

EXPLORING THE EFFECT OF PRECIPITATION AND DROUGHT ON *CAMPYLOBACTER*
AND *SALMONELLA* INFECTIONS IN THE SOUTHWEST UNITED STATES

by

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Dedication

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Abstract

Weather variability affects enteric infections in people through the complex interaction of human, animal, and environmental factors. The studies presented in this dissertation examine the relationship between weather variability on *Campylobacter* and *Salmonella* infections in humans. In a review exploring pathogen-specific estimates for *Campylobacter* infections, research shows significant associations with myriad weather variables that might explain the changes in *Campylobacter* cases in different regions around the world (Aim 1). Specifically, research shows significant positive associations with temperature, precipitation, and relative humidity. Proximity to animal operations was not considered by the majority of papers, indicating a significant gap in our knowledge. Using the approaches described in the review, the associations with precipitation and drought were explored via an ecological analysis of *Campylobacter* (Aim 2) and *Salmonella* (Aim 3) infections in four Southwest US states from 2009-2021. Together the analyses show a significant and positive association between precipitation and *Campylobacter* and *Salmonella* incidence after adjusting for average temperature and drought. Variability in antecedent drought modifies this relationship, whereby infections increase following a heavy precipitation event during wet conditions (*Campylobacter*) or during early stages of drought (*Salmonella*) and are significantly decreased during extreme drought conditions for both pathogens. Proximity to animal operations modify this relationship between precipitation and incidence. Counties that have a high density of chicken and poultry, sheep and goats, or leafy green operations, have 2-3 fold increase in cases compared to counties without farm operations. Identifying the connection between weather variability and enteric infections provides insight into the complex mechanisms that drive increases in cases when no common risk factor is identified. The results of this dissertation will support public health departments in responding to and preparing for extreme weather events as they become more common with climate change.

Chapter 1. Introduction

Destabilization of the water system, including more variation in dry and rainy periods and extremes, is expected with projected climate change.¹ This increased variation will affect the intensity and frequency of both drought and extreme flood events across the globe. Previous studies in the UK² and Canada³ have shown how increases in flooding and intensity of drought will affect the incidence of enteric illness. However, while the connection between extreme flooding events and enteric illness is well known,⁴⁻⁷ the risk posed by drought conditions coupled with extreme precipitation events is less known.⁷

Previous systematic reviews have attempted to summarize the research literature in this area and have concluded there is a significant research gap in our understanding of concurrent and antecedent meteorological events on enteric illness.^{4,7} Further, there are no studies that have explored the direct, or indirect, relationship between drought and pathogen-specific enteric illness in the United States (US). In one systematic review that aimed to understand how different weather events worked together to affect enteric illness, two thirds of eligible papers were excluded because they did not consider antecedent environmental conditions preceding an outbreak.⁴ It has become clear that regionally-specific effects of climate change are needed because the relationship between weather variation and diarrheal diseases can be modified by other weather events such as extreme temperature and drought. Further, in arid and semiarid regions, the seasonal timing, frequency, and intensity of precipitation events in relation to drought level can be more important than precipitation totals overall.⁸ If we were to explore just the effect of one weather variable on enteric illness, we may miss important nuances of meteorological events working together to affect infectious diseases.

One previous study has summarized the effect of temperature on enteric illness in the US, but they focused solely on seafood and coastal waters, and it is more than 20 years old.⁹ This review may have missed important associations in landlocked states and since it is older, may have missed significant extreme weather events that have occurred due to climate change in the previous decade. More recent studies found that antecedent drought status in the previous 12 and 24 months significantly increased diarrheal illness in children in developing countries.¹⁰ However, the approach of aggregating all diarrheal diseases together to understand the effect of weather on incidence is not ideal. Pathogen-specific estimates would allow for targeted public health responses and provide more accurate estimates of the effect of weather on incidence. A more comprehensive approach to understanding the effect of antecedent and concurrent weather conditions on pathogen-specific enteric illness in the US is thus needed.

The proposed studies will elucidate how antecedent weather contributes to and exacerbates bacterial enteric illness. This work will inform public health responses, messaging strategies, and target resources effectively following extreme flooding and precipitation events. Determining how antecedent weather affects enteric illness will allow us to determine what support is needed to respond appropriately to and prepare for outbreaks following extreme weather. Understanding how weather events can lead to an increased risk of contamination events in the greater environment may help inform policy and land use decisions for mitigating risk following

weather events. This research will contribute to our collective knowledge of how climate change affects human health.

Chapter 2. Background

In the United States (US), 31 pathogens cause an estimated 9.4 million cases of foodborne illness, 56,961 hospitalizations, and 1,351 deaths each year.¹¹ The leading bacterial enteric pathogens in the US include: nontyphoidal *Salmonella spp.*, *Campylobacter spp.*, *Listeria monocytogenes*, *Escherichia coli*, *Bacillus cereus*, *Clostridium perfringens*, and *Staphylococcus aureus*. The top two bacterial pathogens contributing to domestically acquired foodborne illness are *Campylobacter spp.* and non-typhoidal *Salmonella spp.*¹¹

Campylobacter spp.

Microbiology

Campylobacter is a gram-negative microaerophilic curved or spirochete bacteria. The majority (90%) of human infections are caused by *Campylobacter jejuni*. *C. jejuni* is ubiquitous in the environment and a key feature of the bacteria is its ability to survive in a biofilm under aerobic stress.¹² However, there is debate about if this viable but non-culturable cell state can result in animal or human infections.^{12,13} The bacteria also have flagella which contributes to its motility (ability to self-propel itself).¹² The growth temperature range for *C. jejuni* is between 30 – 50 °C with an optimum growth temperature of 42 °C.^{12,13}

Reservoirs

Environment

While *Campylobacter* infections are often thought to be foodborne exposures, some have estimated that 30-50% of *C. jejuni* infections may be a result of infection from exposures in the wider environment.¹⁴ *Campylobacter* has been shown to persist in soils and water for 28 days, but it is extremely sensitive to dry weather and UV radiation.¹⁵ Wet conditions or high relative humidity can aid in *Campylobacter* survival, and clay soils typically found in arid environments have been shown to increase the risk of it being spread further during surface-water flow events.² Despite being microaerophilic, the bacteria has regulatory mechanisms which allow it to withstand aerobic, oxidative, and nutrient-poor conditions.¹²

Animal

Most warm-blood animals are reservoirs of *Campylobacter* including wild animals (birds and pigs), farm animals (poultry, cattle, pigs, sheep), and domesticated animals (cats and dogs).^{16,17} Animals can have *Campylobacter* without it causing disease or symptoms. Flies are important carriers for *Campylobacter* as they are able to contaminate both humans and animals and are especially active during the summer months when their larvae grow and mature.¹⁸

Epidemiology of *Campylobacter spp.* Infections

Campylobacteriosis is caused by infection with *Campylobacter* and is characterized by diarrhea (often bloody), fever, stomach cramps as well as nausea and vomiting. The incubation period for *Campylobacter* is 2-5 days with a range of 1-10 days, and is transmitted through the fecal-oral route via contaminated foods, water, and animals. In the United States (US), *Campylobacter* causes 845,024 infections (90% Credible Interval (CrI): 337,031–1,611,083), 8,463 hospitalizations (CrI: 4,300–15,227), and 76 deaths (CrI: 0-332) annually.¹¹ Taking into account underreporting and challenges with culturing *Campylobacter*, the CDC estimates 1.5 million

Campylobacter infections occur each year.¹⁹ *Campylobacter* infections are generally self-limiting but some people who acquire *Campylobacter* also go on to develop post-infectious sequelae including Guillain-Barre syndrome, reactive arthritis, and post-infectious irritable bowel syndrome. These sequelae account for 74% of the average 22,500 Disability Adjusted Life Years associated with *Campylobacter* disease burden.¹¹

Transmission Routes

Transmission of *Campylobacter* in the environment to animals can be horizontal (e.g. colonization where animals are bred, deposition of feces via wild birds) or vertical (e.g. hen to chick, cow to calf).¹⁷ *Campylobacter* is typically transmitted to humans from contaminated animals or animal products during processing, through deposition of feces on food products, or through contamination of the environment and water which is used during food production.¹⁶ The primary niche for *Campylobacter* is the intestinal tracts of avian species,¹⁷ and handling or consuming raw or undercooked poultry contributes to 50-70% of human infections.²⁰ The consumption of raw milk, raw red meat, and contaminated fruits and vegetables are all important routes of transmission to humans. Studies have shown presence and persistence of *Campylobacter* in leafy greens and other vegetables (e.g. Brandl et al.²¹), but few outbreaks have been attributed to vegetables²² and this remains a less significant transmission route. Additionally, from 1997 to 2008, 9.2% of *Campylobacter* outbreaks in the US were waterborne and *Campylobacter* is often implicated in waterborne outbreaks around the world.²³

Non-typhoidal *Salmonella* spp.

Microbiology

Non-typhoidal *Salmonella* is a gram negative facultatively anaerobic rod-shaped bacteria. There are over 2,500 serotypes of *Salmonella* grouped into nine serogroups (A-I) determined by its antigenic structure.²⁴ Non-typhoidal *Salmonella* (NTS) includes all serotypes except for Typhi, Paratyphi A, Paratyphi B, and Paratyphi C.²⁵ *Salmonella* can persist for months or years in the environment and survives best in wet and warm environments. The growth temperature range for *Salmonella* is between 6 – 45 °C with an optimum growth temperature of 37 °C.²⁵

Reservoirs

Environment

Non-typhoidal *Salmonella* are wide-spread in nature, however their persistence and virulence factors can vary by subtype.²⁶ *Salmonella* can survive in very acidic environments as well as outside its animal hosts in the environment for extended periods of time (up to 332 days).^{27,28} Ambient air temperature has been associated with increased *Salmonella* infections in the US, and around the globe. *Salmonella* even persists during extreme heat events, particularly in coastal areas or in areas with farming operations.^{29,30} Kovats et al. showed that for every 1 °C increase in temperature above 6 °C across 10 European countries, *Salmonella* cases increased 5-10%.³¹ They attributed this large increase to *Salmonella* 's ability to survive in high temperatures and persist in the environment through various animal hosts.

Animal

Salmonella spp. have a range of hosts including livestock, wildlife, poultry, and domesticated animals.²⁴ The main animal host of *Salmonella* is poultry. The most common poultry-associated

serotypes of *Salmonella* include Kentucky, Enteritidis, Heidelberg, Montevideo, and others.³² *Salmonella* naturally occurs in the intestinal tract of poultry, wild birds, reptiles, amphibians, and other small mammals. Animals can carry *Salmonella* but many do not show symptoms. Many outbreaks of *Salmonella* in humans have occurred following direct contact with animals, particularly with backyard chickens and reptiles (e.g. pet bearded dragons, turtles, and via rodents fed to pet snakes).³³

Epidemiology of *Salmonella* spp. Infections

Salmonellosis is caused by infection with *Salmonella* and usually includes fever, abdominal pain, diarrhea, nausea, and vomiting. The incubation period for *Salmonella* is 12-36 hours with a range of 6-72 hours and is transmitted through the fecal-oral route via contaminated foods, and contact with animals.²⁴ In the United States (US) non-typhoidal *Salmonella* causes 1,027,561 infections (90% Credible Interval (CrI): 644,786–1,679,667), 19,336 hospitalizations (CrI: 8,545–37,490), and 378 deaths (CrI: 0–1,011) annually.¹¹ The CDC estimates 1.35 million infections occur each year. *Salmonella* infections are generally self-limiting but some people who acquire *Salmonella* also go on to develop post-infectious sequelae including reactive arthritis, and post-infectious irritable bowel syndrome. These sequelae account for 61% of the average 32,900 Disability Adjusted Life Years associated with *Salmonella* disease burden.¹¹

Transmission Routes

Water is the main route of transmission of *Salmonella* from the environment to humans via dispersal and runoff.²⁷ *Salmonella* can be flushed into water sources for human consumption following rain events, via splash dispersal on fruits and vegetables from soil, and released from soil sediments during extreme rain events.^{27,28} The pathogen load of *Salmonella* in animals has also been shown to increase with higher temperatures, leading to greater transmission to humans during food processing and production activities.³⁴ Morgado et al. showed that extreme heat events above the 95th percentile were associated with increased rates of infection by different *Salmonella* serovars in areas with a high density of animal feeding operations.³⁰ Drought stress and higher temperatures also result in the greater internalization of *Salmonella* in plant structures, particularly lettuce.^{35,36} *Salmonella* was implicated in 11% of leafy green vegetable outbreaks from 1973-2012, and seeded vegetable outbreaks linked to *Salmonella* frequently involve multiple states and a large number of illnesses and hospitalizations in the US.³⁷

Public Health Surveillance for *Salmonella* and *Campylobacter*

Both *Salmonella* and *Campylobacter* are reportable conditions in the US. *Salmonella* surveillance is conducted through laboratory-confirmation and many state and territorial health departments receive funding for this surveillance.³⁸ *Campylobacter* did not become nationally notifiable until 2015 and health departments do not receive funding for surveillance. The Foodborne Diseases Active Surveillance Network or FoodNet for short has conducted active surveillance for both pathogens since 1996.¹⁹ Surveillance for enteric diseases are conducted using standardized case definitions which are a set of uniform criteria health departments can use to classify and count cases across jurisdictions. The Council for State and Territorial Epidemiologists (CSTE) and CDC determine case definitions for these pathogens. Health

departments can choose which definition to follow, but they generally use the latest version available.

It is important to consider how case definitions have changed over time with the advent of new testing capabilities. When culture-independent diagnostic testing (CIDT) became available, many laboratories started to use this method for detection of enteropathogens because they are often cheaper and quicker than culture-confirmation.³⁹ However, while CIDT is good at detecting *Salmonella* (positive percent agreement (PPA): 95.8%), depending on the test used, CIDT performance can vary widely for *Campylobacter* (PPA: 59.2-100%).⁴⁰ The increasing use of CIDTs can affect public health surveillance data via a reduction in collection of isolates, limiting our ability to detect pathogen subtypes, determine antibiotic resistance, monitor trends, and detect outbreaks.^{39,41}

Seasonality of Infections

Both *Salmonella* and *Campylobacter* vary seasonally, with an initial late spring/early summer peak; however the reasons behind this variation are multifaceted and not well understood.⁴² To understand this seasonality, studies have explored the effect of weather variability including temperature,^{29,43-45} extreme flooding,⁴⁶ and precipitation^{4,29,47} on enteric disease incidence. Weather variability can favor increased survival, growth, persistence, and spread of pathogens in the environment. For example, both *Salmonella* and *Campylobacter* favor warmer temperatures and wet or moist environments. While several studies have explored the unique effect of individual weather variables on *Salmonella* and *Campylobacter* infections, few have explored the combination or effect of antecedent conditions on incidence. Understanding how weather affects incidence will help prepare health departments for the effects of climate change on health.

Experts agree that the destabilization of the water system, including variation in dry, high temperatures and quick but intense rainy periods, is expected with projected climate change.¹ In the US, floodplain systems in arid and semiarid regions can have substantially different flows depending on drought and meteorological events.⁷ These changes may lead to more outbreaks, higher case counts, and a larger burden on health departments to track and reconcile enteric diseases in their jurisdictions. Extreme weather events are part of a complex system of weather patterns, however researchers have largely focused on the effect of individual weather events in enteric diseases rather than the system as a whole. In a recent systematic review and meta-analysis, Kraay et. al.⁴ found 32.4% of studies (36/111) reported more than one weather association (rainfall, extreme precipitation, and flooding events), even less assessed multiple geographic locations (21.6%, 24/111), or multiple pathogens (18%, 20/111). Additionally, 55% of articles (33/60) considered confounding by temperature but there was considerable variation in how temperature was defined.⁴ A new hypothesis in this field aims to disentangle the effects of multiple weather variables, considering antecedent conditions prior to an extreme weather event. Understanding the complex interactions among weather events will provide a more comprehensive picture of their effects on enteric diseases.

Concentration Dilution Hypothesis

The concentration dilution hypothesis posits that a lack of rain can cause pathogens to accumulate in the environment (creating concentration of the pathogens in soils and dirt), then

after a heavy rainfall event (extreme precipitation), the risk of an outbreak can increase as the pathogens are flushed into surface water delivering a concentrated dose.^{4,48,49} Conversely, in areas of the world that experience consistent rain events, rainfall may regularly flush pathogens into water sources creating a dilution effect.

A notable study in this area by Lee et al. explored the effect of antecedent conditions on salmonellosis in Georgia, US. The authors found that when conditions the preceding week were dry, salmonellosis risk was decreased (IRR: 0.93, 95% CI: 0.90, 0.96) whereas during wet conditions, it was increased (IRR: 1.03, 95% CI: 1.00, 1.06). This relationship was more pronounced when looking at environmental serovars – extreme rainfall events following wet periods were associated with a 34% increase in risk (20% following dry conditions).²⁸ While no studies have explored this relationship with *Campylobacter*, others have explored the effect of antecedent conditions of general diarrheal incidence. Carlton et al.⁴⁹, Mertens et al.⁵⁰, and Wang et al.¹⁰ reported stronger positive associations following heavy precipitation events preceded by dry conditions compared to wet conditions. These studies were conducted in Ecuador,⁴⁹ India,⁵⁰ and across multiple sites in the MAL-ED cohort¹⁰ which may explain some of the differences observed due to agricultural practices, living conditions, water sources, and pathogen-specific estimates vs. general diarrheal illness.

In arid and semiarid regions, like the US Southwest, that have a low average annual precipitation but a large variability in the intensity and frequency of precipitation events, defining and monitoring drought over time is difficult.⁸ For example cool-season precipitation in the form of snow and prolonged rains provides essential water for agriculture and water resources. Summer rains during the North American monsoon system can support warm-season forage production and result in significant flooding events.^{51,52} This seasonal variation in Southwest makes it a unique environment to explore the effect of drought on enteric disease incidence.

Projected Impacts due to Climate Change

One of the primary motivations for analyzing the relationship between weather variability and enteric incidence in the Southwest is because the impacts of climate change are likely to vary by region.⁵³ Previous research in this area has mainly focused on coastal, temperate, and subtropical climates.^{10,29} The Southwest US will be disproportionately affected by climate change, especially in terms of drought, extreme heat, and variation in dry and rainy periods.⁵⁴ Due to low annual precipitation, the Southwest is a particularly interesting area to study in this research field. Specifically, drought is expected to increase in its duration and severity over time in the Southwest. The Southwest may also experience more extreme precipitation events, but less overall rainfall throughout the year.⁵⁴ Additionally, due to variations in sea level pressure in the Pacific measured by the Southern Oscillation Index (SOI), weather far away will also drive particularly warm and dry years, or years with significant monsoons and precipitation in some areas.^{55,56} Taken together, this means that precipitation may fall in large quantities during particularly dry conditions more frequently in the future. It is important to explore the effect of precipitation during different drought conditions in order to estimate the burden of enteric illness in the future.

Present Study

The format of this dissertation includes three research manuscripts in the following three chapters. This section summarizes the data sources as well as a primer on the statistical methods used for Aims 2 and 3.

Data Sources

There are many different data sets available to explore the effect of weather variability on enteric illness. The following paragraphs describe the datasets selected for study and motivations for selecting these data over others.

Public health surveillance

Sources of human health case data for *Campylobacter* and *Salmonella* include public health surveillance, hospital records, and death records. To capture all cases reported in a jurisdiction, public health surveillance efforts provides the best records, as both pathogens are reportable to local health departments. Many health departments will approve identifiable data requests (including address-level and daily-level case reports) with Institutional Review Board (IRB) review and signed data use agreements. However, this level of data may pose security risks to patient confidentiality and may take considerable time to review and approve given health department time constraints. De-identified data reduces some of the security risks and does not require the same level of approval. For this study we requested county-level data as that was the finest spatial resolution available.

Date reported to the health department was used for all temporal analyses, as surveillance varies between states, and onset, collection, and laboratory result date may have more missingness due to interview and reporting capacities in each jurisdiction. Another decision point of concern would be the most meaningful time scale to analyze. We requested daily-level data in order to analyze data at different time scales (daily, weekly, monthly). Daily-level analyses suffer from lack of efficiency whereas monthly-level analyses can be good in jurisdictions with few cases, but they might obfuscate important time trends. Weekly-level analyses are the sweet spot between the two by providing enough granularity to see changes over time, but without a loss in efficiency for modeling.

Weather and climate

Weather data were derived from the Parameter-elevation Regressions on Independent Slopes Model (PRISM),⁵⁷ including daily county-level minimum, maximum, and average precipitation (inches), and minimum, maximum, and average temperature (°F) by county centroid. PRISM interpolates weather station data within an area, so in larger counties this may capture a more complete picture of precipitation and temperature on a given day. In PRISM, weather stations are weighted by their physiographic similarity to the grid of interest (in this case, county-level centroid). Typically with denser station data, more data is interpolated, and the more likely that stations within the county contributed to the centroid prediction. In areas with sparse weather station data, values may be influenced by weather stations outside of county boundaries. This is the same limitation that would result if we used a nearby weather station instead, as not every county has its own weather station. The benefit of using PRISM over individual weather stations is that PRISM pulls from multiple stations capturing a more holistic picture of weather

variability. PRISM data was aggregated to week and precipitation values for all days in a week which were summed to determine the total precipitation in a week, following similar research approaches in this area.

There are many drought indices available to explore the effect of antecedent drought.⁵⁸ The choice of which drought index to use relies heavily on the regional characteristics. For this study we chose the Palmer Drought Severity Index (PDSI) which is most often used by drought researchers, and is readily available for analysis. PDSI generally considers the drought level in the current month, and the previous 9 months on a rolling basis.⁵⁹ Other drought indices of interest include the US Drought Monitor (USDM), and the Standardized Potential Evapotranspiration Index (SPEI). The USDM is a newer ensemble drought index that considers multiple numeric inputs from different drought indices, satellite-based assessments, indicators of vegetation and soil moisture, as well as snowpack. The SPEI is a grid-based and relational index which accounts for precipitation and potential evapotranspiration on a range of timescales from 1-48 months. PDSI is particularly good at capturing drought on timescales less than 12 months in low and middle latitudes, whereas the SPEI is better used for long-term drought studies. PDSI is also readily available whereas SPEI and USDM both require advanced calculations or data manipulation. PDSI by month for each county were derived from the National Centers for Environmental Information (NCEI) via NOAA.⁶⁰

To understand the effect of El Niño and La Niña, we used the Southern Oscillation Index (SOI) by month for the time period. El Niño is characterized by a negative SOI value, neutral when SOI is zero, and La Niña when the SOI is positive.⁶¹ This index is not location-dependent, meaning there is one value for the month and it does not vary by location.

County-level data

County-level information such as whether a county is majority urban vs rural, its climate zone, as well as population density may be important confounders to consider in analyses of weather variability exposures. To account for this potential confounding, we collected county-level 2020 US Census designations of majority urban vs rural for each county.⁶² Additionally we abstracted the 2020 US Census population estimate for each state to calculate incidence rates over time. We used the Köppen-Geiger Climate Classification scheme to analyze data across the four states, as incidence of enteric illnesses may vary by flooding in different climate zones.⁶³

Animal data

As mentioned above, previous studies have shown that the incidence of enteric illnesses is modified by proximity to animal operations. To estimate these effects, we used data for the number of operations with sales in a county from the 2017 USDA Farm census Quick Stats 2.0. We pulled data on the number of operations for poultry, sheep and goats, sheep only, cattle, and leafy greens.

Generalized Estimating Equations

To model the effect of weather variability on incidence, we used negative binomial generalized estimating equations (NBGEE). This model was chosen over others because our data are longitudinal, correlated, and not independent. The GEE method was first developed by Liang and

Zeger,⁶⁴ and Zeger and Liang⁶⁵ in 1986. GEEs use a quasi-likelihood approach meaning, “we specify only the relationships between the outcome mean and covariates and between the mean and variance” in contrast to the likelihood method in which we only need to pre-specify the form of the distribution of the dependent variable. There are three main questions to consider when using a GEE model: 1) What is the best link function? 2) What is the distribution of my response variable? and 3) What is the likely form of correlation within my response variable?⁶⁶⁻⁶⁸

What is the best link function?

The link function is determined by the nature of the dependent variable. Our outcome variable is cases of *Campylobacter* or *Salmonella* in a given week in a given county. Since we are using count data, the most appropriate link function involves modeling the log of the mean.

The form of a negative binomial model is:

$$\ln(E[Y]) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_n x_n$$

where (E[Y]) is the natural log of the predicted value of the dependent variable Y, a constant (α), and the coefficients (β) of the model which quantify the effect of each x_i as a predictor. By exponentiating the coefficients, we get an incidence rate ratio (IRR). The IRR can be interpreted as a percent increase or decrease in the number of cases given a one unit increase in the predictor. The GEE develops a population average or marginal model which provides the average estimate or response of observations sharing the same covariates, as a function of the covariates.⁶⁸ In the present study, the IRR can be interpreted as the average percent increase or decrease in the number of cases across all counties in the area of interest from 2009-2021 for a one unit increase in the predictor.

What is the distribution of my response (predictor) variables?

Since we are using counts of cases in a given week, we cannot assume normality because our dependent variable must always be greater than or equal to zero (you cannot have negative *Campylobacter* cases in a week). When we explore the distribution further, we find data used in Aims 2 and 3 follow a negative binomial distribution. In a Poisson distribution the mean is equal to the variance, in a negative binomial distribution, the variance is greater than the mean. In our data, the variance is greater than the mean for all variables (including lags) that can be used as a dependent variable in the model.

What is the likely form of correlation within my response variable?

Our predictor variables of interest include weather at the county level over time. There are three correlation structures to choose from, and that may be of interest: independent (Ind), exchangeable (Exc), or autoregressive (AR). Independent correlation structures are good when observations are independent of each other; this sacrifices some of the benefits of the GEE model in modeling longitudinal data that is correlated. Exchangeable correlation structures are good when there is no logical ordering of observations within a cluster and are not time-series data. Autoregressive correlation structures are best when data are correlated within cluster over time. Because it is likely that measurements taken closer together are more correlated than those taken farther apart, the best correlation structure is likely autoregressive. If a user incorrectly specifies

the correlation structure, they will likely have inefficient parameter estimates and the estimates may be attenuated.

To determine the best correlation structure, Stata users can explore Pan's quasi-likelihood under the independence model information criterion (QIC). This metric is an extension of Akaike's information criterion (AIC).^{69,70} The QIC that is lowest is determined to be the best model. To start, users pre-specify variables of interest in order to determine the best correlation structure and combination of variables. In the present study, these include: total precipitation, drought severity, and average temperature. Across the three correlation structures, the autoregressive model had the lowest QIC (Ind: 94619.2, Exc: 94640.5, AR: 94472.6).

To account for the population size of the county in the AR model, we also explored the effect of different transformations of population size on QIC including: county population (continuous) (QIC=69485.1), logged county population (QIC=45747.0), county population per 100,000 (QIC=69693.1), and using incidence rather than case counts for the main outcome measure (QIC=108375.8). The autoregressive model which included logged county population was the best fit. Logging the county population transformed the distribution of the values from negative binomial to a fairly normal distribution. After further investigation, including population in the model (in any form) significantly attenuated estimates (>10% change) in final models and in ways that did not make biological sense. Models without population included as a variable of interest were explored further to aide in interpretation of model results, to align with previous research in this area, and to pick the best model of the set.

After selecting the variables of interest, the final step is to explore the effect of different combinations of variables. While the best model was the model without drought severity included, this is a key variable of interest in the analysis. We chose to move forward with the autoregressive model which includes total precipitation, drought severity, and average temperature.

Approval

This study was approved by the University of Arizona IRB as exempt, minimal risk research (#00001514). We initially requested address-level information from collaborators in these studies. However, we pivoted to using de-identified, case reports for analyses in Aims 2 and 3 due to time constraints and delays in approval with the state IRB due to the COVID-19 pandemic.

Summary

While studies have looked at extreme weather events independently, researchers have not fully considered the effect of antecedent drought preceding extreme precipitation events on enteric illness.⁷ *Salmonella* and *Campylobacter* infections vary seasonally, however the role that weather plays in this seasonal peak is not well understood. This dissertation aims to understand how precipitation and drought affect *Salmonella* and *Campylobacter* infections in an arid and semi-arid region of the US, contributing to this gap in our knowledge.

Chapter 3. Dissertation Objectives

This dissertation seeks to understand the role that weather plays in *Campylobacter* and *Salmonella* infections in four states (Arizona (AZ), Colorado (CO), New Mexico (NM), and Utah (UT)) with the following three aims.

Aim 1

Using a systematic review approach, this aim synthesizes the peer-reviewed literature exploring the effect of climate change and weather variability on *Campylobacter* infections. This study summarizes what is known using the following research questions:

1. How does weather variability affect *Campylobacter spp.* incidence?
2. Does proximity to agricultural animals and animal operations modify the association between weather variability and enteric infections with *Campylobacter spp.*?
3. What gaps exist for future research in this area?

Aim 2

Using negative binomial generalized estimating equations (NBGEE), this aim seeks to assess the effect of antecedent precipitation on the incidence of *Campylobacter* in four states of the Southwest region from 2009-2021. We hypothesize that precipitation will increase *Campylobacter* incidence, and that this relationship will be modified by antecedent drought.

Aim 3

Using NBGEE, this aim seeks to assess the effect of antecedent precipitation on the incidence of *Salmonella* in four states of the Southwest region from 2009-2021. We hypothesize that precipitation will increase *Salmonella* incidence, and that this relationship will be modified by antecedent drought.

Chapter 4. Aim 1: Systematic review exploring the impact of weather variability on the incidence of *Campylobacter* infections in people

Introduction

Contamination of the environment with *Campylobacter* can lead to transmission and subsequent enteric illness in humans. Multiple transmission pathways exist including environmental contamination via water, soil, air and dust; exposure to wildlife, rodents, and wild birds; exposure to wildlife or pests within animal operations; contamination along the food production and distribution chain; or through a combination of these.⁷¹ Increased contamination in the environment can lead to a greater chance of direct and indirect transmission of *Campylobacter* to humans. Weather variability may affect these contamination pathways.

Weather variability such as variation in dry and rainy periods, fluctuations in the intensity and frequency of drought, and extreme flooding events are associated with current and projected climate change.⁷² These changes may affect the pathogen load in our environment and food products, thereby contributing to greater enteric illness overall. Previous systematic reviews have described the association between climate change and general diarrheal illnesses finding strong associations between temperature and precipitation, but few have explored pathogen-specific effects including none that have explored *Campylobacter spp.* specifically.^{71,73-75} Because of the variability in pathogen-specific risk factors and contamination pathways for food products, it is important to explore their unique effects where data allow.

Using existing peer-reviewed literature, systematic review aims to synthesize the effect of climate change and weather variability on *Campylobacter* infections. Due to its strong connection with environmental exposure pathways, and the existence of significant literature that allows its association with these pathways to be analyzed independently of other pathogens, we specifically focus on *Campylobacter*. Using data from peer-reviewed research, we summarize the effect of weather on *Campylobacter* infections, addressing the following questions: 1) How does weather variability affect *Campylobacter spp.* incidence? 2) Does proximity to agricultural animals and animal operations affect the association between weather variability and enteric infections with *Campylobacter spp.*? and 3) What gaps exist for future research in this area?

Methods

Eligibility

We used the PRISMA 2020 Statement for reporting of our systematic review.⁷⁶ The review was registered with PROSPERO (Protocol # 351884). A priori search terms were used to define extreme weather events associated with climate change following the latest Intergovernmental Panel on Climate Change (IPCC) Sixth Assessment Report and previous systematic reviews in this area.^{71,73,74} We included primary analysis studies that met the following criteria: a) primary exposure was an antecedent weather event; and b) the primary outcome was human enteric illness caused by *Campylobacter*. A full list of inclusion and exclusion criteria is included in Table 1.

Table 1. Inclusion and exclusion criteria for a systematic review exploring the effects of precipitation and climate change on *Campylobacter spp.* incidence

Criteria	Inclusion	Exclusion
Date Range	Published up to September 1, 2022	Published after September 1, 2022
Study Design	Primary data analysis	Opinion; letters to the editor; case studies or reports; reviews (systematic, scoping, and/or meta-analyses)
Population	Humans	Animal-only studies; laboratory or diagnostic testing; environmental sampling without a connection to human illness
Publication Language	English	Non-English
Publication Status	Peer-reviewed publication	Pre-prints
Pathogen	<i>Campylobacter spp.</i>	Other bacteria, viruses or parasites, toxins or other contaminants, non-enteric health outcomes (e.g. sepsis or wound infections)
Weather Events	Climate change, climate variability (El Niño, La Niña), global warming, extreme weather (temperature), precipitation events (flood*, rain*, storm), drought (arid*, water scarcity)	No connection to climate change or antecedent weather event, including only description or analysis of seasonal changes in infections
Study Results and Outcome	Studies exploring association between weather events and subsequent human enteric illness	Studies only exploring animal-environment connections without human health outcomes

Information Sources & Search Strategy

The search strategy was developed in collaboration with a health sciences librarian, enteric disease experts (KPB, AW, EWS), and a climate change expert (HB). Search queries were conducted in PubMed, Embase, GEOBASE, the Agriculture and Environmental Science Database, and CABI Global Health. We restricted our search to title and abstract only, English articles, and articles published up to September 1, 2022. While we excluded systematic reviews and meta-analyses in our search, we hand searched reference lists from each to identify additional included papers as well as reference lists of included articles. The initial search was conducted on September 1, 2022 and produced 785 results.

Selection Process

Covidence [Veritas Health Innovation, Melbourne, Australia] was used to compile and deduplicate studies obtained from the final search query.⁷⁷ Three independent reviewers initially screened on title and abstract (EA, SW, KH), before moving to full text reviews. Following full text review, a fourth reviewer (AW) resolved conflicts related to the inclusion or exclusion of articles.

Data Collection Process

We created a data extraction tool in REDCap to summarize data from each article including: article information, pathogen(s) studied, climate change related weather event(s), datasets used, analysis methods, data limitations and challenges, and recommendations for future work. A full list of data items and definitions is available in Supplemental Table 1. We piloted the tool with the first 10% of articles included in the final extraction, before finalizing the data items and completing extraction for the remaining articles.

Quality Assessment

We summarized the quality and weight of evidence for each climate-related weather event including the frequency and proportion of studies showing a significant positive association, significant negative association, and null/no association. To assess bias we used the Cochrane Risk of Bias tool.⁷⁸ After data extraction, each reviewer completed the risk of bias assessment independently. We report on the results of the assessment using the 4-category grading scale for reaching the overall risk of bias judgment (low risk, some concerns, high risk, very high risk). Because some of the domains were not applicable to all articles, each article's individual domain scores were averaged across applicable domains (4 domains for all articles, 6 for those which used controls, and 7 for those with follow-up) to generate an average risk of bias score.

Data Synthesis

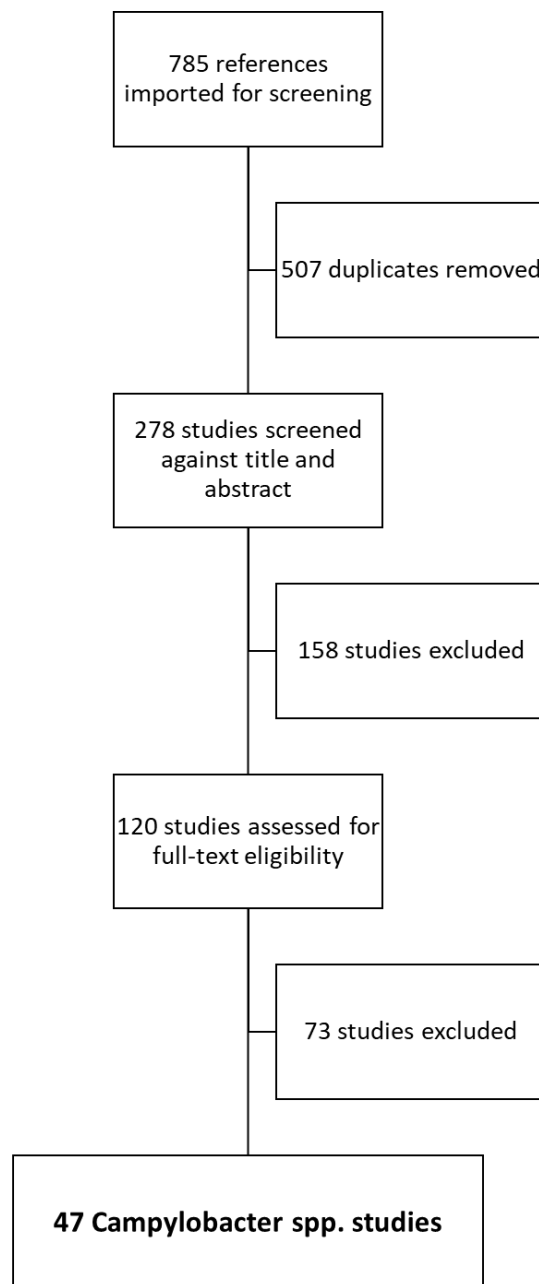
We summarized the overall results from the literature review including the frequency and proportion of articles by weather events. We qualitatively summarized outbreaks, ecological studies analyzing general associations with numerous weather variables, and any articles using a modeling approach. For articles that completed modeling, we summarized their dataset, analysis methods, confounding factors, and any data limitations and challenges. Finally, we summarized best practices for models, data lags, considerations, covariates, and other data analysis methods which will be useful for future work in this area.

Results

Study Characteristics

Of 278 unique articles identified in the initial search, 194 were excluded following title and abstract review and 37 were excluded following full text review for the following reasons: 15 did not include weather analysis, 7 did not include a weather event or exposure, 7 were not a primary data analysis, 5 analyzed pathogens other than *Campylobacter*, 2 were published in other languages, and 1 had no human health outcomes (Figure 1). This review of evidence includes 47 *Campylobacter spp.* articles.^{79–125}

Figure 1. PRISMA Flow Diagram for articles published up to September 1, 2022 and included in a systematic review exploring the effects of weather and climate change on *Campylobacter spp.* incidence



A description of study characteristics is available in Table 2. Briefly, articles spanned study periods from 1985-2019 across the globe: Europe (21), North America (13), Asia (6), Australia (6), Africa (2), South America (1), and multiple continents (1). Most papers analyzed the effect of weather events on incidence (34) and the remaining were outbreak investigation reports (13). Articles explored the effect of precipitation (35), and temperature (30) most often, other weather exposures included relative humidity (7), sunshine (6), and El Niño and La Niña (3). Fourteen articles analyzed animal or land use data in their study.

Table 2. Study information for articles published up to September 1, 2022 and included in a systematic review exploring the effects of weather and climate change on *Campylobacter spp.* incidence

Study Information					Human Data	Animal Data
Article (First Author, Year)	Study Year Start	Study Year End	Country	Study Design	Total Cases	Type of Animal or Land Use Dataset
Allard 2011	1990	2006	Montreal, Canada	Ecological	Not reported	None
Arsenault 2012a	1996	2006	Quebec, Canada	Ecological	25521	Poultry density, ruminant density, slaughterhouse presence
Arsenault 2012b	1996	2006	Quebec, Canada	Ecological	28519	Poultry density, ruminant density, slaughterhouse presence
Auld 2004	2000	2000	Walkerton and Hanover, Canada	Ecological, Outbreak Investigation	Not reported	None
Bartholomew 2014	2012	2012	Darfield, New Zealand	Outbreak Investigation	138	Presence of animals, proximity to paddocks
Bi 2008	1990	2005	Adelaide, Australia; Brisbane, Australia	Ecological	34908	None
Brubacher 2020	2000	2013	British Columbia, Canada	Ecological	42266	Ecological zone, Agricultural vs non-agricultural land use, urban vs rural, aquifer type
Carev 2018	2007	2012	Split Dalmatia County (SDC), Croatia	Ecological	2658	urban vs rural
Cherrie 2018	1998	2014	England and Wales	Ecological	Not reported	None
Colston 2020a	2009	2014	Many*	Case Control	12030	None
Cousins 2020	2005	2014	Ontario, Canada	Ecological, case-crossover	5675	None
Djennad 2019	1989	2014	England, Wales	Ecological	Not reported	None
Fleury 2006	1992	2000	Canada	Ecological	1743	None

Fong 2007	2004	2004	Ohio, USA	Case Control, Outbreak Investigation	1450	None
Gilpin 2020	2016	2016	Havelock North, New Zealand	Cross Sectional, Outbreak Investigation	7570 †	Proximity to sheep
Harder-Lauridsen 2013	2010	2011	Denmark	Retrospective Cohort, Outbreak Investigation	429	None
Hartnack 2009	2001	2007	Germany	Ecological	346427	Broiler chicken flocks
Kim 2015	2003	2012	South Korea	Ecological, outbreak data	Not reported	None
Kovats 2005	1989	2002	Czech Republic; Denmark; England and Wales; Scotland; Spain; Switzerland	Ecological	593981	None
Kuhn 2017	2009	2009	Tune, Denmark	Retrospective Cohort, Outbreak Investigation	163	None
Kuhn 2018	2000	2015	Denmark	Ecological, outbreak data	Not reported	None
Kuhn 2020	2000	2014	Denmark; Finland; Norway; Sweden	Ecological	64034	None
Lake 2009	1989	2006	England and Wales	Ecological	Not reported	None
Lake 2019	2008	2016	Many ‡	Ecological	1784996	None
Lal 2013	1997	2008	New Zealand	Ecological	79193	None
Louis 2005	1990	1999	England; Wales	Ecological	401270	Total labor employed in agriculture, total agriculture land, cattle, pigs, sheep, poultry
Merritt 1999	1997	1997	Queensland	Case Control, Outbreak Investigation	23	Presence of wild animals near water tanks
Millson 1991	1985	1985	Ontario, Canada	Case Control, Outbreak Investigation	57	None
Naumova 2007	1992	2001	Massachusetts, USA	Ecological	14992	None
Nichols 2009	1910	1999	England; Wales	Outbreak Investigation, Case-Crossover	Not reported	None
Oberheim 2020	2001	2014	Germany	Ecological	Not reported	None
Oh 2021	2010	2019	Cheonan, South Korea	Ecological	2300	None
Park 2018b	2011	2015	South Korea	Ecological	Not reported	None
Patrick 2004	1998	2001	Denmark	Ecological	12008	Positive broiler flocks
Pitkanen 2008	2004	2004	Finland	Outbreak Investigation	3	None

Poulsen 2018	2006	2015	Pennsylvania, USA	Ecological	567	Proximity to high density poultry operations
Rosenberg 2018	1999	2010	Israel	Ecological	29,762	None
Rushton 2019	2004	2009	Northeast England	Disease/Economic Burden	Not reported	Number of visits to countryside
Sanderson 2018	2004	2009	Tyne catchment, England	Ecological	Not reported	Soil type, livestock density
Schwartz 2006	1997	1999	Dhaka, Bangladesh	Case Control, Outbreak Investigation	1050	None
Soneja 2016	2002	2012	Maryland, USA	Ecological	4804	Coastal vs noncoastal counties
Spencer 2012	2001	2007	New Zealand	Ecological	36000	Poultry farm distance, sheep density, dairy cattle density
Sung 2022	2015	2019	Republic of Korea (South Korea)	Ecological	9252	None
Tam 2006	1989	1999	England and Wales	Ecological	623817	None
Vucković 2011	2003	2007	Croatia, Balkans	Ecological	30164	None
Weisent 2014	1999	2008	Georgia	Ecological	Not reported	None
Yun 2016	2001	2004	Munich, Germany; Berlin, Germany	Ecological	Not reported	None

Legend: Temp, temperature; Ppt, precipitation; SOI, Southern Oscillation Index; Sun or Cloud, Sunlight or Cloudiness; RH, Relative humidity; * Colston 2020a used data from the following countries: Dhaka, Bangladesh; Fortaleza, Brazil; Vellore, India; Bhaktapur, Nepal; Loreto, Peru; Naushero Feroze, Pakistan; Venda, South Africa; and Haydom, Tanzania; † Gilpin 2020 estimated 7,570 cases were linked to the outbreak (95% CI 6850-8320); ‡ Lake 2019 used data from the following countries: Austria; Czech Republic; Denmark; Finland; France; Germany; Hungary; Ireland; Italy; Lithuania; Luxembourg; Netherlands; Norway; Slovakia; Slovenia; Spain; Sweden; UK

How does weather variability affect *Campylobacter spp.* infections?

We were unable to estimate an overall risk for the association between weather events and *Campylobacter spp.* infections due to disparate and sparse models and results. However, we have provided an overall summary of findings below and by weather exposure in Table 3.

Precipitation and Flooding

Of the 32 studies testing the association between precipitation and flooding yielding 40 unique measures of association, the majority had a positive association (n=23/40, 57.5%). Eight articles found no association with total precipitation including studies conducted in Australia,⁸⁴ Canada,⁸⁹ Croatia,^{86,122} Denmark,¹¹¹ England,¹⁰³ New Zealand,¹⁰² nor in pooled results from international studies.⁹⁶ Five studies found a negative association with precipitation including low mean precipitation,⁸⁰ total precipitation,⁹⁰ and two studies with winter precipitation; one between winter precipitation and *Campylobacter* incidence⁹⁹ and the other between snowfall and hospitalizations with *Campylobacter*.¹¹⁰ While the majority of studies used total precipitation, others used average precipitation, extreme precipitation (over 30-year averages, or above a percentile), or categorized based on when precipitation fell (precipitation during the winter as snow, or summer rainfall). Among the six studies with estimates of risk (Incidence Rate Ratio, Risk Ratio, or Odds Ratio), positive estimates ranges from 1.11 to 1.52, and two found a null association. Three studies explored their model fit using R² values and found that precipitation explained only a small part of the variation and only improved adjusted models slightly.^{103,111,123}

Twelve of the 13 outbreak articles included in this review noted an antecedent heavy precipitation event as the cause for their outbreak.^{82,83,92–94,97,98,104,105,107,112} For example, Bartholomew et al.⁸³ described a *Campylobacter* outbreak following a heavy precipitation event in which 164 mm of rain fell causing high turbidity levels resulting in contamination of the local water supply. Similarly, Fong et al.⁹² noted that average monthly rainfall was 200% greater than the 50-year monthly averages for the area during the month in which a *Campylobacter* outbreak at Lake Erie, South Bass Island, Ohio was detected. Some outbreak reports noted a period of light precipitation followed by heavy precipitation. For example, a case-crossover study of drinking water-related outbreaks in England and Wales throughout the 20th century identified a significant association between illness and low rainfall (less than 20 mm) in the three weeks prior to the week before the outbreak followed by heavy cumulative rainfall (over 40 mm) during the 7 days prior to the outbreak.¹⁰⁷

Temperature

Of the 30 studies with 35 unique measures of association for analyzing temperature, the majority found a positive association (n=26/35, 74.3%). This association was consistent around the world – increased mean temperature was associated with an increase in cases in Canada,^{85,89,91} England and Wales,¹⁰⁰ across Europe,¹⁰¹ New Zealand,^{102,119} South Korea,¹²⁰ Massachusetts, US,¹⁰⁶ and in pooled results from international studies.⁹⁶ Among the 11 studies with 13 estimate of risk, positive estimates ranged from 1.01 to 2.00, and all but three were significant. For the 10 studies with 13 correlation or regression coefficients, 10 were positive and three were negative. Three studies explored their model fit using R² values and found that adding temperature to their model explained the majority of the variance better than other weather variables.^{103,111,123}

The literature indicates the existence of complex interactions with other weather events and temperature thresholds in which *Campylobacter* infections no longer concurrently increase with temperature. For example, Soneja et al.¹¹⁸ found no increased risk for campylobacteriosis during extreme heat events during 2002-2012, but during La Niña periods, every additional extreme heat event was associated with a 4% increase in cases (IRR=1.04, 95% CI: 1.01, 1.08). Tam et al.¹²¹ modeled a linear relationship with ambient temperature and incidence, reporting a 5% increase in cases with a 1 °C rise, up to a threshold of 14 °C (RR=1.05, 95% CI: 1.03-1.06). Two studies modeled the relationship between ambient temperature and incidence in Germany, finding no effect below -5 °C, increases with increasing temperatures above that, then plateaus at 18 °C¹²⁵ or 28 °C.¹⁰⁸ Arsenault et al.⁸⁰ found cases decreased above temperatures >6.9 °C but it varied by increasing geographical unit, and not all associations were statistically significant (coefficient range= -17.3, -4).

Within the same country, some studies found different results based on local climate. For example, Bi et al.⁸⁴ compared data from two cities in Australia from 1990 to 2005 in Brisbane (subtropical) and Adelaide (temperate Mediterranean) and found opposite results. In Adelaide they found weekly maximum temperature was associated with decreased cases (coefficient=-0.007). In contrast, weekly maximum temperatures in Brisbane were associated with increased cases (coefficient=0.009). Similarly, Brubacher et al.,⁸⁵ Cousins et al.,⁸⁹ and Fleury et al.⁹¹ all identified associations between increasing cases and increasing temperatures in Canada, although estimates varied across regions. Two studies explored the effect of temperature on incidence by age group; one found young children (0-10 years) to be more sensitive to temperature than other age groups;¹¹⁴ the other study found risk was significantly increased for most age groups (0-34 years of age) when in close proximity to high ruminant density or for 16-34 year olds when in close proximity to poultry operations.⁸¹

Other Weather Exposures

Among the seven studies with 11 estimates for the association with relative humidity, 7 were negative, and 4 were positive. Studies used correlation coefficients to understand this association most often, and no estimates of risk were provided. Of the 6 articles with 4 estimates for the association with sunlight, 3 were negative and 1 was positive. Hours of sunlight were used in two studies assessing model fit using R² values ranging from 0.23-0.72.^{103,111} Patrick et al.¹¹¹ found that increasing hours of sunlight 4 weeks prior and increasing average temperature was the best model for predicting increased campylobacteriosis in Denmark. Additionally, the combination of high average temperature and low relative humidity resulted in greater incidence. Similarly, Louis et al.¹⁰³ found their best model included adjusting for temperature, precipitation and hours of sunshine. One study explored cloudiness and insolation, both exhibiting negative relationships with incidence at a 2-month lag.¹¹⁰

Three studies explored 7 combinations of weather variables with all but one having a positive correlation to *Campylobacter* infections. Of note, all combinations included precipitation (6 with rain and 1 with snow) or a variation of temperature (minimum or average) and relative humidity. The positive relationships were significant in both studies with the outcome of incidence,^{86,103} while the relationship reported for the study with the outcome was hospitalizations was not.¹¹⁰

El Niño and La Niña

Colston et al.⁸⁸, Soneja et al.¹¹⁸, and Lal et al.¹⁰² explored the impact of El Niño and La Niña events on infections. All articles used the Southern Oscillation Index (SOI) which “compares the difference from average air pressure in the western Pacific, measured in Darwin, Australia, to the difference from average pressure in the central Pacific, measured in Tahiti.”⁵⁵ Colston et al.⁸⁸ used data from the MAL-ED cohort, showing that during later periods of a La Niña flooding event in Loreto, Peru, *Campylobacter spp.* risk increased (RR=1.41 95% CI: 1.01,1.97). Soneja et al.¹¹⁸ used data from FoodNet in Maryland, US, and similarly found that risk was considerably higher for precipitation during La Niña periods (IRR=1.09, 95% CI: 1.05, 1.13). They found no elevated risk during El Niño periods, and a 2% risk during neutral periods (as compared to their overall 3% risk). In contrast, Lal et al.¹⁰² found no association with the SOI in New Zealand.

Table 3. Overall associations between weather variables and *Campylobacter* infections from articles published up to September 1, 2022 and included in a systematic review exploring the effects of weather and climate change on *Campylobacter spp.* incidence

Weather event	Effect of weather exposure on human infection	Was the effect modified by presence of animal operations?	Strength of evidence	Selected references
Temperature	Increased infections with increasing temperatures	Yes. Proximity to chicken and poultry operations, and other high animal density significantly increases infections beyond crude analyses.	A	Allard 2011, Brubacher 2020, Bi 2008, Cousins 2020, Djennad 2019, Fleury 2006, Carev 2018, Kovats 2005, Kim 2015, Kuhn 2020, Lake 2009, Lake 2019, Lal 2013, Louis 2005, Naumova 2007, Oberheim 2020, Oh 2021, Park 2018b, Rosenberg 2018, Sanderson 2018, Sung 2022, Tam 2006, Vucković 2011, Yun 2016
	Decreased infections with increased temperatures over 6.9 °C, with maximum temperature, and during heat waves.	Not reported.	B	Arsenault 2012a, Bi 2008, Kuhn 2020
Precipitation	Outbreak following an extreme or heavy precipitation event	Yes. In 4 outbreaks (Gilpin, Kuhn 2018, Merritt 1999, Pitkanen 2008), presence of animals was thought to be the source of <i>Campylobacter spp.</i> contamination which was flushed into water sources after the precipitation event	A	Auld 2004, Bartholomew 2014, Fong 2007, Gilpin 2020, Harder-Lauridsen 2013, Kuhn 2017, Kuhn 2018, Merritt 1999, Millson 1991, Nichols 2009, Pitkanen 2008
	Decreased infections with winter precipitation or snowfall	Not reported.	B	Park 2018b, Kuhn 2020
	Increased infections with increasing precipitation	Yes. Proximity to chicken and poultry operations, and other high animal density significantly increases infections beyond crude analyses.	A	Arsenault 2012a, Arsenault 2012b, Bi 2008, Colston 2020a, Kuhn 2020, Lake 2019, Louis 2005, Park 2018b, Poulsen 2018, Sanderson 2018, Auld 2004, Bartholomew 2014, Fong 2007, Gilpin 2020, Harder-Lauridsen 2013, Kuhn 2017a, Kuhn 2017b, Merritt 1999, Millson 1991, Nichols 2009, Pitkanen 2008, Schwartz 2006

El Niño or La Niña	Inconsistent trend with SOI and infections	Not reported.	C	Colston 2020a, Lal 2013, Soneja 2016
Sunlight and Cloudiness	3 with negative associations, 1 with positive associations with sunshine duration and infection	Potential indirect association with more sun and higher average temperatures increasing outdoor activity and changing human behavior.	B	Cherrie 2018, Louis 2005, Oh 2021, Park 2018b, Patrick 2004, Spencer 2012
Relative Humidity	Positive correlation between increased relative humidity and outbreaks	Not reported.	B	Bi 2008 (Adelaide only), Yong 2015
	7 with negative associations, 4 with positive associations with relative humidity and infection	In one study, Patrick 2004, showed relative humidity was not an important predictor of positive broiler flock prevalence.	B	Bi 2008, Carev 2018, Cherrie 2018, Oh 2021, Park 2018, Patrick 2004

Does proximity to animals and animal operations affect the association between weather variability and enteric infections with *Campylobacter* spp. foodborne disease incidence?

Only 15 articles of the 47 explored the effect of animals or land use in their studies. Three articles noted proximity to animal operations as mediating factors preceding *Campylobacter* related outbreaks attributed to extreme precipitation events. Two noted presence of sheep paddocks or proximity to sheep which then contaminated water sources following heavy rainfall,^{83,93} and one was attributed to wild animal feces, contaminating rainwater tanks following heavy precipitation (546 mm throughout the preceding 3 months).¹⁰⁴

Seven of the 14 studies explored poultry density, positive broiler flocks, or proximity to high density poultry operations in their analysis. Arsenault et al.⁸¹ used both ruminant density per km² and poultry density per km², as well as a presence of 1 or more slaughterhouses geocoded to different geographical units. In their second paper using the same dataset, Arsenault et al.⁸⁰ found high ruminant density, high poultry density, and presence of large slaughterhouses were associated with increased incidence, but this differed by age group – risk was higher for younger age groups and attenuated in older groups. Hartnack et al.⁹⁵ noted that increase in human incidence of *Campylobacter* cases preceded similar increases in *Campylobacter* found in broiler chickens in their convenience sampling of broiler chicken flocks. Patrick et al.¹¹¹ found similar results as Hartnack et al.⁹⁵ finding that as temperature increases there is an increase in the percentage of broiler flocks testing positive at slaughter. Poulsen et al.¹¹³ explored effect modification of precipitation and residential proximity to poultry operations in Pennsylvania, US. They found that extreme precipitation events modified the relationship, whereby cases increased as the number of extreme events increased from none to five. Spencer et al.¹¹⁹ explored poultry farm, sheep, and dairy cattle density in four regions in New Zealand. They found in rural areas, sheep density and dairy cattle density were significantly associated with increased risk (RR=1.04 and 1.07 respectively).

The remaining 5 articles explored the effect of different land use variables including ecological zone, agricultural areas, urban vs rural, coastal vs non-coastal, and human behaviors such as visits to the countryside. Carev et al.⁸⁶ examined total size of utilized agricultural area finding no association between incidence of *Campylobacter* infections and higher agricultural activity. Louis et al.¹⁰³ reported correlations between nine agricultural data variables and *Campylobacter* rates ranging from animal specific variables (e.g. total poultry) to broader variables (e.g. total agricultural land) although they did not explore how this was affected by weather. With 1 exception, eight variables had a positive and statistically significant correlation with *Campylobacter* rates. Rushton et al.¹¹⁵ explored the effect of cattle and sheep stocking rates in their grid-based modeling approach. When accounting for farm animal grazing in their model, the density of cows on stagnogley soils (impervious, poorly draining soil type commonly clay or loam) as well as density of cattle and sheep were risk factors for campylobacteriosis. When they investigated density of cattle and sheep independently of soil type, they found decreased incidence, although for sheep this association was not statistically significant. Beef cattle density and distance from a poultry farm were not significant in any of the regions, but dairy cattle density was significant in one region (Manawatu).

What gaps exist for researchers interested in studying this association in the future?

Researchers interested in studying the association of weather with outbreaks, or incidence, have many components to consider. Kovats et al.'s international study highlighted the need to explore associations at a finer spatial resolution.⁹⁶ Pooling data at a national level, and across countries, obfuscates important local and sub-national effects in different regions. While no significant associations were found in Kovats's study, sub-national studies from countries included in the international study, including Australia,⁸⁴ Canada,^{79-81,85,89} Denmark,¹¹¹ England and Wales,¹⁰⁰ and New Zealand,¹¹⁹ show significant associations with weather variables. In contrast, Lake et al.¹⁰¹ clustered countries from Europe given their seasonal trends and found significant associations with temperature, and precipitation in different clusters. If researchers pool results from multiple countries in the future, they should consider climate, seasonal trends, and environmental conditions as potential confounders or mediators.

A common approach was to account for confounding by secular trends and seasonality by adding cubic-splines, sine-cosine functions, and polynomial smoothers to final models.^{79,89,91,96,100,115,120,121} For example, Allard et al.⁷⁹ used a negative binomial regression model with sine-cosine terms for one year and five harmonics to account for shorter periods within a year to reduce confounding and ensure their estimates were not over-inflated. Other authors categorized and adjusted for season in their model.^{80,84,118} Many articles did not control for seasonality, therefore, whether the measures illustrated the relationship between the weather variable and *Campylobacter* incidence or confirms a larger understanding of *Campylobacter* seasonality is unclear.

Articles explored whether prior case counts contributed to increases in incidence. Allard et al.⁷⁹ found no additional effect of prior case counts in the 6 weeks prior in their final model, whereas Bi et al.⁸⁴ found that the number of cases in the current week was related to cases in the previous 1-4 weeks. To account for population changes over time, Brubacher et al.⁸⁵ included a log-population offset in their model, whereas Rushton et al.¹¹⁵ used a population-adjusted case rate for their dependent variable. To account for possible differences in reporting over time, some authors added terms for year⁸⁴ or for public holidays^{91,100,121} to adjust for trends in reporting. For example, Lake et al.¹⁰⁰ found a significant decrease in cases (RR=0.94) with a public holiday in the current week, and an increase in cases with a holiday in the previous week (RR=1.03).

Some studies were able to exclude travel-associated cases from their analysis,^{111,121} however this data often relies on complete interviews with cases and this data is often sparse or missing in surveillance systems. For example, one study¹⁰¹ excluded 6.8% of their cases due to recent reported travel, but travel status was unknown for 36.9% of cases. Tam et al.¹²¹ used data from self-reported exposures in a sentinel surveillance system to estimate the number of cases reporting foreign travel in the 2 weeks prior to illness. They then subtracted this information from the weekly time series in their analysis. Accounting for travel in analyses, where cases were not exposed to local weather, will help reduce confounding in future estimates.

Two articles projected what cases would look like under different climate change scenarios. Brubacher et al.⁸⁵ found that under the 50th percentile of possible temperature range increases in British Columbia, Canada, *Campylobacter* cases are projected to increase from 26.9% to 30.2%

across health jurisdictions. Allard et al.⁷⁹ estimated that if the mean annual temperature increased by 4.5 °C by 2055, this would result in a 23% increase, resulting in 107 additional cases per year (true incidence of 4,082 cases). These findings are especially helpful in estimating the burden of illness due to climate change in the future.

Risk of Bias

The risk of bias results are included in Table 4. After data extraction, eight articles used data from cohorts, and three articles had follow-up of cases. Overall, the 47 studies were considered to have a low risk of bias on the risk of bias scale (Average=1.61, Range=1-3). Two studies were deemed high risk,^{104,117} both were outbreak-related papers. No studies were deemed very high risk in any domains, or overall.

Table 4. Cochrane risk of bias quality assessment for articles published up to September 1, 2022 and included in a systematic review exploring the effects of weather and climate change on *Campylobacter spp.* incidence

Article	Domain							Overall
	A	B	C	D	E	F	G	
Allard 2011		✓	⚠		⚠	✓		✓
Arsenault 2012a		✓	✓		✓	✓		✓
Arsenault 2012b		✓	✓		✓	✓		✓
Auld 2004		✓	⚠		⚠	✓		✓
Bartholomew 2014		⚠	⚠		✓	✓		✓
Bi 2008		✓	✓		⚠	⚠		✓
Brubacher 2020		✓	✓		✓	✓		✓
Carev 2018		✓	⚠		✗	⚠		⚠
Cherrie 2018		⚠	✓		✗	⚠		⚠
Colston 2020a	✓	✓	⚠	✓	✓	✓	✓	✓
Cousins 2020	✓	⚠	✓	✓	⚠	✓		✓
Djennad 2019		✓	✓		⚠	⚠		✓
Fleury 2006		✓	✓		✗	✓		✓
Fong 2007	✓	✓	⚠	⚠	⚠	✓		✓
Gilpin 2020		✓	⚠		✓	✓		✓
Harder-Lauridsen 2013	⚠	⚠	⚠	✓	⚠	⚠		⚠
Hartnack 2009		✓	⚠		⚠	✓		✓
KimYongSoo 2015		✓	⚠		✗	✓		✓
Kovats 2005		⚠	✓		⚠	✓		✓
Kuhn 2017		⚠	⚠		⚠	✓		⚠
Kuhn 2018		✗	✓		⚠	✓		✓
Kuhn 2020		✓	✓		✓	✓		✓
Lake 2009		✓	✓		✓	✓		✓
Lake 2019		✓	✓		⚠	✓		✓
Lal 2013		✓	✓		⚠	⚠		✓
Louis 2005		✓	⚠		⚠	⚠		⚠
Merritt 1999	✓	⚠	⚠	✓	✗	✗	✓	✗
Millson 1991	✓	⚠	⚠	⚠	⚠	⚠		⚠
Naumova 2007		✓	✓		✗	✓		✓
Nichols 2009	✓	✓	⚠	⚠	⚠	⚠		⚠
Oberheim 2020		✓	✓		⚠	✓		✓
Oh 2021		✓	✓		✗	✓		✓
Park 2018b		✓	⚠		⚠	✓		✓
Patrick 2004		✓	⚠		⚠	⚠		⚠
Pitkanen 2008		⚠	⚠		⚠	⚠		⚠
Poulsen 2018		✓	⚠		⚠	✗		⚠
Rosenberg 2018		✓	✓		✗	⚠		⚠
Rushton 2019		✓	✓		✓	✓		✓
Sanderson 2018		✓	⚠		✓	✓		✓
Schwartz 2006	✓	✓	⚠	✗	✗	✓		✗
Soneja 2016		✓	✓		✗	✓		✓
Spencer 2012		✓	✓		✗	✓		✓
Sung 2022		✓	✓		✗	⚠		⚠
Tam 2006		✓	✓		✗	✓		✓
Vucković 2011		✓	⚠		✗	⚠		⚠
Weisent 2014		✓	✓		✗	⚠		⚠
Yun 2016		✓	✓		✗	✓		✓

Legend: Green check, low risk; Yellow exclamation mark, some concerns; Red x, high risk. The Cochrane Risk of Bias reporting tool⁷⁸ was modified to indicate the exposure, and outcomes of interest. Questions for each domain include: A) Was selection of exposed and non-exposed cohorts drawn from the same population? B) Are you confident in the assessment of exposure (how climate change or the weather event was defined)? C) Are you confident the outcome of interest was not present at the start of the study (that the population didn't already have *Campylobacter*)? D) Did the study match exposed and unexposed for all variables that are associated with the outcome of interest, or did the statistical analysis adjust for those variables? E) Are you confident in the assessment of the presence or absence of confounding factors? F) Are you confident in the assessment of the outcome (how infection was determined)? G) Was follow-up of the cohort adequate?

Discussion

The aim of this systematic review was to synthesize the impact of weather variability on *Campylobacter* infections using peer-reviewed research literature. We found 47 articles, of which 13 were outbreak-related. Overall, the studies found a positive association between temperature and *Campylobacter* infections, although there may exist a threshold or complex interactions with other weather events whereby *Campylobacter* infections no longer increase with increasing temperature. The effect of precipitation on infections was mixed, with some studies finding a positive association, others finding a negative association, and still others finding no association. Of note, 12 of the 13 outbreak articles analyzed outbreaks following extreme or heavy precipitation events. While overall we conclude there is a positive association between precipitation and incidence, the variability in results may be due in part to differences in how precipitation was defined and categorized among studies.

Other weather variables that were analyzed included El Niño and La Niña events, relative humidity, sunlight hours, and wind, among others. While each domain had multiple peer-reviewed studies showing quantifiable trends, the results were inconsistent. When considered together, we found that increased sunshine duration and low relative humidity may be associated with decreased *Campylobacter* infections. This is consistent with the microbiology of *Campylobacter* which is extremely sensitive to dry weather and ultraviolet radiation.¹⁵

The majority of articles did not analyze the effect of proximity to animal operations on *Campylobacter* infections. This may be due to farms not being present in the area of interest, but it is also likely data were not available or were just not explored further. Articles exploring the use of animal data found overall higher incidence in areas with farm operations and high animal density. Farm operations and animal density can be described, and analyzed, in a variety of ways. For example, poultry, ruminant, and cattle density were all associated with increased risk of *Campylobacter* infections in humans in this review, but the presence of farm operations had disparate results. Animal density remains an important indicator of spatial variation in infections for *Campylobacter*, and future research efforts should explore these differences to determine potential thresholds that affect *Campylobacter* incidence.

While this review did not result in a meta-analysis because there were not enough comparable studies, it has many strengths. We used a comprehensive search strategy from multiple databases which helps us to be confident that we captured the full scope of articles for inclusion. We also used standardized and validated methods for understanding the strength of evidence and risk of bias in included studies. We also contributed significantly to our knowledge in this area by summarizing pathogen-specific associations of weather on *Campylobacter*. Among its strengths there are a few limitations to note. We did not search the existing grey literature, dissertations, or

other white papers and reports which may provide additional insight to this review. Demographics of participants, even total cases used in analyses, were often missing from studies which did not allow us to understand the representativeness of the results.

Many statistical analysis approaches were used among the 47 articles. While many approaches exist, to move this area forward, researchers need to provide estimates of risk. Researchers should consider climate, seasonal trends, and environmental conditions as potential confounders or mediators of this relationship and account for prior case counts and risk factors. With estimates of risk we will be able to understand the burden of *Campylobacter* infections attributable to weather events and project what this effect will look like with climate change. Additionally, real-time surveillance that integrates weather and these risk estimates would help public health more readily respond to and prepare for the effect of extreme weather events.¹²⁶

For public health practitioners, considering the effect of weather around the time of an outbreak is important. All of the outbreak papers included here used descriptive statistics, and general descriptions of weather events that preceded outbreaks. There were many articles that hypothesized that weather played a role in their outbreak, but no further investigation was reported (although it may have been conducted) and, thus, they were excluded from this review. Future outbreak investigations should explore and document the effect of weather, particularly extreme precipitation, when investigating causal mechanisms for *Campylobacter* outbreaks particularly during suspected water-borne outbreaks.

Conclusion

This review found that both temperature and precipitation increase *Campylobacter* infections in people, while other weather parameters show inconsistent results. We found that, among studies that investigated it, proximity to agriculture and animal operations significantly increases *Campylobacter* infections, and future research should account for these effects. Future research studies in this area have many components to consider including the complex interaction of multiple weather variables, confounding factors, and choice of modeling. To move this field forward we need estimates of risk which will help us to determine the proportion of enteric illnesses attributable to weather which can be used to project burden due to climate change. This review summarizes some of the key weather exposures we should consider in future research, and contributes significantly to our understanding of pathogen-specific associations related to weather.

Chapter 5. Aim 2: Effect of precipitation events and drought periods on *Campylobacter* incidence in the Southwest US, 2009-2021

Introduction

Campylobacter is a microaerophilic spirochete bacteria that can cause acute gastroenteritis in humans. *Campylobacter jejuni* causes 90% of human infections, and campylobacteriosis is the leading bacterial cause of diarrhea worldwide. In the United States (US), *Campylobacter* causes 845,024 infections (90% Credible Interval (CrI): 337,031–1,611,083), 8,463 hospitalizations (CrI: 4,300–15,227), and 76 deaths (CrI: 0-332) annually.¹¹ Taking into account underreporting and challenges with culturing *Campylobacter*, the CDC estimates 1.5 million *Campylobacter* infections each year.¹⁹ Some people who acquire *Campylobacter* also go on to develop post-infectious sequelae which account for 74% of the average 22,500 Disability Adjusted Life Years associated with *Campylobacter* disease burden.¹¹

While *Campylobacter* infections are thought to be predominantly due to foodborne exposures, some have estimated that 30-50% of *C. jejuni* infections may be a result of infection from exposures in the wider environment.¹⁴ The bacteria is well adapted to survive between 37°C and 42°C, but it is extremely sensitive to dry weather and ultraviolet radiation.¹⁵ *Campylobacter* has a few natural reservoirs including wild animals (birds and pigs), farm animals (poultry, cattle, pigs and sheep) and domesticated animals (cats and dogs).^{16,17} The incidence of *Campylobacter* varies seasonally, with an initial late spring/early summer peak; however the reasons behind this variation are multifaceted and not well understood.⁴² Previous studies in Canada,⁸⁰ Pennsylvania, USA,¹¹³ and two international studies^{88,101} have shown an increased risk of *Campylobacter* following extreme precipitation (risk estimates ranging from 1.11 to 1.52). Others have found no association with either total precipitation or extreme precipitation events.^{89,118} The interaction of human, animal, and environmental sources which contribute to *Campylobacter* infections needs further research.

Wet conditions due to weather can aid in *Campylobacter* survival, and clay soils typically found in arid environments increase the risk of it being spread further during surface-water flow events.² Additionally, in the US from 1997-2008, 9.2% of *Campylobacter* outbreaks were waterborne.¹²⁷ The Southwest US includes four states: Arizona (AZ), Colorado (CO), New Mexico (NM), and Utah (UT). The four states comprise an arid and semi-arid climate which has experienced a long-term drought, characterized by “a deficiency of moisture that results in adverse impacts on people, animals, or vegetation over a sizeable area.”¹²⁸ Drought is expected to increase in its duration and intensity with climate change in the Southwest.^{53,129}

Drought has been linked to numerous health effects including decreased access to safe food and water.¹³⁰ For example, drought can lead to shortages of clean drinking water, resulting in a shift to using water sources not suitable for human consumption or exposure, and reuse of water sources for landscaping (reclaimed water), agriculture (recharged ground water), and for animal consumption.^{10,130,131} These effects can contribute to increasing pathogen loads in the environment resulting in an increased possibility of a contamination event leading to human food or water-borne illness. The effect of drought on diarrheal illnesses has not been explored fully in

the research literature; a systematic review by Levy. et. al.¹³¹ found only three articles, with disparate results. These included a dose-response relationship between drought level and rates of diarrheal illness in Wales,¹³² an outbreak of *E. coli* O157 in Swaziland and South Africa following a heavy precipitation event preceded by drought,¹³³ and a non-significant relationship between diarrhea and drought in Africa from 1980-2000.¹³⁴ Wang et al.¹⁰ reported stronger positive associations following heavy precipitation events preceded by dry conditions compared to wet conditions in the MAL-ED cohort, although pathogen-specific estimates were not explored. While studies have examined temperature and precipitation variability on *Campylobacter* incidence, to our knowledge, no studies have explored the effect of antecedent drought preceding extreme precipitation events on *Campylobacter spp.* incidence.⁷¹

Objectives

The objective of this work is to assess the association of antecedent precipitation on the incidence of *Campylobacter* in four states of the Southwest US from 2009-2021. We hypothesize that precipitation will be associated with an increase in *Campylobacter* incidence, and that this relationship will be modified by antecedent drought.

Methods

Study Design & Setting

We conducted an ecological analysis of public health surveillance data in four states: AZ, CO, NM, UT. While drought has increased in the region over the time period, precipitation varies significantly within each state due to elevation and topographical features. Compared to other regions in the US, these states have not experienced an increase in extreme precipitation events in the same time period, typically defined as rainfall over 1 inch.^{54,135,136} However, when extreme precipitation events do occur they can cause catastrophic damage due to high surface water-flow over poor-absorbing soils.⁵⁴ While all four states have majority arid climate zones, Colorado, New Mexico, and Utah also have continental climate zones using the Köppen-Geiger Climate Zone.⁶³ Arizona and New Mexico's weather is affected by Southern Oscillation Index (SOI) events, which include an intensification of the North American monsoon (El Niño), and an increase in winter precipitation and cooler temperatures (La Niña).^{55,61}

Data Sources

Data were collected from four main sources: 1) public health surveillance from each state, 2) weather data from Parameter-elevation Regressions on Independent Slopes Model (PRISM)⁵⁷ and National Oceanic and Atmospheric Administration (NOAA),⁶⁰ 3) county-level information from the US Census¹³⁷ and Köppen-Geiger Climate Zone,⁶³ and 4) animal and farm data from the United States Department of Agriculture (USDA) 2017 census.¹³⁸ We describe each dataset in depth below.

Public health surveillance

Campylobacter data is collected by each state's respective state health department and was provided for the earliest and latest available years for each jurisdiction (AZ: 2009-2020, CO: 2009-2021, NM: 2009-2021, UT: 2012-2021). De-identified daily reports of confirmed, probable, and suspect *Campylobacter* cases by county during each time period were provided.

Due to data suppression requirements in Utah, only cases reported in counties >20,000 population were included. This resulted in a loss of 7% of the cases (~700 cases) during the time period. Case definitions vary between states, with AZ, CO, and UT using the Centers for Disease Control and Prevention and Council for State and Territorial Epidemiologists (CSTE) case definition, and NM using the FoodNet case definition.¹³⁹⁻¹⁴¹ The primary difference between these case definitions is the exclusion of epidemiologically linked cases in FoodNet. A summary of the definitions and how they have changed over time is available in Table 1.

Table 1. Case definitions for *Campylobacter* spp.

Case Definition Year	Confirmed	Probable	Suspect
2015	Isolation of <i>Campylobacter</i> spp. from a clinical specimen *	Detection of <i>Campylobacter</i> spp. in a clinical specimen using CIDT OR epidemiologically linked to a confirmed or probable case	N/A
2012	Isolation of <i>Campylobacter</i> spp. in a clinical specimen	A clinically compatible case that is epidemiologically linked to a confirmed case	Detection of <i>Campylobacter</i> spp. in a clinical specimen using non-culture based laboratory method
1990	Isolation of <i>Campylobacter</i> spp. in a clinical specimen	A clinically compatible case that is epidemiologically linked to a confirmed case	N/A
FoodNet Case Definition	Isolation of <i>Campylobacter</i> spp. in a clinical specimen	Detection of <i>Campylobacter</i> spp. in a clinical specimen using CIDT Epidemiologically linked cases are not counted as cases	N/A

Date reported to the health department was used for all temporal analyses, as surveillance varies between states, and onset, collection, and laboratory result date may have more missingness due to interview and reporting capacities in each jurisdiction. Because *Campylobacter* is a reportable disease in each state, this dataset comprises all reported human cases in this area. If no cases were reported on a given day in a given county, we imputed a zero for that day and county in order to have a complete case analysis of all days, rather than only days in which a case was reported. This allows us to explore incidence, and not just severity of increasing case counts.

Daily data were aggregated to week of the year (starting on Sunday) for a total of 52 or 53 weeks depending on leap-years using the `lubridate142 week()` function in R Studio version 4.2.2. Month was determined based on day of the year. using the `lubridate142 month()` function.

Weather and climate

Weather data were derived from PRISM,⁵⁷ including daily county-level minimum, maximum, and average precipitation (inches), and minimum, maximum, and average temperature (°F) by

county centroid. PRISM interpolates weather station data within an area, so in larger counties this may capture a more complete picture of precipitation and temperature on a given day. In PRISM, weather stations are weighted by their physiographic similarity to the grid of interest (in this case, county-level centroid). Typically with denser station data, more data is interpolated, and the more likely that stations within the county contributed to the centroid prediction. In areas with sparse weather station data, values may be influenced by weather stations outside of county boundaries. This is the same limitation that would result if we used nearby weather station instead, as not every county has its own weather station. The benefit of using PRISM over individual weather stations is that PRISM pulls from multiple stations capturing a more holistic picture of weather variability.

To aggregate weekly data, precipitation values for all days in a week were summed to determine the total precipitation in a week. The weekly minimum or maximum was determined by imputing the smallest and largest values in a week. We defined three extreme precipitation events comparing weekly PRISM data to 30-year normal data from 1990-2020: (1) heavy precipitation defined as total precipitation in the week over the 30-year normal, (2) total precipitation above the 95th percentile, and (3) total precipitation above the 99th percentile.

Palmer Drought Severity Index (PDSI) by month for each county were derived from the National Centers for Environmental Information (NCEI) via NOAA.⁶⁰ PDSI is available by month and climate division and were applied to month in the dataset. PDSI generally considers the drought level in the current month, and the previous 9 months on a rolling basis.⁵⁹

To understand the effect of El Niño and La Niña, we used the Southern Oscillation Index (SOI) by month for the time period. El Niño is characterized by a negative SOI value, neutral when SOI is zero, and La Niña when the SOI is positive.⁶¹

County-level data

Urbanicity was derived from county-level 2020 US Census designations of majority urban vs rural for each county.⁶² We abstracted the 2020 US Census population estimate for each state to calculate incidence rates over time. We used the Köppen-Geiger Climate Classification scheme to analyze data across the four states.⁶³ Specifically we used the main climate classification data from the latest available observed climate classification map from 1980-2016 to determine the major climate zone by county. We used ArcGIS Online to intersect the climate zone map with county boundaries using the ‘Join Feature’ analysis, and then summarized the majority zones by county using the ‘Summarize Within’ analysis.

Animal data

Data for the number of operations with sales in a county were pulled from the 2017 USDA Farm census Quick Stats 2.0. We pulled data on the number of operations for poultry, sheep and goats, sheep only, cattle, and leafy greens. Data were categorized into three categories based on tertiles given their distribution: no operations, some operations (1-5 for poultry, sheep, cattle, 1-50 for goat and sheep, leafy greens), and high operations (>5 for poultry sheep, cattle, >50 for goat and sheep, leafy greens).

Data Linkage & Transformation

Weekly case counts for each pathogen were linked to weather data by week reported to the health department for each county. Drought data were linked by month, year, and climate division. NCEI provides a table that crosswalks county to climate division that is available in the research compendium. Urbanicity and population was linked by year and county. The full dataset contains weekly weather, health, animal, and county information for each state.

We time set the data to explore the association with 2-week, and 3-weeks lags. These lags were chosen given stakeholder input, differences in incubation periods, and laboratory and reporting delays which make concurrent counts or 1-week lags less meaningful. Upon exploring initial model estimates, results from the 2-week and 3-week lags were similar, so we moved forward with a 3-week lag for the remaining analysis. Weekly lags beyond 3-weeks were not explored as our primary interest was to explore the acute effect of precipitation events following drought. Lags beyond 3 weeks might explain seasonal variations and accumulation of pathogens in the environment over time.

In order to analyze data by week, we used R's lubridate package function week() which "returns the number of complete seven day periods that have occurred between the date and January 1st, plus one."¹⁴² Due to differences in R and Stata, we had to suppress the last week of data from years in order to time set the data for analysis. This resulted in the loss of some data (less than 1% of cases) over the designated time periods in each state (AZ: n=21, CO: n=22, NM: n=13, UT: n=17).

Variables

Our exposure of interest was a heavy precipitation event, defined as a one inch increase in total weekly precipitation. Our outcome is confirmed or probable infection with *Campylobacter* during the respective time period in each state.

Statistical Analysis

We used negative binomial Generalized Estimating Equations (NBGEE)^{64,68} to investigate the relationship between precipitation and counts of reported *Campylobacter* cases using an autoregressive correlation structure. A negative binomial distribution was chosen over others because the variance exceeded the mean with all explored lags of the dependent variable (Table 2).

Table 2. Count, mean, standard deviation, and variance of dependent variables with associated lags

	n	Mean	Standard Deviation	Variance
<i>Campylobacter</i> cases	90012	0.41	1.42	2.01
Lag 1	89871	0.41	1.42	2.01
Lag 2	89730	0.41	1.42	2.02
Lag 3	89589	0.41	1.42	2.02
Lag 4	89448	0.41	1.42	2.02

To understand the connection between precipitation and pathogen incidence by potentially confounding factors, we adjusted for average temperature to adjust for seasonality. The results of different model testing using Pan’s quasi likelihood QIC are shown in Table 2. While models including county population were the best fit according to QIC, estimates were largely unstable. Therefore we chose to include total precipitation, average temperature, and PDSI in final models.

Table 3. Pan’s quasi likelihood (QIC) metrics for determining the best model for different variable combinations

	<i>p</i>	Trace	QIC	QICu	Estimates diverging
Total precipitation	2	1346.8	94456.4	91766.8	
Average temperature	2	576.0	85824.0	84676.0	
PDSI	2	1372.2	94462.4	91722.1	
County population	2				Yes
Total precipitation and Average temperature	3	588.7	85594.3	84422.9	
Total precipitation and PDSI	3	1385.2	94506.8	91742.4	
Total precipitation and County population	3				Yes
Average temperature and PDSI	3	586.6	85550.8	84383.5	
Average temperature and County population	3	930.8	70575.7	68720.0	
PDSI and County population	3				Yes
Total precipitation, Average temperature, and PDSI	4	587.6	85265.5	84098.4	
Total precipitation, Average temperature, and County population	4	1065.0	70756.5	68634.6	
Average temperature, PDSI, and County population	4	557.0	73078.2	71972.2	
Total precipitation, PDSI, Average temperature, and County population	5	715.8	69703.2	68281.7	

Legend: *p*, number of parameters; trace, the product of the independent and robust variance estimators; QIC, Pan’s quasi likelihood under the independence model criterion; QICu, the QIC when trace approximates an independent covariance structure and is equivalent to the number of parameters; Total precipitation, total precipitation in inches in a week; Average temperature, average temperature in °F in a week; PDSI, Palmer Drought Severity Index standardized from 0 to 20 with larger values indicating more severe drought in a month; County population, the county population from 2020 US Census estimates.

We performed stratified analyses for each variable level for each factor including: by state, climate zone, urban vs. rural designation, SOI category, and animal category. The result of the NBGEE model are Incidence Rate Ratios (IRRs) which can be interpreted as a percent increase/decrease in the number of human case events following a 1 inch increase in total weekly precipitation. Datasets were merged in R version 4.2.2¹⁴³ (with the following packages: readxl,¹⁴⁴ dplyr,¹⁴⁵ purr,¹⁴⁶ readr,¹⁴⁷ lubridate,¹⁴² data.table,¹⁴⁸ stringr¹⁴⁹) and analyzed using Stata 17.¹⁵⁰

Sensitivity Analyses

We conducted numerous sensitivity analyses. We used a different drought index, the US Drought Severity Monitor (USDM)¹⁵¹ to explore how the association differs using a different index. During the COVID-19 pandemic, human behaviors changed including isolation and quarantine, healthcare seeking behaviors, and other restrictions.¹⁵² Due to this we conducted a separate analysis to explore only data before 2019 (removing 2020 and 2021 data from the analysis).

Finally, to explore the effect of extreme precipitation events, not just total precipitation, we re-defined our exposure variable as described above to explore heavy precipitation, precipitation above the 95th percentile, and above the 99th percentile. We then ran our primary analysis with this new exposure variable.

Data Access & Cleaning

All data, except health data, are available via the research compendium on GitHub. Instructions for collecting data, as well as code for merging and linking data are available to help others reproduce the results and conduct this work in other areas. Although surveillance data in this analysis are not considered PHI, health data require a data use agreement with each individual state health department in order to gain access.

Results

State-specific characteristics are provided in Table 4. Arizona had the highest statewide annual average temperature, and lowest annual average precipitation during the time period. In contrast, Colorado had the lowest annual average temperature and the greatest annual average precipitation. Incidence of *Campylobacter* ranged from 15.6 to 24.9 per 100,000 across the four states. Across the five farm operation types of interest, the state with the largest number of operations included: cattle (New Mexico), chicken and poultry (Colorado), goats and sheep (Arizona), sheep only (New Mexico), leafy greens (Colorado). Maps of farm operation density by type are available in the supplemental material (Appendix A).

Table 4. State-specific characteristics

	Arizona	Colorado	New Mexico	Utah	Total
Population, n	7,151,502	5,773,714	2,117,522	3,271,616	18,314,354
Years included in analysis	2009-2020	2009-2021	2009-2021	2012-2021	2009-2021
Counties included in analysis, n	15	64	33	29	141
Climate Zone, number of counties n (%)					
B, arid	15 (100%)	34 (53%)	31 (94%)	23 (79%)	103 (73%)
D, continental	0 (0%)	30 (47%)	2 (7%)	6 (21%)	38 (27%)
Urbanicity					
Urban	8 (53%)	40 (63%)	26 (79%)	16 (55%)	90 (64%)
Rural	7 (47%)	24 (37%)	7 (21%)	13 (45%)	51 (36%)
Statewide annual precipitation, mean	12.26	17.95	13.88	13.39	
Statewide annual temperature, mean (min, max)	59.7 (45.6, 73.8)	44.9 (31.0, 58.7)	53.2 (38.3, 68.1)	47.8 (35.1, 60.5)	
Total Counts of <i>Campylobacter</i>	13,416	13,274	6,865	5,227	38,782

Count of Confirmed Cases of <i>Campylobacter</i>	10,213	8,325	4,440	3,835	26,813
Percent Confirmed Cases of <i>Campylobacter</i>	76%	63%	65%	73%	69%
Incidence Rate of <i>Campylobacter</i> per 100,000 population per year	15.6	17.7	24.9	16.0	18.6
Farm Operations with Sales (USDA), n					
Cattle	51	53	91	63	258
Chicken and Poultry	69	262	65	79	475
Goats and Sheep	3437	1692	2883	1393	9405
Sheep only	73	184	205	149	611
Leafy greens	802	943	802	270	2817

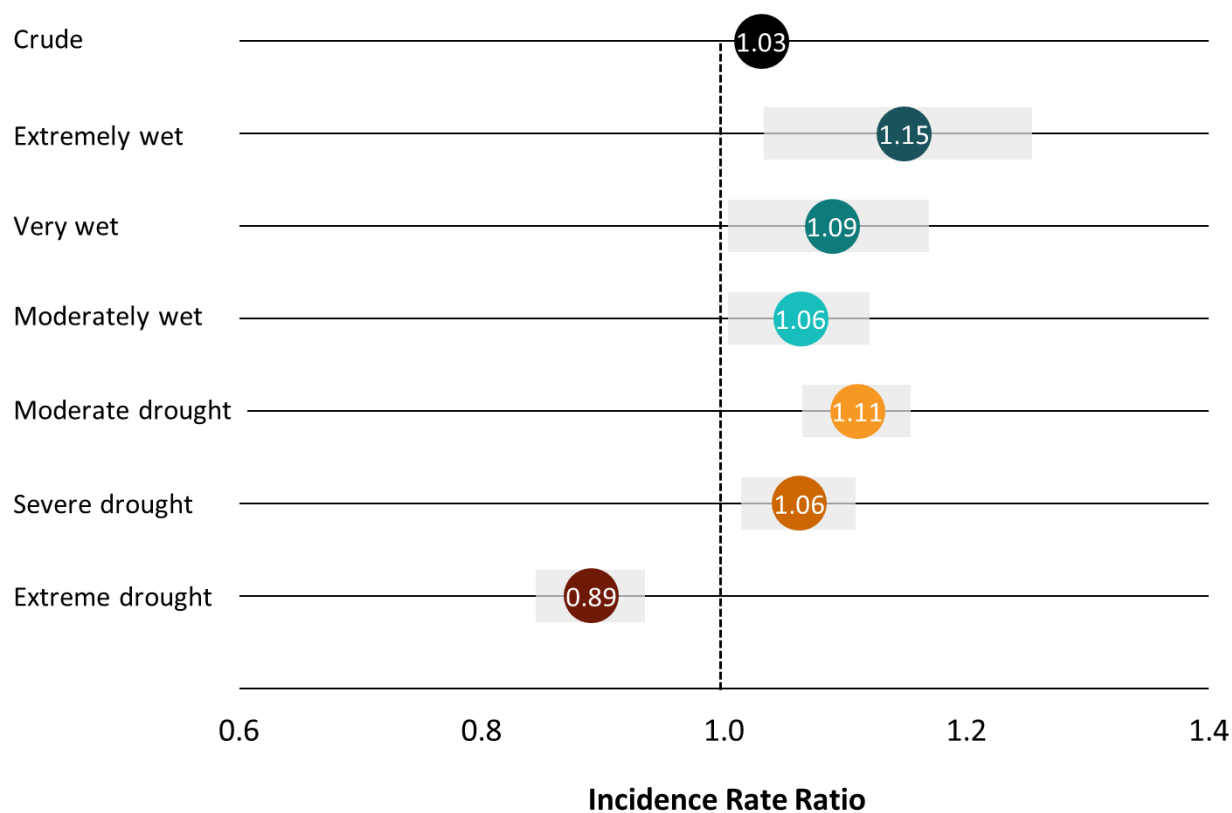
For every one inch increase in precipitation, *Campylobacter* cases (lagged 3-weeks) increased by 3% (IRR: 1.03, 95% CI: 1.02, 1.04) after adjusting for average temperature and PDSI. Cases were still increased when redefining the exposure variable, although results are not statistically significant (Table 5).

Table 5. IRR and 95% CI for different levels of precipitation (exposure) on *Campylobacter* cases after adjusting for temperature and drought severity

Definition of exposure	IRR (95% CI)
Total precipitation in a week	1.03 (1.02, 1.04)
Heavy precipitation, total precipitation in a week over a 30 year normal	1.01 (0.98, 1.05)
Total precipitation above the 95th percentile	1.00 (0.97, 1.02)
Total precipitation above the 99th percentile	1.03 (0.97, 1.08)

Figure 1 shows the effect of a one inch increase in precipitation accounting for antecedent drought levels. We see that PDSI is an effect modifier of the relationship between precipitation and *Campylobacter* cases. During wet conditions, cases are significantly increased (IRR range: 1.06-1.15) whereas in the most extreme drought conditions, cases are significantly decreased (IRR: 0.89, 95% CI: 0.85, 0.94).

Figure 1. IRR (marker) and 95% CI (band) for the effect of a one inch increase in precipitation during different levels of drought via the PDSI



Legend: dashed line indicates null value, where the risk of the outcome in both the exposed and non-exposed groups are equal

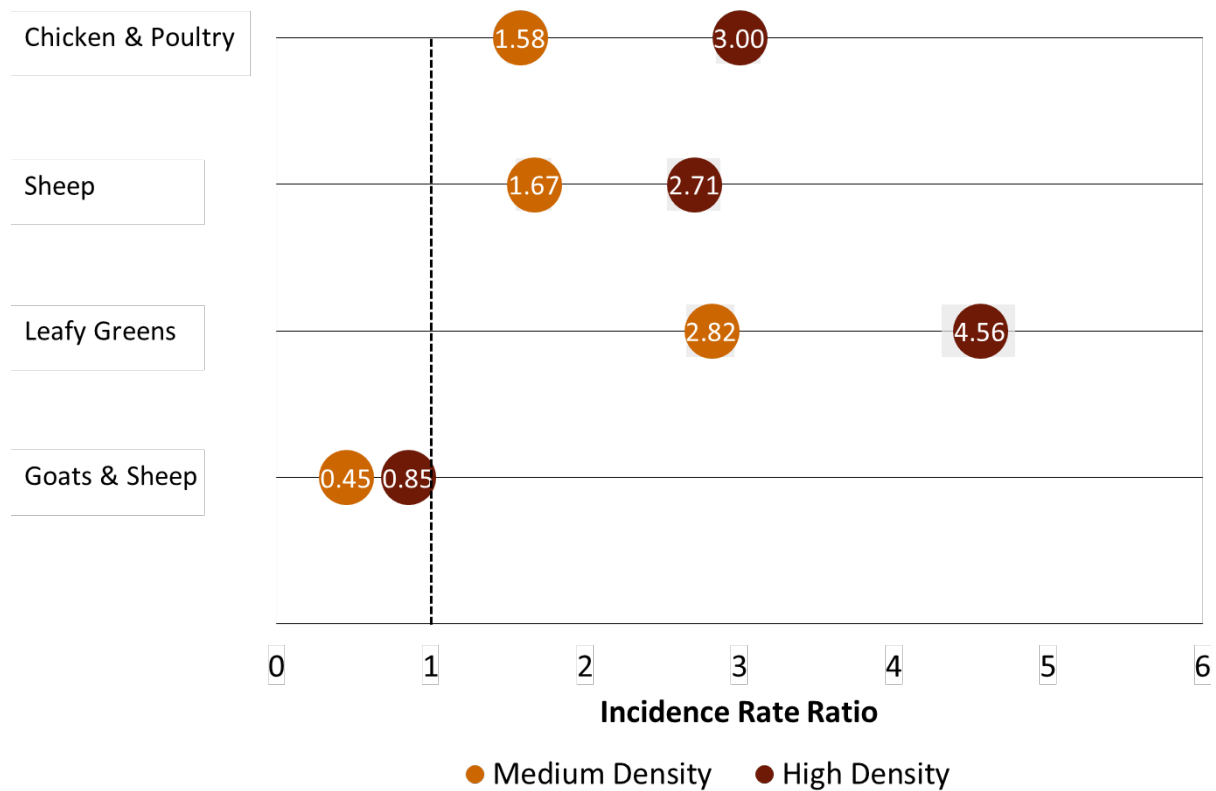
This association, increased cases following wet spells which decreases with increasing drought, remained consistent regardless of the spatial scale we explored (state, climate zone, urban vs. rural (census), urban-rural scheme (NCHS)). This relationship also remained consistent when we restricted the analysis to the years prior to the COVID-19 pandemic, as well as after adjusting for SOI. The results of these analyses are included in supplemental material (Appendix B). The results of our sensitivity analysis for using a different drought index, also remained similar – cases were still increased up to the moderate drought category, and were significantly decreased in severe to exceptional drought categories (Table 6).

Table 6. IRR and 95% CI for a one inch increase in precipitation on *Campylobacter* cases at different levels of drought severity via the USDM

US Drought Monitor Category	IRR (95% CI)
None (reference)	1.0 (ref)
Abnormally dry	1.1 (1.06, 1.14)
Moderate drought	1.11 (1.06, 1.15)
Severe drought	0.94 (0.9, 0.99)
Extreme drought	0.87 (0.82, 0.92)
Exceptional drought	0.72 (0.65, 0.8)

Presence of farm operations was a significant effect modifier of the relationship between precipitation and *Campylobacter* cases. Compared to counties with no operations, counties with chicken and poultry, sheep, and leafy green farms, had a significantly increased risk of *Campylobacter* cases following a one inch increase in precipitation (Figure 2). Compared to counties with no operations, counties with goat and sheep operations had a significant decrease in cases following a one inch increase in precipitation (medium density IRR: 0.45 95% CI: 0.42, 0.48); high density IRR: 0.85, 95% CI: 0.80, 0.91).

Figure 2. IRR (marker) and 95% CI (band) for the effect of a one inch increase in precipitation in counties with medium and high density of operations, compared to counties with no operations



Legend: dashed line indicates null value, where the risk of the outcome in both the exposed and non-exposed groups are equal

When exploring the effect of drought on this relationship, cases decreased following increasing drought severity, but remained significantly elevated (except for goats and sheep). For example, counties with chicken and poultry operations have a 99-152% increase in cases following an extreme precipitation event, even with drought (Table 7).

Table 7. IRR and 95% CI for the relationship between precipitation and *Campylobacter* cases in counties with farm operations.

	PDSI continuous	PDSI categorical		
		Moderate drought	Severe drought	Extreme drought
Cattle	1.26 (1.21, 1.31)	1.35 (1.28, 1.43)	1.29 (1.22, 1.37)	1.07 (1.01, 1.14)
Chicken and Poultry	2.33 (2.22, 2.46)	2.52 (2.37, 2.68)	2.41 (2.26, 2.57)	1.99 (1.86, 2.14)
Goats and Sheep	0.61 (0.57, 0.67)	0.66 (0.60, 0.72)	0.63 (0.58, 0.70)	0.53 (0.48, 0.58)
Sheep only	2.16 (2.01, 2.32)	2.31 (2.13, 2.50)	2.20 (2.02, 2.38)	1.83 (1.68, 1.99)
Leafy greens	3.53 (3.34, 3.74)	3.78 (3.54, 4.03)	3.59 (3.36, 3.84)	2.93 (2.73, 3.15)

Legend: PDSI, Palmer Drought Severity Index.

Discussion

This analysis explored the effect of precipitation on *Campylobacter* cases in the Southwest US from 2009-2021. We found that a one inch increase in precipitation results in a 3% increase in cases of *Campylobacter* in this region after adjusting for temperature and drought. Further, this relationship is modified by antecedent drought level – during wet conditions cases are increased (from 6-15%) and in the most extreme drought conditions, *Campylobacter* cases are significantly decreased by 11%. Finally, we explored how the effect of precipitation might differ in counties with different farm operations and found statistically significant increases in cases in counties with a medium density of farm operations (58-182%) and still greater in counties with a high density of farm operations (171-356%).

Our results are similar to Poulsen et al.¹¹³ who found that as the number of extreme precipitation events increased, the odds of *Campylobacter* infections were 1.52 times higher in the highest quartile of poultry operations compared to the lowest quartile (95% CI: 1.11, 2.09). Similarly, our results are consistent with Arsenault et al.⁸⁰ which found higher *Campylobacter* incidence in areas with a high density of ruminants (≥ 20 per km²) for most age groups. We found that areas with goats and sheep were significantly decreased whereas sheep alone were significantly increased. We hypothesize this may be in part due to the lack of human exposure to goats (e.g. meat consumption, dairy, or as pets). Previous reports on the census of agriculture showed that the majority of goat operations are small (fewer than 500 goats) with 42.4% for meat production, 10% for dairy (only 2.8% of that 10% sold commercially), and the remaining were used as brush control, pets, livestock and as pack animals. Additionally, it may be that the presence of goats and sheep means there are not chicken and poultry operations, one of our farm operations with the highest estimates. In fact, the majority of counties with 1-5 goat and sheep operations were in counties without chicken and poultry operations (36%) and only 19% of counties had a high density of both. In contrast there was much more overlap between counties with chicken and poultry operations and just sheep operations (data not shown).¹⁵³

While Wang et al.¹⁰ explored the effect of drought on diarrheal incidence using a longer-term drought index (6-month to 24-months), their 6-month estimate of diarrheal risk for children under 5 was similar to our results found here. Specifically they found that diarrheal risk for 6-month mild drought was 1.07 (95% CI: 1.05, 1.09) and 6-month severe drought was 1.11 (95% CI: 1.08, 1.14). We found similar results using PDSI (typically considered drought in the

previous 9-months). However our model explored the effect of a heavy precipitation event during different drought states, and for total population not just children, which may explain some of the variation in estimates we found.

One of the greatest strengths of this study is its contribution to our knowledge of the effect of precipitation accounting for antecedent drought. Previous studies have noted this as a limitation in the extant research literature. Our results do not support the concentration-dilution hypothesis which posits that rainfall following dry periods can deliver a concentrated dose of pathogens into surface water thereby increasing diarrheal illness. Whereas rainfall during wet periods dilute pathogen concentration reducing risk.⁷³ In contrast, our results showed elevated risk during wet periods, and only in the most extreme drought states was risk decreased. Our results are in alignment with Kraay et al.'s stratified analysis showing that bacterial diarrhea was more common during rainy seasons (IRR: 2.70, 95% CI: 1.60, 4.40).⁷³ This difference in results may speak to the importance of developing pathogen-specific estimates in understanding the risk posed by weather on different enteric illnesses.

While our study has many strengths, there are a few limitations. Our weather data, from PRISM is not county based, but grid based, so it will incorporate station data from the surrounding area, regardless of county boundaries. These stations are weighted by their physiographic similarity to the grid cell being modeled. So the grid cell prediction could be influenced by stations both inside and outside the county boundaries. Typically, the denser the station data, the smaller the contributing area, and the larger the county, the more likely that stations within the county contributed to the centroid prediction. We chose PRISM for this region, because it provides a better estimate of the weather occurring in the county than if we used one weather station (data not shown). While we were limited to county-level, PRISM is also grid-based, so if a county within this analysis wanted to use a finer spatial scale to explore this association further, they could. We have provided the relevant code and data for our collaborators on the project to do this, as well as provided the protocol, code and data to a public repository on GitHub. We also used report date instead of onset date for this analysis given data confidentiality restraints. This allowed us to use a larger dataset as onset date is usually only collected during case interviews and interview rates vary by state. We also did not exclude travel-associated cases for this same reason. These limitations should be taken into account when considering these estimates. The model we chose to use for this analysis is also a great strength. NBGEE takes into account the non-independence of our outcome data, as well as the correlation between our weather variables. Accounting for these limitations in our data allowed us to explore an overall estimate for this region, contributing significantly to our understanding in this area.

Conclusion

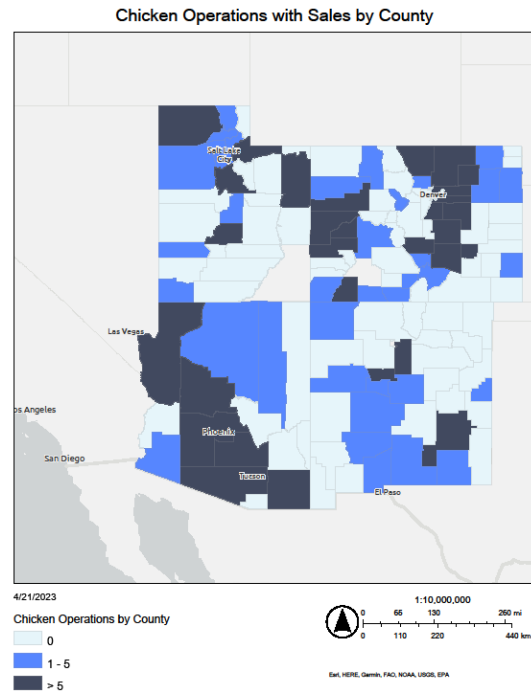
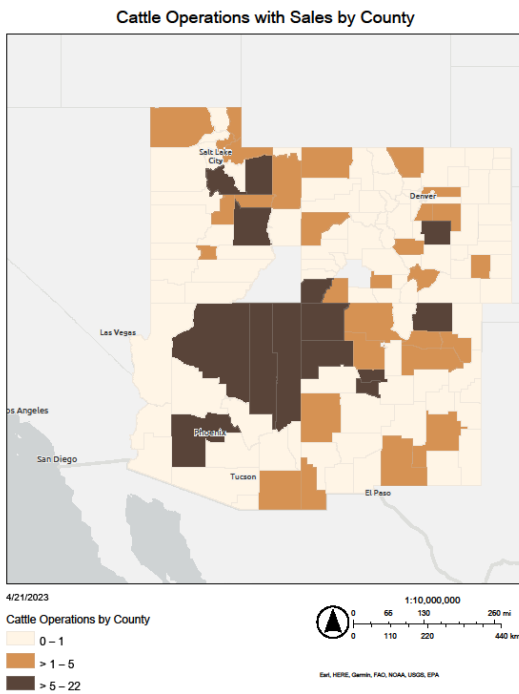
In this study we find that *Campylobacter* infections are increased following an increase in total precipitation, and that this relationship is modified by antecedent drought level. We showed that where the precipitation falls also matters – counties with farm operations had a significant increase in cases following heavy precipitation and as the density of operations increased, so did *Campylobacter* infections in people. These results contribute to our knowledge about the many ways that weather variability affects our health. With projected climate change, as drought

becomes more severe and extreme weather events become more common, counties may see increases in infections during wet periods and a decrease in infections during extreme drought conditions.

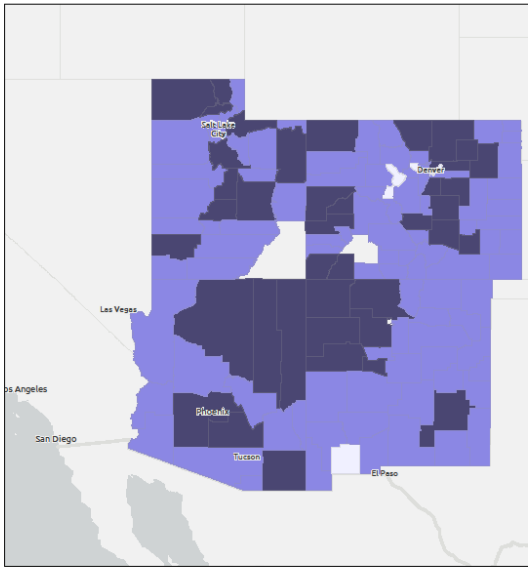
Supplemental Material

Appendix A

The following appendix includes maps of farm operation density by county for Arizona, Colorado, New Mexico, and Utah from the 2017 USDA Animal Census for cattle, chicken and poultry, goats and sheep, sheep, and leafy greens.

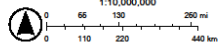


Goat & Sheep Operations with Sales by County



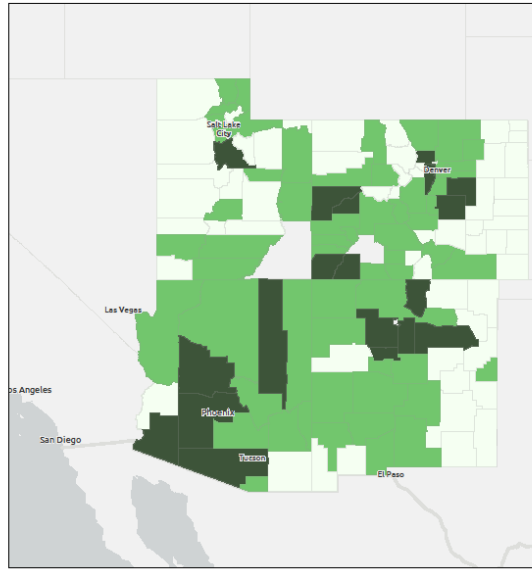
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Goat & Sheep Operations by County



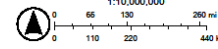
Est. HERE, Garmin, FAO, NOAA, USGS, EPA

Leafy Green Operations with Sales by County



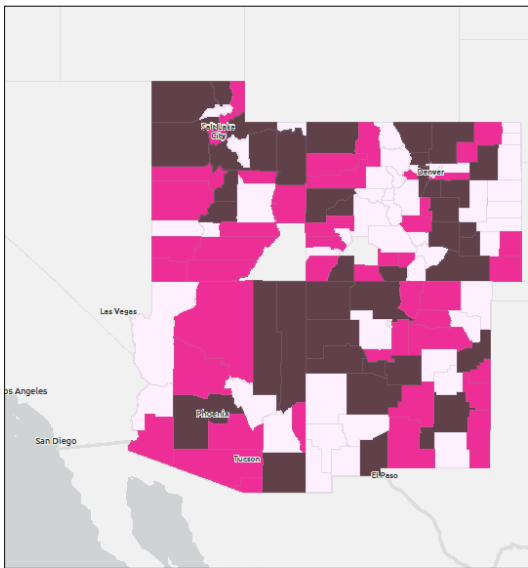
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Leafy Green Operations by County



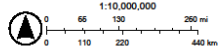
Est. HERE, Garmin, FAO, NOAA, USGS, EPA

Sheep Operations with Sales by County



4/21/2023

Sheep Operations by County



Est. HERE, Garmin, FAO, NOAA, USGS, EPA

Appendix B

The following table provides estimates (IRR (95% CI)) for the analysis exploring the effect of precipitation on *Campylobacter* cases stratified by different spatial scales, restricting to certain years, and adjusting for SOI.

	PDSI Continuous	PDSI Categorical		
		Moderate drought	Severe drought	Extreme drought
Multivariate model	1.03 (1.02, 1.04)	1.11 (1.07, 1.16)	1.06 (1.02, 1.11)	0.89 (0.85, 0.94)
State				
Arizona	1.02 (1, 1.03)	1.05 (1, 1.09)	1.03 (0.98, 1.08)	0.99 (0.93, 1.06)
Colorado	1 (0.97, 1.02)	1.28 (1.19, 1.39)	1.1 (1.01, 1.2)	0.84 (0.77, 0.91)
New Mexico	0.95 (0.91, 1)	0.98 (0.89, 1.07)	0.89 (0.81, 0.98)	0.79 (0.71, 0.87)
Utah	1.03 (0.99, 1.08)	1.35 (1.19, 1.52)	1.45 (1.29, 1.64)	1.43 (1.25, 1.64)
Köppen-Geiger Climate Zone				
B, arid or semi-arid climate	1 (0.99, 1.02)	1.1 (1.05, 1.14)	1.04 (0.99, 1.09)	0.91 (0.86, 0.96)
D, continental climate	1.01 (0.97, 1.05)	1.41 (1.28, 1.57)	1.29 (1.16, 1.43)	0.89 (0.8, 0.99)
Urbanicity				
Urban	1 (0.99, 1.01)	1.1 (1.06, 1.14)	1.05 (1, 1.09)	0.89 (0.85, 0.94)
Rural	0.92 (0.84, 1.01)	1.07 (0.89, 1.28)	0.87 (0.71, 1.05)	0.82 (0.69, 0.99)
NCHS Urban-Rural Classification Scheme*				
Large central metro (>1 million or more population, contain largest city in MSA)	1.01 (1, 1.02)			
Large fringe metro (>1 million adjacent to largest city)	1.02 (0.98, 1.06)			
Medium metro (250,000 to 999,999 population)	1 (0.98, 1.03)			
Small metro (<250,000 population)	0.99 (0.93, 1.04)			
Micropolitan (1 urban cluster of 10,000 to 49,999 population)	0.99 (0.95, 1.04)			
Non-core	0.97 (0.88, 1.07)			
Pre-COVID years (2009-2019)	1 (0.99, 1.02)	1.15 (1.1, 1.2)	1.09 (1.03, 1.14)	0.95 (0.9, 1)
Adjusting for Southern Oscillation Index	1.01 (0.99, 1.04)	1.09 (1.05, 1.14)	1.05 (1, 1.1)	0.88 (0.83, 0.93)

Legend: PDSI, Palmer Drought Severity Index.

* stratified analysis for NCHS scheme not conducted due to non-convergence of estimates

Chapter 6. Aim 3: Effect of precipitation events and drought periods on *Salmonella* spp. incidence in the Southwest US, 2009-2021

Introduction

Non-typhoidal *Salmonella* spp. is a gram negative rod-shaped bacteria with over 2,500 different serotypes, grouped into nine serogroups (A-I) determined by its antigenic structure.²⁴

Salmonellosis is caused by infection with *Salmonella* and usually includes fever, abdominal pain, diarrhea, nausea, and vomiting. In the United States (US) non-typhoidal *Salmonella* causes 1,027,561 infections (90% Credible Interval (CrI): 644,786–1,679,667), 19,336 hospitalizations (CrI: 8,545–37,490), and 378 deaths (CrI: 0–1,011) annually.¹¹ The CDC estimates 1.35 million infections occur each year.²⁴

Salmonella spp. has a range of hosts including livestock, wildlife, poultry, and domesticated animals,²⁴ however the main animal host of *Salmonella* is poultry. *Salmonella* is frequently transmitted via the fecal-oral route most commonly through contaminated food (poultry, meat products, eggs, and fresh produce) or direct animal contact. *Salmonella* can survive in very acidic environments as well as outside its animal hosts in the environment for extended periods of time (up to 332 days).^{27,28} Ambient air temperature has been associated with increased *Salmonella* infections in the US, and around the globe. *Salmonella* even persists during extreme heat events, particularly in coastal areas or in areas with farming operations.^{29,30} Kovats et al. showed that for every 1 °C increase in temperature above 6 °C across 10 European countries, *Salmonella* cases increased 5-10%.³¹ They attributed this large increase to *Salmonella*'s ability to survive in high temperatures and persist in the environment through various animal hosts. Drought stress and higher temperatures also result in the greater internalization of *Salmonella* in plant structures, particularly lettuce.^{35,36} *Salmonella* was implicated in 11% of leafy green vegetable outbreaks from 1973-2012, and seeded vegetable outbreaks linked to *Salmonella* frequently involve multiple states and a large number of illnesses and hospitalizations in the US.³⁷

The southwest US includes four states: Arizona (AZ), Colorado (CO), New Mexico (NM), and Utah (UT). The four states comprise an arid and semi-arid climate which has experienced a long-term drought, characterized by “a deficiency of moisture that results in adverse impacts on people, animals, or vegetation over a sizeable area.”¹²⁸ Drought is expected to increase in its duration and intensity with climate change in the southwest.^{53,129}

Drought has been linked to numerous health effects including decreased access to safe food and water.¹³⁰ For example, drought can lead to shortages of clean drinking water, resulting in a shift to using water sources not suitable for human consumption or exposure, and reuse of water sources for landscaping (reclaimed water), agriculture (recharged ground water), and for animal consumption.^{10,130,131} These effects can contribute to increasing pathogen loads in the environment resulting in an increased possibility of a contamination event leading to human food or water-borne illness. The effect of drought on diarrheal illnesses has not been explored fully in the research literature; a systematic review by Levy. et. al.¹³¹ found only three articles, with disparate results. These included a dose-response relationship between drought level and rates of

diarrheal illness in Wales,¹³² an outbreak of *E. coli* O157 in Swaziland and South Africa following a heavy precipitation event preceded by drought,¹³³ and a non-significant relationship between diarrhea and drought in Africa from 1980-2000.¹³⁴ Wang et al.¹⁰ reported stronger associations following heavy precipitation events preceded by dry conditions compared to wet conditions in the MAL-ED cohort, although pathogen-specific estimates were not explored. Because *Salmonella* has been shown to persist in soils and the environment, even with drying as occurs during a drought, more research is needed to explore the pathogen-specific risk of *Salmonella* which may occur following antecedent drought and extreme precipitation events.

Objectives

The objective of this work is to assess the effect of precipitation on the incidence of *Salmonella* in the four states in the southwestern region from 2009-2021. We hypothesize that precipitation will increase *Salmonella* incidence, and that this relationship will be modified by antecedent drought.

Methods

Study Design & Setting

We conducted an ecological analysis of public health surveillance data in four states: AZ, CO, NM, UT. While drought has increased in the region over the time period, precipitation varies significantly within each state due to elevation and topographical features. Compared to other regions in the US, the southwestern states have not experienced an increase in extreme precipitation events in the same time period, typically defined as rainfall over 1 inch.^{54,135,136} However, when extreme precipitation events do occur they can cause catastrophic damage due to high surface water-flow over poor-absorbing soils.⁵⁴ While all four states have majority arid climate zones, Colorado, New Mexico, and Utah also have continental climate zones.⁶³ Arizona and New Mexico's weather is affected by Southern Oscillation Index (SOI) events, which include an intensification of the North American monsoon (El Niño), and an increase in winter precipitation and cooler temperatures (La Niña).^{55,61}

Data Sources

Data were collected from four main sources: 1) public health surveillance from each state, 2) weather data from Parameter-elevation Regressions on Independent Slopes Model (PRISM)⁵⁷ and National Oceanic and Atmospheric Administration (NOAA),⁶⁰ 3) county-level information from the US Census¹³⁷ and Köppen-Geiger Climate Zone,⁶³ and 4) animal and farm data from the United States Department of Agriculture (USDA) 2017 census.¹³⁸ We describe each dataset in depth below.

Public health surveillance

Non-typhoidal *Salmonella* data is collected by each state's respective state health department and was provided for the earliest and latest available years for each jurisdiction (AZ: 2009-2020, CO: 2009-2021, NM: 2009-2021, UT: 2012-2021). De-identified daily reports of confirmed, probable, and suspected *Salmonella* cases by county during each time period were provided. Due to data suppression requirements in Utah, only cases reported in counties >20,000 population were included. This resulted in a loss of 7% of the cases (~700 cases) during the time period.

Case definitions vary between states, with AZ, CO, and UT using the Centers for Disease Control and Prevention (CDC) and Council for State and Territorial Epidemiologists (CSTE) case definition, and NM using the FoodNet case definition.¹⁵⁴⁻¹⁵⁷ The primary difference between these case definitions is the exclusion of epidemiologically linked cases in FoodNet. A summary of the definitions and how they have changed over time is available in Table 1.

Table 1. Case definitions for *Salmonella*

Case Definition Year	Confirmed	Probable	Suspect
2017	Isolation of <i>Salmonella spp.</i> from a clinical specimen †	Detection of <i>Salmonella spp.</i> in a clinical specimen using a CIDT or epidemiologically linked to a confirmed or probable case	N/A
2012	Isolation of <i>Salmonella spp.</i> from a clinical specimen	A clinically compatible case that is epidemiologically linked to a confirmed case	Detection of <i>Salmonella spp.</i> from a clinical specimen using a non-culture based method
2005	Isolation of <i>Salmonella spp.</i> from a clinical specimen	A clinically compatible case that is epidemiologically linked to a confirmed case	N/A
1997	Isolation of <i>Salmonella spp.</i> from a clinical specimen	A clinically compatible case that is epidemiologically linked to a confirmed case	N/A
FoodNet Case Definition	Isolation of <i>Salmonella spp.</i> in a clinical specimen	Detection of <i>Salmonella spp.</i> in a clinical specimen using CIDT Epidemiologically linked cases are not counted as cases	N/A

Legend: CIDT, culture independent diagnostic test (CIDT).

* A case should not be counted as a new case if laboratory results were reported within 30 days of a previously reported infection in the same individual.

† A case should not be counted as a new case if laboratory results were reported within 365 days of a previously reported infection in the same individual. When two or more different serotypes are identified from one or more specimens from the same individual, each should be reported as a separate case.

Date reported to the health department was used for all temporal analyses, as surveillance varies between states, and onset, collection, and laboratory result date may have more missingness due to interview and reporting capacities in each jurisdiction. Because *Salmonella* is a reportable disease in each state, this dataset comprises all reported human cases in this area. If no cases were reported on a given day in a given county, we imputed a zero for that day and county in order to have a complete case analysis of all days, rather than only days in which a case was reported. This allows us to explore incidence, and not just severity of increasing case counts.

Daily data were aggregated to week of the year (starting on Sunday) for a total of 52 or 53 weeks depending on leap-years using the lubridate¹⁴² week() function in R Studio version 4.2.2. Month was determined based on day of the year. using the lubridate¹⁴² month() function.

Weather and climate

Weather data were derived from PRISM,⁵⁷ including daily county-level minimum, maximum, and average precipitation (inches), and minimum, maximum, and average temperature (°F) by county centroid. PRISM interpolates weather station data within an area, so in larger counties this may capture a more complete picture of precipitation and temperature on a given day. In PRISM, weather stations are weighted by their physiographic similarity to the grid of interest (in this case, county-level centroid). Typically with denser station data, more data is interpolated, and the more likely that stations within the county contributed to the centroid prediction. In areas with sparse weather station data, values may be influenced by weather stations outside of county boundaries. This is the same limitation that would result if we used nearby weather station instead, as not every county has its own weather station. The benefit of using PRISM over individual weather stations is that PRISM pulls from multiple stations, capturing a more holistic picture of weather variability.

To aggregate weekly data, precipitation values for all days in a week were summed to determine the total precipitation in a week. The weekly minimum or maximum was determined by imputing the smallest and largest values in a week. We defined three extreme precipitation events comparing weekly PRISM data to 30-year normal from 1990-2020: (1) heavy precipitation defined as total precipitation in the week over the 30-year normal, (2) total precipitation above the 95th percentile, and (3) total precipitation above the 99th percentile.

Palmer Drought Severity Index (PDSI) by month for each county were derived from the National Centers for Environmental Information (NCEI) via NOAA.⁶⁰ PDSI is available by month and climate division and were applied to month in the dataset. PDSI generally considers the drought level in the current month, and the previous 9 months on a rolling basis.⁵⁹

To understand the effect of El Niño and La Niña, we used the Southern Oscillation Index (SOI) by month for the time period. El Niño is characterized by a negative SOI value, neutral when SOI is zero, and La Niña when the SOI is positive.⁶¹

County-level data

Urbanicity was derived from county-level 2020 US Census designations of majority urban vs rural for each county.⁶² We abstracted the 2020 US Census population estimate for each state to calculate incidence rates over time. We used the Köppen-Geiger Climate Classification scheme to analyze data across the four states.⁶³ Specifically, we used the main climate classification data from the latest available observed climate classification map from 1980-2016 to determine the major climate zone by county. We used ArcGIS Online to intersect the climate zone map with county boundaries using the ‘Join Feature’ analysis, and then summarized the majority zones by county using the ‘Summarize Within’ analysis.

Animal data

Data for the number of operations with sales in a county were pulled from the 2017 USDA Farm census Quick Stats 2.0. We pulled data on the number of operations for poultry, sheep and goats, sheep only, cattle, and leafy greens. Data were categorized into three categories based on tertiles given their distribution: no operations, some operations (1-5 for poultry, sheep, cattle, 1-50 for

goat and sheep, leafy greens), and high operations (>5 for poultry sheep, cattle, >50 for goat and sheep, leafy greens).

Data Linkage & Transformation

Weekly case counts for each pathogen were linked to weather data by week reported to the health department for each county. Drought data were linked by month, year, and climate division. NCEI provides a table that crosswalks county to climate division that is available in the research compendium. Urbanicity and population was linked by year and county. The full dataset contains weekly weather, health, animal, and county information for each state.

We time set the data to explore the association with 2-week, and 3-weeks lags. These lags were chosen given stakeholder input, and differences in incubation periods and laboratory and reporting delays which make concurrent counts or 1-week lags less meaningful. Upon exploring initial model estimates, results from the 2-week and 3-week lags were similar, so we moved forward with a 2-week lag for the remaining analysis. Weekly lags beyond 3-weeks were not explored as our primary interest was to explore the acute effect of precipitation events following drought. Lags beyond 3 weeks might explain seasonal variations and accumulation of pathogens in the environment over time.

In order to analyze data by week, we used R’s lubridate package function week() which “returns the number of complete seven day periods that have occurred between the date and January 1st, plus one.”¹⁴² Due to differences in R and Stata, we had to suppress the last week of data from years in order to time set the data for analysis. This resulted in the loss of some data (less than 1% of cases) over the designated time periods in each state (AZ: n=21, CO: n=22, NM: n=13, UT: n=17).

Variables

Our exposure of interest was a heavy precipitation event, defined as a one inch increase in precipitation. Our outcome is confirmed or probable infection with *Salmonella* during the respective time period in each state.

Statistical Analysis

We used negative binomial Generalized Estimating Equations (NBGEE)^{64,68} to investigate the relationship between precipitation and counts of reported *Salmonella* cases using an autoregressive correlation structure. We used a negative binomial distribution because the variance exceeded the mean for the dependent variable and all associated lags (Table 2).

Table 2. Count, mean, standard deviation, and variance of dependent variables explored in model

	n	Mean	Standard Deviation	Variance
<i>Salmonella</i> cases	90012	0.31	1.12	1.26
Lag 1	89871	0.31	1.12	1.27
Lag 2	89730	0.31	1.13	1.27
Lag 3	89589	0.31	1.13	1.27
Lag 4	89448	0.31	1.13	1.27

To understand the connection between precipitation and pathogen incidence by potentially confounding factors, we adjusted for average temperature to adjust for seasonality. The results of different combinations of variables and their effect on model fit are shown in Table 3. While models including county population were the best fit according to QIC, estimates were largely unstable. Therefore we chose to include total precipitation, average temperature, and PDSI in final models.

Table 3. Pan’s quasi likelihood (QIC) metrics for determining the best model for different variable combinations

	p	Trace	QIC	QICu	Estimates diverging
Total precipitation	2	1144.299	82740.19	80455.59	
Average temperature	2	539.708	75982.87	74907.45	
PDSI	2	1160.74	82774.91	80457.43	
County population	2				Yes
Total precipitation and Average temperature	3	534.911	75803.66	74739.84	
Total precipitation and PDSI	3	1164.151	82775.22	80452.92	
Total precipitation and County population	3				Yes
Average temperature and PDSI	3	547.489	75931.55	74842.57	
Average temperature and County population	3	1600.771	62324.37	59128.83	
PDSI and County population	3				Yes
Total precipitation, Average temperature, and PDSI	4	554.891	75675.35	74573.57	
Total precipitation, Average temperature, and County population	4	1024.886	61336.41	59294.64	
Average temperature, PDSI, and County population	3	1059.217	61215.78	59103.35	
Total precipitation, PDSI, Average temperature, and County population	5				Yes

Legend: p, number of parameters; trace, the product of the independent and robust variance estimators; QIC, Pan’s quasi likelihood under the independence model criterion; QIC_u, the QIC when trace approximates an independent covariance structure and is equivalent to the number of parameters; Total precipitation, total precipitation in inches in a week; Average temperature, average temperature in °F in a week; PDSI, Palmer Drought Severity Index standardized from 0 to 20 with larger values indicating more severe drought in a month; County population, the county population from 2020 US Census estimates.

We performed stratified analyses for each variable level for each factor including: by state, climate zone, urban vs. rural designation, SOI category, and animal category. The result of the NBGEE model are Incidence Rate Ratios (IRRs) which can be interpreted as a percent increase/decrease in the number of human case events following a 1 inch increase in total precipitation. Datasets were merged in R version 4.2.2¹⁴³ (with the following packages: readxl,¹⁴⁴ dplyr,¹⁴⁵ purr,¹⁴⁶ readr,¹⁴⁷ lubridate,¹⁴² data.table,¹⁴⁸ stringr¹⁴⁹) and analyzed using Stata 17.¹⁵⁰

Sensitivity Analyses

We conducted numerous sensitivity analyses. We used a different drought index, the US Drought Severity Monitor (USDM)¹⁵¹ to explore how the association differs using a different index. During the COVID-19 pandemic, human behaviors changed including isolation and quarantine, healthcare seeking behaviors, and other restrictions.¹⁵² Therefore, we conducted a separate

analysis to explore only data before 2019 (removing 2020 and 2021 data from the analysis). Finally, to explore the effect of extreme precipitation events, not just total precipitation, we re-defined our exposure variable as described above to explore heavy precipitation, precipitation above the 95th percentile, and above the 99th percentile. We then ran our primary analysis with this new exposure variable.

Data Access & Cleaning

All data, except health data, are available via the research compendium on GitHub. Instructions for collecting data, as well as code for merging and linking data are available to help others reproduce the results and conduct this work in other areas. Although surveillance data in this analysis are not considered PHI, health data require a data use agreement with each individual state health department in order to gain access.

Results

State-specific characteristics are provided in Table 4. Arizona had the highest statewide annual average temperature, and lowest annual average precipitation during the time period. In contrast, Colorado had the lowest annual average temperature and the greatest annual average precipitation. Incidence of *Salmonella* ranged from 11.1 to 19.3 per 100,000 across the four states. Across the five farm operation types of interest, the state with the largest number of operations included: cattle (New Mexico), chicken and poultry (Colorado), goats and sheep (Arizona), sheep only (New Mexico), leafy greens (Colorado). Maps of farm operation density by type are available in the supplemental material (Chapter 5, Appendix A). Due to instability in estimates for cattle, results are not shown.

Table 4. State-specific characteristics

	Arizona	Colorado	New Mexico	Utah	Total
Population, n	7,151,502	5,773,714	2,117,522	3,271,616	18,314,354
Years included in analysis	2009-2020	2009-2021	2009-2021	2012-2021	2009-2021
Counties included in analysis, n	15	64	33	29	141
Climate Zone, number of counties n (%)					
B, arid	15 (100%)	34 (53%)	31 (94%)	23 (79%)	103 (73%)
D, continental	0 (0%)	30 (47%)	2 (7%)	6 (21%)	38 (27%)
Urbanicity					
Urban	8 (53%)	40 (63%)	26 (79%)	16 (55%)	90 (64%)
Rural	7 (47%)	24 (37%)	7 (21%)	13 (45%)	51 (36%)
Statewide annual precipitation, mean	12.26	17.95	13.88	13.39	
Statewide annual temperature, mean (min, max)	59.7 (45.6, 73.8)	44.9 (31.0, 58.7)	53.2 (38.3, 68.1)	47.8 (35.1, 60.5)	
Total Counts of <i>Salmonella</i>	11,551	8,878	5,305	3,616	29,350

Count of Confirmed Cases of <i>Salmonella</i>	10,906	8,255	5,132	3,387	27,680
Percent Confirmed Cases of <i>Salmonella</i>	94%	93%	97%	94%	94%
Incidence Rate of <i>Salmonella</i> per 100,000 population per year	13.5	11.8	19.3	11.1	13.9
Farm Operations with Sales (USDA), n					
Cattle	51	53	91	63	258
Chicken and Poultry	69	262	65	79	475
Goats and Sheep	3437	1692	2883	1393	9405
Sheep only	73	184	205	149	611
Leafy greens	802	943	802	270	2817

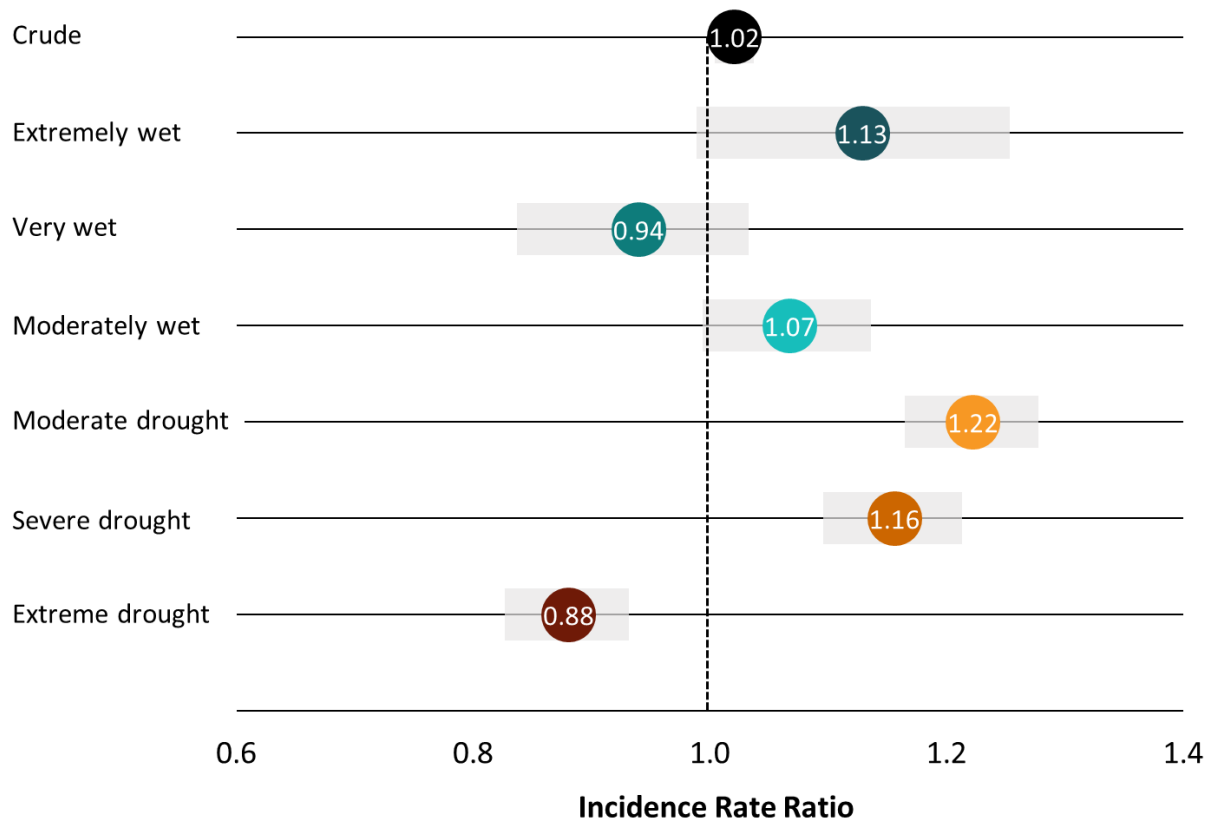
For every one inch increase in precipitation, *Salmonella* cases (lagged 2-weeks) increased by 2% (IRR: 1.02, 95% CI: 1.00, 1.04) after adjusting for average temperature and PDSI. At higher levels of rain: above a 30-year normal, above the 95th percentile, and above the 99th percentile, *Salmonella* cases increased more (8%, 6% and 4% respectively) (Table 5).

Table 5. IRR and 95% CI for different levels of precipitation (exposure) on *Salmonella* cases after adjusting for temperature and drought severity

Definition of exposure	IRR (95% CI)
Total precipitation in a week	1.02 (1.00, 1.04)
Heavy precipitation, total precipitation in a week over a 30 year normal	1.08 (1.04, 1.13)
Total precipitation above the 95th percentile	1.06 (1.03, 1.10)
Total precipitation above the 99th percentile	1.04 (0.98, 1.12)

Figure 1 shows the effect of a one inch increase in precipitation during different antecedent drought levels. During extremely wet and moderately wet conditions, cases are significantly increased (IRR range: 1.07-1.13). In moderate and severe drought categories, we see the highest significant increase in cases (22% and 16% respectively). In the most extreme drought conditions, cases are significantly decreased (IRR 0.88, 95% CI: 0.83, 0.93).

Figure 1. IRR (marker) and 95% CI (band) for the effect of a one inch increase in precipitation during different levels of drought via the PDSI



Legend: dashed line indicates null value, where the risk of the outcome in both the exposed and non-exposed groups are equal

When exploring different spatial scales, this association remains consistent. Cases are increased during moderate drought conditions and decreased during extreme drought conditions. In rural counties, *Salmonella* cases remain increased, even with increasing drought severity, although not all results are significant (IRR range: 1.06-1.21). This relationship also remained consistent when we restricted the analysis to the years prior to the COVID-19 pandemic, as well as after adjusting for SOI. The results of these analyses are included in supplemental material (Appendix B). The results of our sensitivity analysis for using a different drought index are included in Table 6. We see similar results as in our main analysis, elevated cases during abnormally dry to severe drought conditions, and decreased cases during extreme and exceptional drought periods.

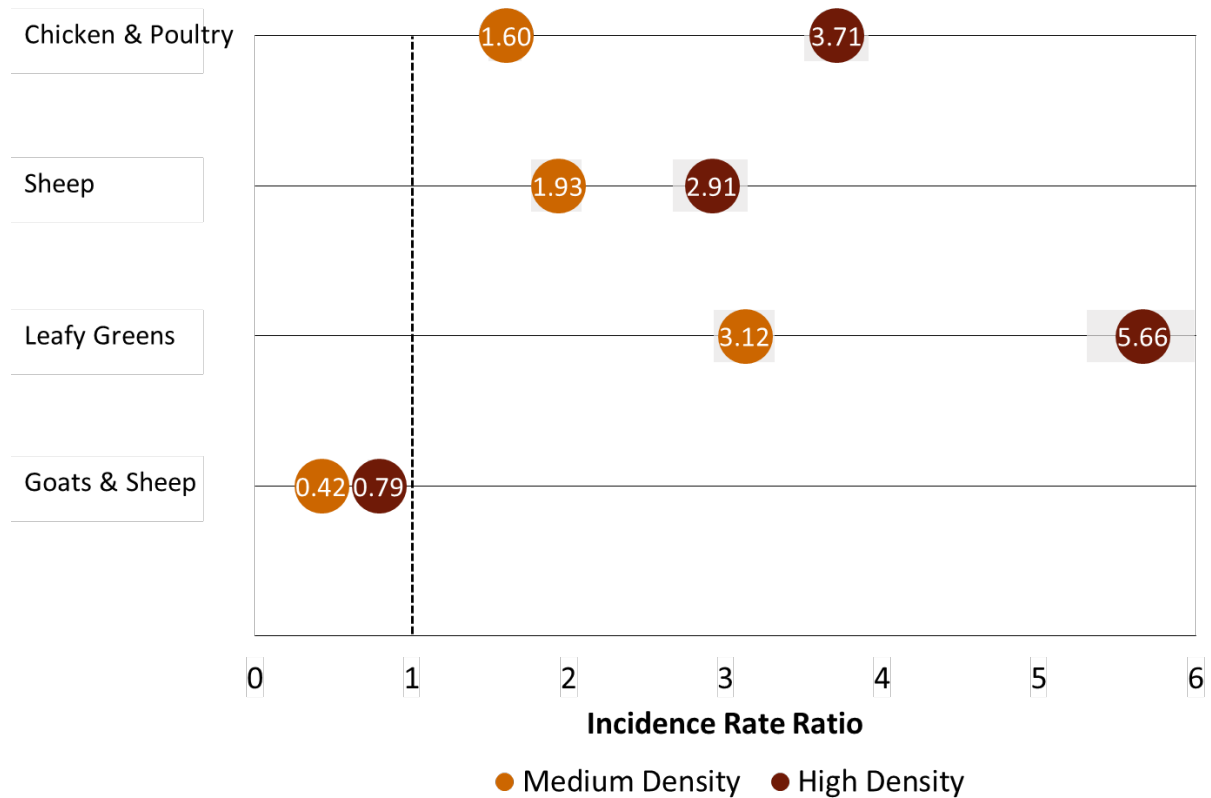
Table 6. IRR and 95% CI for a one inch increase in precipitation on *Salmonella* cases at different levels of drought severity via the USDM

US Drought Monitor Category	IRR (95% CI)
None (reference)	1.0 (ref)
Abnormally dry	1.14 (1.09, 1.19)
Moderate drought	1.27 (1.22, 1.34)
Severe drought	1.13 (1.07, 1.19)
Extreme drought	0.93 (0.87, 0.99)

Exceptional drought	0.73 (0.64, 0.82)
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Presence of farm operations was a significant effect modifier of the relationship between precipitation and *Salmonella* cases. Compared to counties with no operations, counties with chicken and poultry, sheep, and leafy green farms, had a significantly increased risk of *Salmonella* cases following a one inch increase in precipitation (Figure 2). Compared to counties with no operations, counties with goat and sheep operations had a significant decrease in cases following a one inch increase in precipitation (medium density IRR: 0.42 95% CI: 0.39, 0.46); high density IRR: 0.79, 95% CI: 0.72, 0.86).

Figure 2. IRR (marker) and 95% CI (band) for the effect of a one inch increase in precipitation in counties with medium and high density of operations, compared to counties with no operations



Legend: dashed line indicates null value, where the risk of the outcome in both the exposed and non-exposed groups are equal

When exploring the effect of drought on the relationship between precipitation and farm operations, we see that cases decrease following increasing drought severity, but remain significantly elevated (except for goats and sheep). For example, counties with chicken and poultry operations have a 131-231% increase in cases following an extreme precipitation event, even with drought (Table 7). Given the number of produce outbreaks associated with

Salmonella, the results for counties with leafy green operations are telling – a 245-384% increase in cases following a precipitation event, even with increasing drought severity.

Table 7. IRR and 95% CI for the relationship between precipitation and *Salmonella* cases in counties with farm operations.

	PDSI continuous	PDSI categorical		
		Moderate drought	Severe drought	Extreme drought
Cattle	1.37 (1.31, 1.43)	1.63 (1.54, 1.73)	1.54 (1.45, 1.64)	1.16 (1.08, 1.25)
Chicken and Poultry	2.71 (2.55, 2.88)	3.21 (2.99, 3.45)	3.06 (2.84, 3.3)	2.31 (2.13, 2.51)
Goats and Sheep	0.57 (0.52, 0.62)	0.68 (0.61, 0.75)	0.64 (0.58, 0.71)	0.49 (0.44, 0.55)
Sheep only	2.38 (2.19, 2.58)	2.81 (2.56, 3.08)	2.65 (2.41, 2.91)	2.02 (1.82, 2.23)
Leafy greens	4.17 (3.91, 4.45)	4.84 (4.5, 5.22)	4.6 (4.26, 4.96)	3.45 (3.18, 3.74)

Legend: PDSI, Palmer Drought Severity Index.

Discussion

In this study we explored the effect of precipitation and drought on *Salmonella* incidence in four southwest states of the US from 2009-2021. We find that *Salmonella* cases increased by 2% following a one inch increase in weekly total precipitation. Interestingly when we changed the exposure variable to extreme precipitation over a 30-year normal, cases increased by 8% (95% CI: 1.04, 1.13) and were still elevated with precipitation above the 95th percentile (6%) and 99th percentile (4% although not significant). We found the highest increase in cases during moderate (22%) and severe (16%) drought categories, but cases significantly decreased during extreme drought (12% decrease). Further, presence of farm operations significantly modified the relationship between precipitation and *Salmonella* cases with 2 to 3 times higher estimates in medium and high density of operations respectively.

These results partially support the concentration-dilution hypothesis.⁷³ When precipitation fell during dry periods, cases were highest, although cases did decrease in the most extreme drought conditions. We found mixed results during wet conditions which may be due to the low number of weeks in the analysis that were considered very wet or moderately wet. Our results in this study, finding the highest elevated risk during dry periods are in contrast to Kraay et al.’s⁷³ stratified analysis showing bacterial diarrhea is more common during rainy seasons. Further our results are opposite of results found in Lee et al.’s study in the Georgia, US. They found extreme rainfall in wet periods had a 9% increase in *Salmonella* cases, whereas in dry periods there was a 2% increase (not significant).²⁸ When stratifying to environmental serovars, Lee et al. found an elevated risk regardless of antecedent rainfall conditions, similar to our results. Morgado et al.³⁰ also showed elevated risks in areas with a high density of poultry operations in alignment with our results presented here. We hypothesize that the difference in results is likely due to differences in climate region and how antecedent conditions were defined.

One of the largest estimates we found in this analysis was for the effect of precipitation in counties with leafy green operations. A one inch increase in precipitation in counties with leafy green operations had significantly elevated increases in *Salmonella* cases compared to counties without. Infections were increased even during drought conditions. Previous studies have shown

drought stress and higher temperature may inhibit plant structures allowing for the great internalization of *Salmonella* particularly in leafy greens like lettuce.^{35,36} Leafy green outbreaks attributable to *Salmonella* have been increasing over time and often result in multi-state outbreaks with a large disease burden.³⁷ Our results support these findings, showing that cases increase in areas with leafy green operations following precipitation even after accounting for drought.

While our study has many strengths, there are a few limitations. Our weather data, from PRISM is not county based, but grid based, so it will incorporate station data from the surrounding area, regardless of county boundaries. These stations are weighted by their physiographic similarity to the grid cell being modeled. So the grid cell prediction could be influenced by stations both inside and outside the county boundaries. Typically, the denser the station data, the smaller the contributing area, and the larger the county, the more likely that stations within the county contributed to the centroid prediction. We chose PRISM for this region, because it provides a better estimate of the weather occurring in the county than if we used one weather station (data not shown). While we were limited to county-level, PRISM is also grid-based, so if a county within this analysis wanted to use a finer spatial scale to explore this association further, they could. We have provided the relevant code and data for our collaborators on the project to do this, and have shared the protocol, code and data through a public repository on GitHub: ([link when public](#)). We also used report date instead of onset date for this analysis given data confidentiality restraints. This allowed us to use a larger dataset, as onset date is usually only collected during case interviews and interview rates vary by state. We also did not exclude travel-associated cases for this same reason. These limitations should be taken into account when considering these estimates. The model we chose to use for this analysis is also a major strength. NBGEE takes into account the non-independence of our outcome data, as well as the correlation between our weather variables. Accounting for these limitations in our data allowed us to explore an overall estimate for this region, contributing significantly to our understanding in this area.

Conclusion

In this study, we found that *Salmonella* cases are increased following precipitation events and are increased even more during moderate and severe drought conditions. We also showed that even with drought, *Salmonella* cases increase by 2 to 3 times more in counties with farm operations compared to those without. Our results differ from previous work in this area showing the importance of pathogen-specific and regional estimates of risk. These results contribute to our knowledge about the many ways that weather variability affects our health. With projected climate change, as drought becomes more severe and extreme weather events become more common, counties may see increases in *Salmonella* infections during moderate and severe drought conditions, and a decrease in infections during extreme drought. Public health departments will likely also see increases in *Salmonella* infections following extreme precipitation events over historic averages.

Supplemental Material

Appendix A

The following table provides estimates (IRR (95% CI)) for the analysis exploring the effect of precipitation on *Salmonella* cases stratified by different spatial scales, restricting to certain years, and adjusting for Southern Oscillation Index.

	PDSI Continuous	PDSI Categorical		
		Abnormally dry	Moderate drought	Severe drought
Multivariate model	1.02 (1, 1.04)	1.22 (1.17, 1.28)	1.16 (1.1, 1.22)	0.88 (0.83, 0.93)
State				
Arizona	1.03 (1.01, 1.04)	1.07 (1.01, 1.12)	1.08 (1.02, 1.15)	0.98 (0.91, 1.06)
Colorado	0.98 (0.95, 1.02)	1.43 (1.3, 1.57)	1.24 (1.12, 1.37)	0.87 (0.79, 0.96)
New Mexico	0.98 (0.93, 1.03)	1.05 (0.94, 1.17)	0.92 (0.82, 1.04)	0.86 (0.76, 0.97)
Utah	1.1 (1.04, 1.17)	1.5 (1.3, 1.73)	1.44 (1.25, 1.66)	1.3 (1.1, 1.53)
Köppen-Geiger Climate Zone				
B, arid or semi-arid climate	1.02 (1.01, 1.04)	1.18 (1.12, 1.24)	1.14 (1.08, 1.2)	0.91 (0.85, 0.97)
D, continental climate	1.02 (0.97, 1.07)	1.6 (1.42, 1.81)	1.32 (1.16, 1.5)	0.84 (0.74, 0.95)
Urbanicity				
Urban	1.01 (1, 1.03)	1.19 (1.14, 1.24)	1.14 (1.08, 1.19)	0.86 (0.81, 0.91)
Rural	1.03 (0.93, 1.14)	1.21 (0.98, 1.48)	1.06 (0.86, 1.32)	1.09 (0.9, 1.33)
NCHS Urban-Rural Classification Scheme*				
Large central metro (>1 million or more population, contain largest city in MSA)	1 (0.98, 1.02)			
Large fringe metro (>1 million adjacent to largest city)	0.99 (0.94, 1.03)			
Medium metro (250,000 to 999,999 population)	1.01 (0.98, 1.04)			
Small metro (<250,000 population)	1.06 (0.99, 1.12)			
Micropolitan (1 urban cluster of 10,000 to 49,999 population)	1.05 (1, 1.12)			
Non-core	1.07 (0.95, 1.19)			
Pre-COVID years (2009-2019)	1.02 (1, 1.04)	1.26 (1.2, 1.32)	1.21 (1.14, 1.27)	0.94 (0.88, 1)
Adjusting for Southern Oscillation Index	1.02 (0.99, 1.04)	1.22 (1.16, 1.28)	1.15 (1.09, 1.22)	0.88 (0.83, 0.93)

Legend: PDSI, Palmer Drought Severity Index.

* stratified analysis for NCHS scheme not conducted due to non-convergence of estimates

Chapter 7. Conclusion

Campylobacter and *Salmonella* are the most common bacterial enteric pathogens of concern in the US. Both pathogens peak in the summer, but the reasons behind this seasonal peak are less understood and vary by region. There may exist a complex interaction with weather that may explain some of this seasonality. This set of studies aimed to understand how weather variability is associated with enteric infections in the Southwest US, an area with a unique climate and highly variable rainfall.

The first study aimed to describe the effect of weather variability on *Campylobacter* infections using a systematic review approach. In this study we found that researchers have used a variety of weather variables to describe the increase or decrease of *Campylobacter* cases in different countries around the world including increases of infections following precipitation events and increases in temperature. This review is the first of our knowledge to summarize pathogen-specific associations with weather events. The results discovered for precipitation and temperature in this study, helped guide the methodology and approaches for the remaining two aims.

The second study aimed to understand the effect of precipitation on *Campylobacter* incidence using public health surveillance data. We found a positive relationship between precipitation and *Campylobacter* infections after adjusting for temperature and drought status. Further, we discovered that *Campylobacter* infections are highest when precipitation falls during wet periods and remain elevated in the beginning stages of drought. In the most extreme drought categories, precipitation decreased *Campylobacter* infections. This was the first study to our knowledge to provide pathogen-specific estimates for the effect of precipitation accounting for antecedent drought status. Our findings for the effect of precipitation in counties with a high density of farm operations in the Southwest aligns with other regions around the world.

The third study applied a similar approach for *Salmonella* infections. We found a positive relationship between precipitation and *Salmonella* infections, although the effect was smaller than *Campylobacter*. In contrast to *Campylobacter*, we found the highest increase in cases of *Salmonella* during moderate and severe drought categories, with elevated increases during some of the wet conditions. Similar to *Campylobacter*, we found cases decreased following precipitation during the most extreme drought category. We found significant and very large estimates in counties with farm operations for *Salmonella*, particularly chicken and poultry and leafy greens.

Taken together, these studies contribute to our collective knowledge about the myriad ways that weather can affect *Campylobacter* and *Salmonella* infections in humans. We find that precipitation and antecedent drought are important predictors of seasonal variation for both pathogens, and that this relationship is modified by other environmental factors like farm operation density. These studies are all novel contributions to this field of research. The consistency in estimates at various spatial scales speaks to the importance of weather variability as an important predictor of human infections. The inconsistencies across pathogen estimates shows that determining the pathogen-specific burden of enteric illness due to weather exposures is important.

Future Directions

Given these findings, future studies should aim to explore region-specific and pathogen-specific estimates for the effect of weather on enteric infections. Doing so would allow for future meta-analyses, and contribute to our understanding of the role that weather plays in disease burden. Projecting the disease burden will help health departments prepare for the effects of climate change in the future.

While risk factor data was not available for these studies, this remains an important area of future research. Risk factor analyses could include restricting analyses to cases without recent travel, exploring recent food or animal exposures in relation to weather events, and exploring demographic characteristics which might indicate populations most at risk. Future research should also explore the confounding effect of other weather variables including relative humidity, sunshine duration, seasonal differences, as well as exploring weather events prior to outbreak events for these pathogens. All of these variables were cited as potential predictors of interest in the review, but they could not be explored in the studies here.

Finally, this research describes just one piece of this complex puzzle. Climate change will drive significant and serious changes to all of our lives. Future research which estimates the burden of climate change on the health of our planet, the people, and our animals will help us to understand, prepare for, and mitigate its effects. These studies herein address some gaps in our knowledge in this area and provide striking evidence of the effect of weather on human health. Further, the approaches herein provide a model for researchers to explore this association in the future. Together these studies show that the weather outside affects our health inside.

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