving and doubling of the number of knots controlling for temperature (Table 7).

Table 7. Sensitivity analysis for the degree of smoothing in the temperature spline for the association between precipitation and diarrheal disease using the national model. Rate ratio (RR) estimate for the final model fit with one knot per 5 degree Celsius change in temperature. Below that are model estimates for halving (one knot per 10˚C) and doubling (one knots per 2.5˚C) spline flexibility.

Model*	RR	95% CI LL	95% CI UL
Less Flexible *1 knot/10˚C*	1.0108	1. 0046	1. 0170
Final Model *1 knot/5˚C*	1.0104	1. 0042	1. 0166
More flexible *1 knot/2.5˚C*	1. 0102	1. 0041	1. 0164

CI = 95% confidence interval; LL = lower limit; UL = upper limit
*Controlling for time, average high temperature and region

Estimates, however, were sensitive to changes in the control of time. Increases in the number of knots per year in time's cubic spline resulted in a decreased estimated association, which lost significance and appeared to level off at 8 knots per year (Figure 6). Estimate sensitivity to time control confirms that it is indeed a strong confounder in this analysis. We felt that 4 knots per year was sufficient to remove confounding effects of seasonality in a sensible way without overcontrolling.

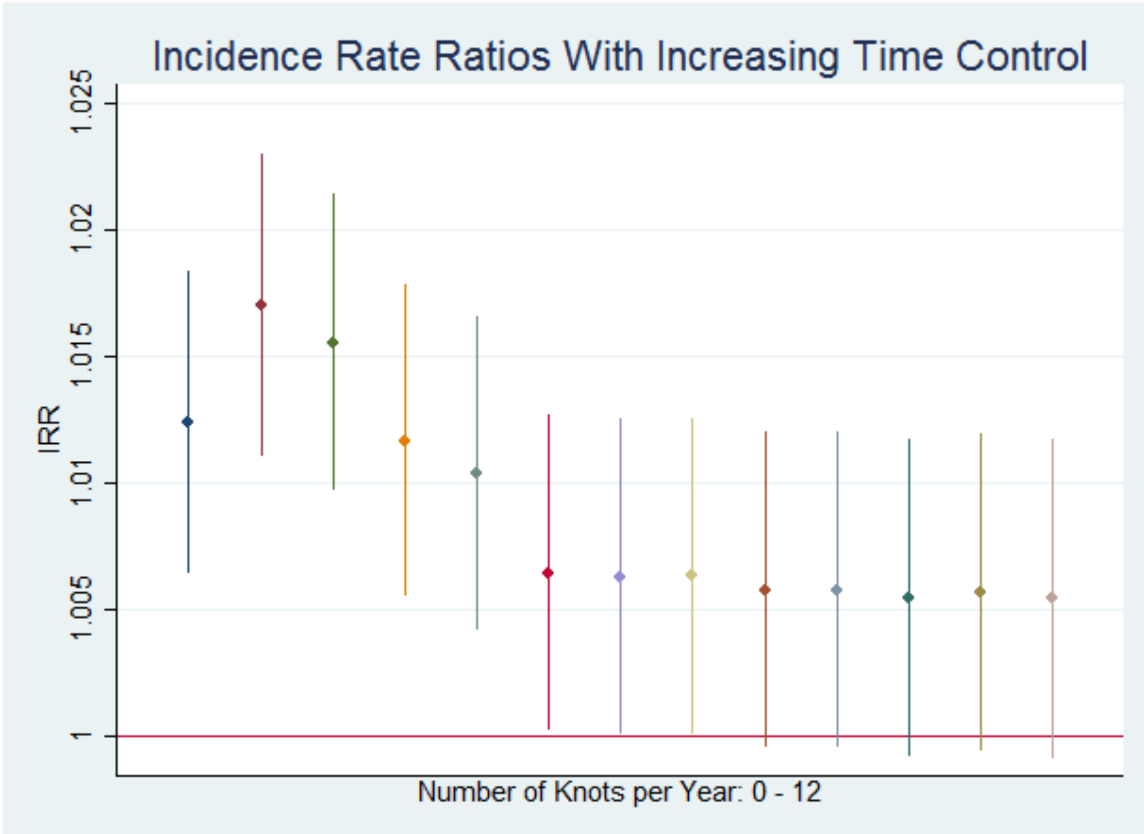

Figure 6. Rate Ratios (and 95% confidence intervals) of diarrheal disease associated with precipitation at the national level with increasing control of time, 0-12 knots per year (left to right). As a sensitivity analysis, time is adjusted for with varying control by altering the number of knots per year. Estimates are sensitive to changes in time adjustment. All estimates control for time (varyingly), temperature, and region.

Exploratory Analyses

Precipitation Lag

Consistent with prior research and to allow for pathogen incubation, illness presentation, and the subsequent clinical visit requirement to be included as a case count, it was decided *a priori* to lag the wet day variable four weeks. To test our *a priori* decision to use a four-week lagged association, we estimated RRs (with 95% CIs) for lags from zero-eight weeks in our national model, controlling for time, average maximum temperature, and region (Figure 7). Consistent with existing studies, the four-week lag had the strongest association between wet days and diarrheal disease.

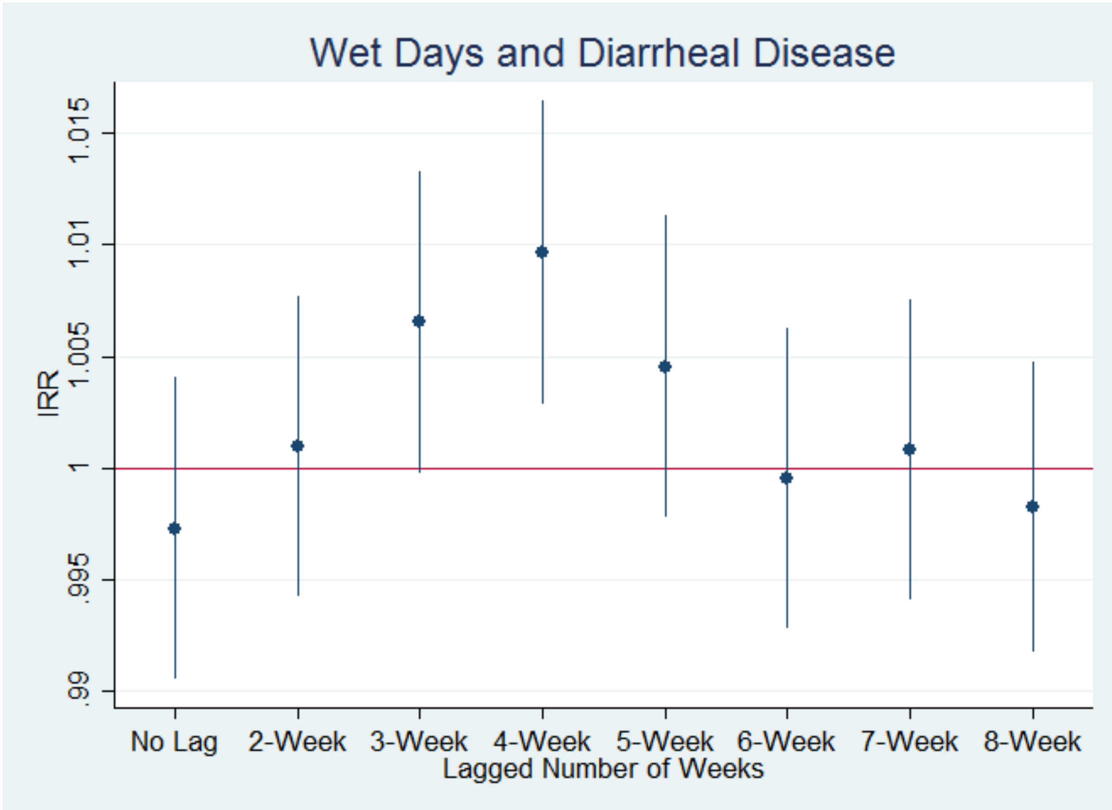

Figure 7: Rate Ratios and 95% confidence intervals for diarrheal disease associated with precipitation at various lags (0-8 weeks), controlling for time, average maximum temperature, and region.

Temperature Lag

Existing literature has displayed an association between temperature and diarrheal disease. Specifically, Carlton et al.'s (2015) global systematic review of temperature and diarrheal disease found all-cause diarrheal disease and bacterial diarrhea to be positively associated with ambient temperature. Their meta-analysis estimated a seven percent increase in all-cause diarrheal disease for each degree Celsius increase in temperature. Bandyopadhyaya et al.'s (2012) examination of temperature and childhood diarrhea in 14 sub-Saharan African countries found a one degree Celsius increase in the average maximum temperature to increase diarrhea prevalence by one percent. One explanation as to how high temperatures may increase diarrheal disease is that warmer temperatures cause increased pathogen proliferation in food and water sources. (Singh et al. 2001 and D'Souza, et al. 2004).

Much like precipitation, there is often a lagged relationship between temperature and diarrheal disease. Prior studies have used temperature lags ranging from zero to eight weeks when examining all-cause diarrheal disease (Carlton et al. 2016). Bandyopadhyaya et al. (2012) and Vance et al. (2013) used a four-week lag for their studies of temperature and diarrheal disease in sub-Saharan Africa and Botswana, respectively. However, others have found the strongest association during the same week (Hashizume 2007). As such, we began our exploration by examining various lags to determine the strongest association between diarrheal disease and temperature in our data. We fit our national model with temperature as the predictor of interest and distributed lags of zero to eight weeks (all of the lagged terms are included in the model simultaneously). Our data had the largest association at no lag (Figure 8).

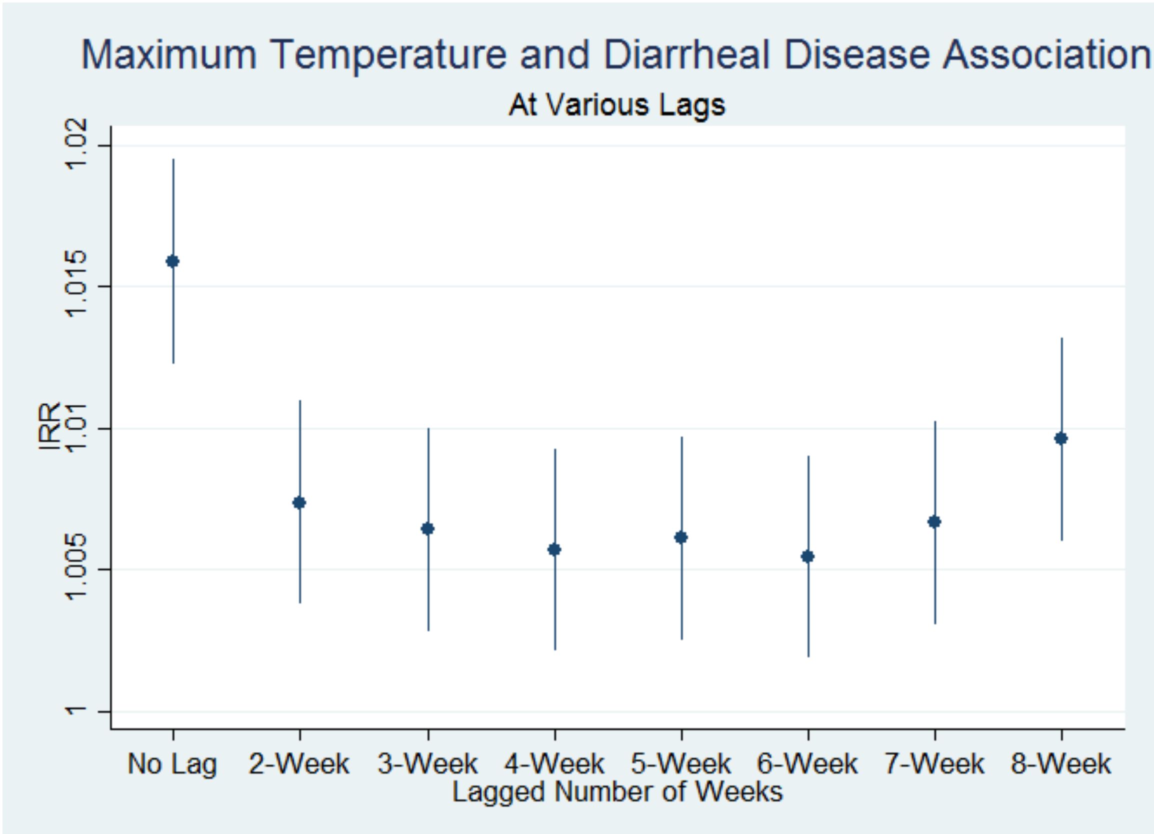

Figure 8: Rate Ratios and 95% confidence intervals for diarrheal disease associated with maximum temperature (˚C) at various lags (0-8 weeks), controlling for time, average maximum temperature, and region.

Temperature Association

Informed by our findings that the strongest association between maximum temperature and diarrheal disease was at no lag, we estimated this association in the concurrent week using our national and regional models. These models adjusted for time and region/district. However, rather than temperature adjustment, the number of wet days was adjusted for using a cubic spline.

The national model estimated that each one degree C increase in the hottest day of the week was associated with a 3.64% increase in diarrheal disease during the concurrent week (95% CI: 3.35, 3.93%).

Regional estimates varied. We observed a 1.45% (95% CI: 0.77, 2.13), 1.87% (95% CI: 1.44, 2.30), 5.74% (95% CI: 5.18, 6.29), and 2.15% (95% CI: 1.51, 2.80) increase in diarrheal disease in the northern, central, coastal, and southern regions, respectively, associated with each one degree C increase in maximum temperature (Figure 9). The coastal region is perhaps the most sensitive to increases in temperature because it has the lowest average maximum temperature of all four regions, as well as the smallest range between it's highest and lowest maximum temperatures.

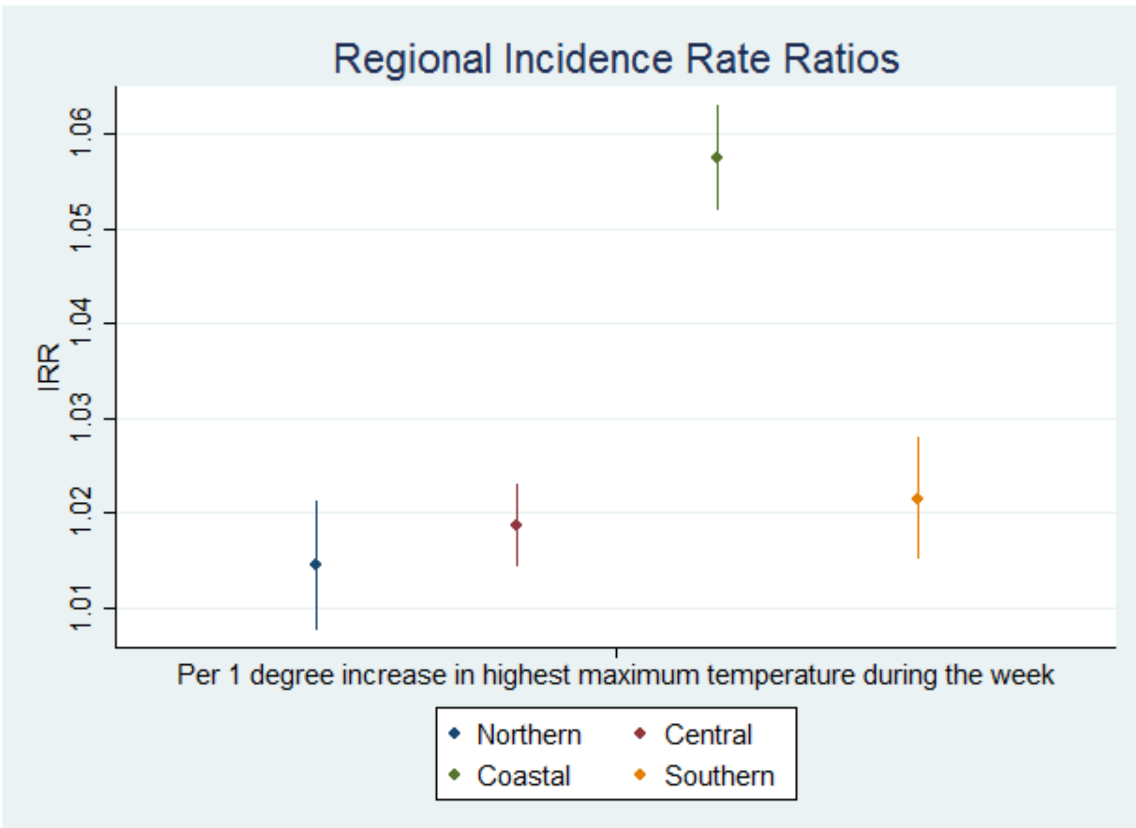

Figure 9. Rate Ratios and 95% confidence intervals for diarrheal disease associated with maximum temperature (˚C) in Mozambique's four regions, controlling for time, number of wet days, and district.

DISCUSSION

Our results indicate that in Mozambique, precipitation is positively associated with diarrheal disease. This association was found nationally and in all four regions, to varying degrees. These analyses suggest that without implementing additional interventions, the number of cases of diarrheal disease would be expected to increase over coming decades if there is an increase in the number of wet days as climate change alters precipitation patterns.

Exploratory analyses of the association between maximum temperature and diarrheal disease also revealed a significant positive association nationally and in all four regions. Interestingly, while the coastal region's diarrheal disease burden had the smallest association with an additional wet day, its RR was the most sensitive to an increase in the maximum temperature. There are a range of reasons why this might be the case, including warmer weather behavioral changes that may increase transmission of diarrheal diseases and the replication rate and transmission cycle for the causative pathogens in different regions. However, these results must be interpreted with caution as they are purely exploratory and were not pre-specified. We're unable to interpret any further.

Though research has shown diarrheal diseases to be impacted by weather, existing studies have revealed pronounced heterogeneity in the association between all-cause diarrhea and precipitation and there is limited evidence of this association in sub-Saharan Africa.

Increased diarrheal disease following precipitation events represents a burden on health systems to treat these additional cases, which climate change is expected to exacerbate as it alters the hydrological cycle. Climate change will continue to increase heavy precipitation events in Mozambique, suggesting that the country can expect to see additional cases of diarrheal disease if no additional interventions are implemented. The magnitude and pattern of future burdens of diarrheal disease will depend on the magnitude and patterns of changes in weather and climate in the four regions of Mozambique, the rate of population increase, the effectiveness of efforts to increase access to safe water and improved sanitation, the effectiveness of adaptation, and other interventions to prevent contamination of food and water with disease-causing pathogens.

Our study has several limitations. Inherent to the ecological study design is a lack of data at the individual level, opening us up to the possibility of the ecological fallacy. Another limitation common to ecological studies is unmeasured confounding. We adjusted for time as a proxy for various unmeasured confounders that may vary over time, but for which we do not have information on (Gasparrini et al. 2010). This may include year-to-year variation in population, the number of reporting health clinics over the years of follow-up, and access to improved sanitation or safe water. However, inclusion of time may not sufficiently control for these confounding effects (Peng et al. 2006 Hashizume et al. 2008, Singh et al. 2001). Further, a concern of time series analysis is that results may be sensitive to model choices when controlling for confounding. This was a valid concern in our study as our association of interest was indeed sensitive to variations in time control.

A common limitation of ecologic studies of this variety is underreporting of diarrheal disease. We are limited in that our aggregated health clinic counts only include individuals who sought medical care for their illness and may not capture people without the means or access to care or those with mild symptoms. Individual-level factors may influence health-seeking behavior, such as education, demographics variables, social status, and religious beliefs. However, we may be less concerned with bias from individual-level characteristics given that our unit of analysis is the district rather than individual (Gasparrini et al. 2010).

A limitation widespread in existing literature examining weather and diarrheal disease, of which our study is not exempt, is that a wide range of pathogens can cause diarrheal disease but diarrheal disease surveillance systems often do not routinely capture the pathogen responsible for each case (Vance et al., 2013). Pathogen testing is often cost prohibitive and unfeasible in resource-limited settings, leaving us to examine clinical or self-reported diarrheal illness of unknown etiology. Within the large number of pathogens can cause diarrheal disease, not all are associated with temperature or precipitation. For those pathogens that are affected by weather, the specific associations vary by pathogen. For example, Carlton and colleagues (2016) found that temperature increased bacterial diarrhea but had no impact on viral pathogens. Two reviews of

African rotavirus trends found seasonal peaks during the dry season (Cunliffe et al. 1998; Waggie et al. 2010) whereas several African-based studies found cryptosporidium peaks during the rainy season (Siwila et al. 2011; Tellevik et al. 2015). We're unable to tease out heterogeneous pathogen-specific associations with our data.

Etiologic information on each diarrheal disease case would allow identification of more specific associations between weather variables and pathogens, as well as permit inclusion of the lag most relevant to each pathogen in the model. This could result in more precise estimates of the impacts of climate variability and change, and increase the effectiveness of prevention programs and interventions. Better understanding is needed of the pathogens associated with outbreaks of diarrheal disease in Mozambique so that interventions can be most effectively targeted.

Our study had several strengths. First, 18 years of time series data at the weekly resolution is rare, especially in an African country where health infrastructure is often weak and data collection may be inconsistent (Vance et al. 2013). Existing studies have relied on much smaller geographic areas, such as specific villages or districts (Oloukoi et al. 2013; Rabassa et al. 2014; Bonkoungou et al. 2013; Tornheim et al. 2010) and, many have not had the resolution to examine the direct association between weather and diarrheal disease, but rather focused on seasonal trends (Azage et al. 2015; Vance et al. 2013). Additionally, studies examining seasonal disease peaks and variability seldom estimate the direct association between precipitation and disease, even after including adjustment of seasonal and temporal confounders.

Climate variability and change present current and future risks to human health. Low-income regions, such as sub-Saharan Africa, are expected to experience larger increases in the burden of diarrheal disease with climate change because these regions will, in many cases, have higher exposure to climate-related hazards, such as extreme precipitation or temperature events, and because these regions have low capacity to manage those risks. Africa is particularly vulnerable because it is already facing weather conditions conducive to the spread of diarrheal disease that climate change is expected to exacerbate (Smith et al. 2014).

These additional cases of diarrheal disease are potentially preventable using the increasing skill in forecasting precipitation over seasonal timescales. Having advance warning (e.g. an early warning and response system) that a week is expected to be wetter than normal would provide valuable time to put interventions in place, such as increasing access to oral rehydration in local health care centers, increasing education on appropriate use and handling of water (such as boiling drinking water), and on sanitation practices that can reduce transmission of diarrheal pathogens. Developing and deploying such an early warning system would increase population resilience to outbreaks of diarrheal disease over coming decades.

This study is an important first step to understanding climate-drivers of diarrheal disease in Mozambique in order to inform disease prevention efforts and begin development of an early warning system for outbreaks.

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ANNEX

Figure 1A. Map of Mozambique's ten provinces and 141administrative districts. Source: List of Maps, *The New Zealand Digital Library*

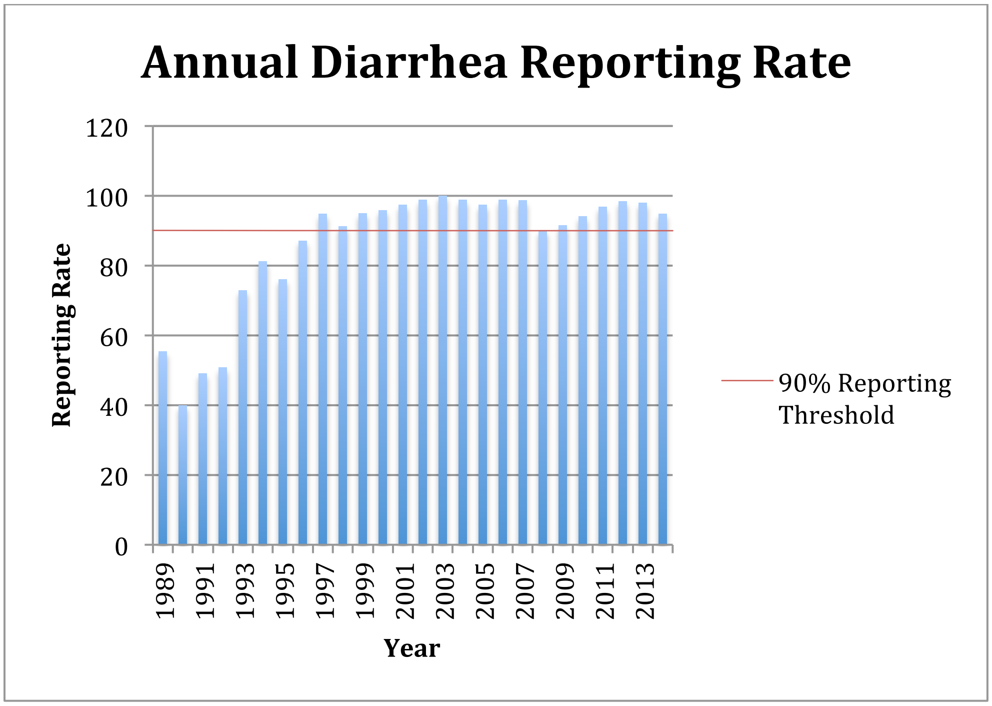

Figure 2A: Annual diarrheal disease reporting percentages in Mozambique for the years 1989-2014. The reporting rate is the percentage of weeks that disease counts were reported each year, out of all possible weeks among the districts.

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