Climate change and salmonella, New York State

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CLIMATE CHANGE AND SALMONELLA, NEW YORK STATE

by

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ABSTRACT

A study of climate change and *Salmonella* was conducted, serving as the evidence-based results for action to mitigate adverse *Salmonella* outcomes for the population of New York State (NYS), and to facilitate dissemination of findings in regard to validated approaches for broader use to mitigate climate change and adverse communicable disease outcomes in a variety of other settings. This study bolsters understanding of dynamic exposures and outcomes for improved and targeted public health approaches to localized climate change and communicable disease outcomes. The approach was developed and refined through continuously validated and calibrated methodology for the enhancement of disease control and prevention.

A multi-faceted, systematic review of disparate sources of information with multiple research domains was conducted, ensuring sufficient coverage of all perspectives to produce a dynamic etiologic profile of *Salmonella* as well as a comprehensive causal process diagram. This validated subsequent methods (and variables included in the analysis) specific to researching *Salmonella* in the appropriate context. The study design followed established guidelines for a systematic literature review and incorporation of a qualitative meta-analysis to develop a causal process diagram. Research on the spatiotemporal risk of salmonellosis and ambient air temperature was then conducted using a case-crossover study design, which incorporated the validated variables identified from the systematic literature review processes. Statistical analyses characterize changes to the profile of *Salmonella* in NYS over time with a high level of specificity and validity to ensure robust next steps to address this problem (i.e., orientation for further, focused study; and/or, as orientation for public health practice with evidence-based intervention).
An adaptable framework was formed and implemented for the specific context; the implementation is reported in the form of a tool, discussing specific research components and the conclusions both specific to the tool as well as the implications for the adaptability of the framework for use outside of the tool’s context. This integrates the formative aspects throughout, the implementation of the methodologies, and the specific research findings of each for a comprehensive and robust discussion indicating how the implementation for Salmonella can be used as a model for application for other diseases and framed as a validation step for this tool. Integration of analyses and information pertaining to next steps are described to ensure appropriate development and implementation of advanced methodologies for further study (and subsequently for improving the quality and performance of prospective intervention areas), which incorporate aggregate climate variables to demonstrate cumulative effects, study of the effect of lag between climatic exposure and case occurrence, and the case-crossover design with comparative analyses.
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Chapter 1. Introduction

Climate change threatens human health through multi-level environmental effects via a myriad of exposure pathways and outcomes. There is interplay between and among these multi-level effects: morbidity and mortality likelihood can be a result of changing distributions of infectious diseases through altered ecology and biology of pathogens, vectors, and hosts, or any intermediary organisms (Butler et al. 2010). Changes to human health are difficult to predict because of the complex nature, and multifaceted and dynamic influences of host-agent-environment interactions and relationships (Bradley et al., 2005; National Academy of Sciences 2015). Changes in the ecosystem may shift or expand the range of infectious agents and associated organisms, potentially exposing human or reservoir populations. Environmental contaminants and pollution may proliferate and persist due to climate change, overwhelming immune systems of vulnerable groups, leading to increased disease occurrence (Kendrovski et al. 2011; Tirado et al., 2010; Jiang et al. 2015). Climate change combines geographic and temporal elements, and therefore related issues are challenging to combat due to limited information or theoretical models predicting wide ranges of outcomes; as local climatic conditions affect the biology of an organism, predictable communicable disease patterns from mapped seasonal fluctuations and expected variances become less reliable.

A robust understanding of the effects of climate change on human health can lead to improved public health planning and preparedness. Research methodologies must take into account past trends on climate and epidemiology, as well as present effects of climate change on the incidence of the disease, using existing data and theory to confirm and extrapolate disease patterns based on various climate change scenarios (National Academy of Sciences 2015). Applicable to such scenarios, critical needs among the scientific and public health communities
include location-specific policy, systems, and strategies, approaches, and intervention, with a balance of cost and benefit (Webber et al. 2016). Given the multi-level environmental effects and the sensitivity of the epidemiological triad to climate change, there has been an increased interest in the development of data collection, analysis, and reporting mechanisms, for efficient and cost-effective exploratory study. Such mechanisms require the increased granularity of data at finer temporal and spatial resolutions. Demand for accurate data on smaller geographical areas with frequent measurement has increased; without this, significant disparities across smaller areas may be less evident, and ecological fallacies may result in insufficient action. Public health agencies need ways to provide localized data that is accessible, inexpensive, feasible to update, and sufficiently generalizable with consideration to time and space.

As the technologies and methodologies improve, there is an increased reliance on geographic-specific indicator projects that disaggregate data at increasingly smaller levels (Webber et al. 2016). Datasets from disparate sources, which are often readily available electronically, enable customized indicators for a given problem. Reporting with graphing, sorting, and mapping of these indicators can provide a way to identify disparate areas where an interplay of social, environmental, and/or health conditions drive outcomes, and can be incorporated into strategies for evidence- and community-based intervention, resource allocation, and delivery and expansion of health services. This data can be used for benchmarking, establishing goals, evaluating progress, and can be customized to better understand spatiotemporal trends. In addition to identifying new areas for intervention, projects which customize specific indicators can inform strategies of agencies and organizations already working in specific areas and promote collaboration across domains and industries.
OVERVIEW

Climate Change

Climate is one aspect of the environment, and refers to the prevailing weather conditions in a given area over a period of time (EPA 2016). Climate change is the significant, sustained change in the measures of climate. This includes major changes in temperature, precipitation, wind patterns and other effects that occur over an extended period of time.

Climate change has been linked to increasing atmospheric concentrations of gaseous carbon dioxide, methane, chlorofluorocarbons and nitrous oxide (the “greenhouse gases”); contributing to the greenhouse effect and climatic warming (IPCC 2018, NASA 2018). Solar energy, in the form of infrared radiation, is partially reflected and leaves the planetary atmospheric system; greenhouse gas molecules absorb and emit this radiation at a higher rate in comparison to more reflective atmospheric constituents. Radiation is then emitted in all directions, including downwards to the planet’s surface. Increased energy, retained in the system, contributes to warming oceanic temperatures, with much of the rest of the energy contributing to continental and atmospheric warming [NAS 2015, Hansen et al. 2005].

Greenhouse gases are released into the atmosphere through both natural and anthropogenic mechanisms. Around the start of the Industrial Revolution, increased burning of fossil fuels (which contain high levels of carbon dioxide formed in the geological past from the remains of living organisms, and include coal, petroleum, and natural gas) resulted in demonstrable warming effects as more greenhouse gases were released in the atmosphere (NAS 2015). Increasing levels of these gases in the atmosphere compound the greenhouse effect, heating the continental surface and the lower atmosphere. The global average surface
temperature rises, as well as average sea temperature. Snow cover and ice sheets, particularly in Greenland and the Arctic, are melting at an increased rate, leading to sea level rise. The current increased planetary warming is called global warming, and scientists have ascertained that the increase is associated with anthropogenic activities.

Global warming is the recent and ongoing rise in surface temperatures of the planet caused mostly by the effect of greenhouse gases in the atmosphere. Global warming is causing climate patterns to change, though it is only one aspect of climate change (FSA 2005). Global warming has been a contentious issue and not all causes have been determined, and for a long time the risk of global warming was questioned (NAS 2015, Weber et al. 2005). The clearest evidence comes from studying historical thermometer readings throughout the world. There is evidence that between 1800 and 2012, concentrations of carbon dioxide in the atmosphere have increased by over 40%, and the average surface temperature has increased 0.8 degrees Celsius (1.4 degrees Fahrenheit) since 1900 (Weber et al. 2005). Solar energy is the primary source of heat for the planet, but little variation has been observed that could account for global warming. Atmospheric scientists have documented an 11 year cycle in which solar energy varies up to 0.1%, and this has been shown to effect atmospheric conditions. However, modeling shows that the observed changes in ozone, temperature, and winds at different levels of the atmosphere are more consistent with anthropogenic activities, rather than the 11 year solar cycle (NAS 2015). The associated meteorological effects of global warming lead to the significant redistribution of regional weather patterns over time, leading to climate change. The extent and impact of climate change differs from region to region (Tett et al. 1999, Giorgi et al, 2006).

Prior to the industrial revolution, there was a balance in the amount of greenhouse gases being exchanged between the atmosphere and the biosphere, the ocean through gas exchange,
and volcanic eruptions and erosion (Kump et al, 2000). This can be traced in climate records; looking at different isotopes of carbon reveal greater associations with human activity rather than natural causes. Similar to carbon dioxide, methane, chlorofluorocarbons and nitrous oxide are released into the atmosphere through certain human activities and have accelerated the greenhouse effect in a way not predicated to occur by natural causes of climate change (Anju et al. 2014). Average surface temperature and atmospheric temperature increases, as well as stored oceanic energy, atmospheric moisture levels, changing sea levels, and land ice cover and sea ice patterns (NAS 2015) have been studied since atmospheric scientists have hypothesized about these changes, and modeled the projected impact of human activity and natural changes. Expected changes over time fit best with the human activity model and are consistent with observed changes (NAS 2015, Coward et al. 2004).

**Climate Change and Public Health**

Human health is impacted by climate change, with over 150,000 deaths worldwide annually attributed to diseases caused by fluctuations in climate (Patz et al. 2005). The environment interacts with human health, and future climate change may result in unforeseen impacts on health based on the complexity of influences from multi-level effects (Butler et al. 2010). The magnitude and extent of these effects vary across the globe, and can be classified as primary, secondary, or tertiary effects.

Primary effects are direct harm to human health from the environment, whereas secondary and tertiary effects occur through indirect associations. Primary effects include morbidity and mortality from the direct trauma of heat waves, brush fires, storms, and floods associated with climate change (Patz et al. 2005, Butler et al. 2010). Examples are injuries, heat
stroke, drowning, etc. Secondary effects harm through the influence of environmental factors on the level of infectious, atopic, and respiratory diseases. Secondary effects change the distribution of infectious diseases by altering the ecology and biology of pathogens, vectors, and hosts, or any intermediary organisms (Butler et al. 2010). For example, warmer temperatures promote the proliferation and longevity of organisms which were previously limited in their development and ability to survive (Bradley et al. 2005). Organism development rates may be accelerated or decelerated, which may promote transmission of disease. Surviving organisms tend to be ones that increase the transmission of diseases such as West Nile Virus and Lyme disease (Bradley et al. 2005, Keesing et al. 2010). Organisms more likely to disappear serve as buffers against infectious disease transmission. Biodiversity is subject to environmental stress and a loss in biodiversity can be detrimental to human health. Propagation of HIV/AIDS, tuberculosis, and other infectious diseases may be caused by societal determinants such as poverty and poor nutrition, sanitation and hygiene (Butler et al. 2010, Costello et al. 2009).

Tertiary effects harm through the repercussions of governance as a result of climate change and human and non-human ecology. Governance refers to the process-oriented activities through which formal and informal authorities implement order in societies. Tertiary effects impact population health and governance, and are a function of policy, ecology, and climate (Butler et al. 2015). Tertiary effects include widespread water scarcity, food insecurity, and population displacement which may lead to escalating crisis and conflict.

Human behaviors are contingent on environmental factors, and in turn, changing behaviors impact health (Bradley et al. 2005). Tertiary effects of climate change may promote human migration, creating populations vulnerable to negative health outcomes. Changes in the ecosystem may shift or expand the range of infectious agents and associated organisms,
potentially exposing immunologically naive human or reservoir populations. Environmental contaminants and pollution may proliferate and persist due to climate change, overwhelming immune systems of vulnerable groups, leading to increased disease occurrence. Ultimately, future changes are difficult to predict because of the complex nature and multifaceted influences of the host-agent-environment interactions and relationships.

The epidemiologic triad is highly sensitive to climate change (Tirado et al. 2010). The pathogen, vector, and host are all sensitive to the local environment, which may be altered by sustained, re-distributed weather patterns, such as warmer ambient temperatures. For example, the pathogen and the vector organism may lack sufficient thermostatic mechanisms due to being small and simpler organisms, so local climatic conditions can lead to stress on their systems (Patz et al. 2003). Therefore, the range of climate variables must be narrow in order for these organisms to survive and reproduce in such cases. Alternatively, survival and reproduction rates may increase as a result of a variable influenced by climate change (Jiang et al. 2015, Kendrovski et al. 2011). As a result, negative health outcomes can be amplified and enhanced, such as *Salmonella* proliferation in warmer, wetter environments.

The influence of climate change on the proliferation of food and waterborne pathogens is an important aspect of public health research. Due to the complex mechanisms involved, negative health outcomes as a result of climate change impacting food and waterborne pathogens are challenging to combat due to limited information and theoretical models predicting diverse outcomes (FSA 2015). When local climatic conditions affect the biology of an organism, predictable disease patterns from mapped seasonal fluctuations and climate variances are no longer reliable due to the climate change (NAS 2015, Coward et al. 2004, Patz et al. 2003). In order to create a robust understanding, research must take into account past trends on climate and
epidemiology, as well as present effects of climate change on the presence of the disease, using existing data and theory to confirm and extrapolate disease patterns based on various climate change scenarios. A robust understanding of the effects of climate change on human health can lead to improved public health planning and preparedness.

**Climate Change in NYS**

NYS has a humid continental climate across its diverse topography, which includes highlands, mountains, and plateaus, as well as a large metropolitan area that is significantly warmer than surrounding areas due to anthropogenic activities (NCDC 2015). Between autumn and spring, precipitation falls from extra-tropical cyclones and lake-effect snowstorms off inland bodies of water. Precipitation levels depend on proximity to large bodies of water, such as the Atlantic Ocean and Great Lakes. The western part of the state is generally cloudier and experiences higher levels of precipitation due to cold air damming east of the Appalachian mountain range. Warmer temperatures occur between the summer months of June to August, and drier, winter weather with freezing temperatures peak in January and February.

NYS has experienced the effects of climate change, with indications that, on average, the climate has been and will continue to become wetter and warmer (Horton et al. 2014, Karl et al. 2009). Retrospective analysis of climate data suggests increasing frequency of high precipitation events. According to the National Climate Assessment (NCA), the Northeastern region of the United States (including NYS) has experienced a 71% increase in precipitation during the biggest 1% precipitation events, the most dramatic increase across the entire country (Horton et al. 2014). Between 1948 and 2008, the number of heavy precipitation days increased nearly 1 day per decade, and consecutive precipitation days increased by half a day per decade (Insaf et
Extreme weather events, such as heat waves and superstorm events, have led to increased morbidity and mortality in NYS (Horton et al., 2014). These effects are projected to increase, and additional climate change impacts may be experienced. For example, extreme variations may occur between precipitation events and drought events in this region.

By the end of the century, extreme weather events, as well as mean temperature and precipitation, are predicted to significantly increase in NYS (Horton et al. 2014, Luber et al. 2014). The annual mean temperature of NYS is predicted to increase 3.5-8.5 degrees Fahrenheit with the NCA model, and up to 4-14 degrees Fahrenheit with the ClimAID model. Heat waves and heavy downpours are predicted to increase intensity and prevalence. Precipitation is expected to increase 3-9%. This likely would impact the state's local ecosystems, potentially changing the ranges of organisms that affect public health.

Due to diverse topography and geography of NYS, the climate is inherently diverse, and climate change affects NYS in variable extent and magnitude (Insaf et al. 2013). From 1948-2008, the eastern and the Great Lakes regions of NYS were found to be most affected by climate change. The Coastal region, Champlain Valley, Northern Plateau, Hudson Valley and the Great Lakes regions were found to have increasingly warmer nighttime temperatures (an indicator of overall warmer weather), and an increase in ice days (an indicator of overall colder weather). Many areas of eastern and western NYS were found to have warmer weather, except Central Lakes and Western Plateau regions which had decreasing nighttime temperatures. Across all indicators, the most warming occurred in the Hudson Valley and Great Lakes regions. Fewer frost days, an indicator of cold weather, were occurring in Great Lakes, Hudson Valley, and Eastern Plateau regions. Coastal and Great Lakes regions’ growing season length, an indicator of warming, was found to increase significantly. In regards to precipitation, all regions of the state
were found to be increasingly wetter, although the highest levels of increasing precipitation were occurring in the Hudson Valley region. These regional differences in climate reflect the large area and diverse geography. Thus the changes in meteorological variables will not necessarily be the same across the entire state, and may reflect areas of NYS that are more or less impacted by climate changes.

In NYS, multi-level effects as a result of climate change would be expected based on local trends (Luber et al. 2014, US Census Bureau 2015). Those areas experiencing elevated temperatures will have increased risk of primary effects such as heat-associated morbidity and mortality. The secondary effects can include changes in disease outcomes with increased incidence and geographic spread. Tertiary effects include increased food insecurity, and sewage/potable water treatment plants can be overwhelmed, leading to increased waterborne disease. Concerns pertaining to communicable diseases include those that are foodborne and waterborne (such as salmonellosis, vibriosis, and Legionnaires’ disease), as well as vector-borne (such as Lyme disease, West Nile Virus, and Eastern Equine Encephalitis), which already occur in NYS (NYS 2015).

Setting

*Salmonella* are a genus of bacteria found globally in the environment and in cold- and warm-blooded animals, which serve as a reservoir (Ryan et al. 2004). *Salmonella* are facultative intracellular bacteria of which over 2,000 serotypes have been recognized as pathogenic to humans (CDC 2015, Wikso & Hall 2012, FoodNet 2014). Salmonellosis, the disease caused by *Salmonella* infection, is primarily transmitted through oral consumption of food or water contaminated with fecal matter. Transmission is also through exposure to infected animals and
person to person. The bacteria are in the Enterbacteriaceae family, of which there are two non-typhoidal species that cause disease in humans, S. enterica and S. bongori. Within each species, *Salmonella* are grouped by serotype, which is defined by distinctive surface structures. Of the 2,000 serotypes of *Salmonella*, fewer than 100 account for most human infections (CDC 2015). Certain serotypes are associated with more severe disease. Serotypes Enteriditis and Typhimurium are the most common in the United States.

An estimated 1.2 million people are infected with *Salmonella* each year in the U.S., leading to nearly 400 deaths (CDC 2015, Scallan et al. 2011). The annual U.S. incidence was estimated to be 15.89 cases per 100,000, according to FoodNet data in 2015 (CDC 2015, Huang et al. 2016). *Salmonella* outbreaks are not uncommon. In 2015, the CDC reported nine outbreaks infected over 1,600 people. The most serious outbreak, which peaked in August and September of 2015, occurred across 40 states with 907 cases and 6 deaths (CDC 2016a, 2016b). The highest incidence of *Salmonella* was found among children under 5 years of age, females, and Asian/Pacific Islanders (FoodNet 2014). For severe and invasive infection, high risk groups include children <5 years old, adults >65 years old, and immunocompromised individuals (Crum-Cianflone 2008, Feasey & Gordon 2013). In addition, increased risk of infection has been associated with reduced gastric acid (achlorhydria) or certain medications used to reduce gastric acid for relief.

*Salmonella* infection is the most costly foodborne disease in the U.S. (USDA 2016, ERS). In 2013, the cost of *Salmonella* exceeded $3.6 billion, accounting for nearly a quarter of the total economic burden of foodborne disease to the U.S. ($15.5 billion). Much of the *Salmonella* cost is due to premature death ($3.2 billion). The mean cost of a premature death
exceeded $8.6 million, which highlights the importance of focusing on preventing these costly deaths through evidence-based intervention.

**Signs and Symptoms**

Clinical signs and symptoms of *Salmonella* infection include fever, which is almost always present, as well as sudden onset of diarrhea and abdominal cramps (CDC 2015, Cummings et al. 2012). Less frequent signs and symptoms include hematochezia (blood in stool), nausea, vomiting, and headache. The incubation period is approximately 12-72 hours. Duration of illness is usually four to seven days, and cases usually do not require treatment. However, in some patients, diarrhea is severe enough to require hospitalization, with 23,000 hospitalizations occurring annually in the U.S (CDC 2015, Crum-Cianflone 2008, Krueger et al. 2014, Hannu et al. 2006, Carter & Hudson 2009). Invasive *Salmonella* occurs when the infection becomes extra-intestinal, and is a potentially life threatening situation. Invasive disease can lead to bacteremia, osteomyelitis, septic or reactive arthritis, and meningitis, with serious and long lasting effects. Approximately 8% of laboratory-confirmed *Salmonella* cases become invasive.

**Treatment**

Oral rehydration is sufficient treatment for most cases (Cummings et al. 2012, Krueger et al. 2014). If hospitalized for severe diarrhea, intravenous rehydration is used. Antibiotics can be used to treat *Salmonella*, but antibiotic resistance is a concern with some serotypes. First line antibiotics (i.e. fluoroquinolones, cephalosporin, and ampicillin) may have reduced efficacy as *Salmonella* becomes increasingly resistant (Crum-Cianflone 2008, Krueger et al, 2014, Whichard et al. 2007). If there is resistance, second and third line antibiotics may be used, though these may have toxic side effects, less efficacy, or greater cost. According to the National Antimicrobial Resistance Monitoring System (NARMS), 5% of S. enterica and S. bongori are
highly resistant, with at least five antibiotics not effectively treating the disease. Responsible prescription of antibiotics by physicians helps mitigates resistance (Crum-Cianflone 2008). Antibiotic treatment has no effect on whether or not a case develops more severe signs such as reactive arthritis (Hannu et al. 2006, Carter & Hudson 2009). Chronic reactive arthritis can be difficult to treat, and complications can develop such as ocular irritation and dysuria. Bacterial shedding in the stool can continue for weeks after clinical signs and symptoms disappear, and bowel habits may take several months to return to normal (CDC 2015, Acheson 2001, Zaidi et al. 2008). Some studies indicate that antibiotics can prolong bacterial shedding (Acheson 2001), so they are usually reserved for severe cases including infants.

**Reservoirs**

The principal reservoirs for *Salmonella* include pigs and poultry, in which bacteria are shed in feces (Jiang et al. 2015, Smadi et al. 2012). The bacteria can also enter the environment through incidental hosts such as wildlife. Raw poultry, eggs, red meat, and unwashed produce are common vehicles for food-borne *Salmonella* transmission. Inappropriate storage, inadequate cooking, and preparing food too far in advance are risk factors. Scrutinizing practices at each level of the food chain helps identify areas of concern, such as the contamination of crops at the production level (Cheng et al. 2013, Strawn et al. 2013). Crops, such as leafy green vegetables, are produced in large volumes and may be consumed raw. Farming practices vary in different regions and parts of the world, and sources and pathways of *Salmonella* contamination are impacted in various ways by these practices. Although the bacteria can be destroyed during storage and through composting techniques, improper agricultural processes may propagate contamination. There is particular concern because at the production point early in the food chain, the environment is less controlled, and there is greater likelihood of exposure. Crops are
grown in open fields, where exposure to infected wildlife and contaminated manure and irrigation water is difficult to control.

Inadequate water and wastewater infrastructure may contribute to the distribution of *Salmonella* (Hunter 2003, Bell et al. 2015). Heavy precipitation can change direction of water system flows, leading to abnormal surges through new channels. In this manner, contaminated feces may end up in the drinking water supply, or storm drain overflows combine with sewage, leading to fecal contamination of rivers. This can be exacerbated from additional stress on water treatment systems due to increased surface water turbidity after heavy precipitation events.

**Control**

Steps should be taken to reduce likelihood of transmission by ensuring proper food handling, storage, and hygiene. Best practices should be used in food production and transportation, as well as tracking all ingredients, to ensure proper surveillance and outbreak response. Serotyping *Salmonella* helps trace infections to identify outbreak sources (Cummings et al. 2012, Thiagarajan et al. 1994, Threlfall et al. 2014). Serotyping helps inform control measures, such as when the Enteriditis serotype was identified in association with eggs and transovarian transmission in chickens. Institutions working with high risk groups should take extra precautions, and policies should be implemented, regulated, and enforced for appropriate industries (Bambrick et al. 2008). Health communication and education programs can promote best practices.

The incidence of *Salmonella* is expected to increase due to changes in environmental influences, such as climate change (Jiang et al. 2015, Smadi et al. 2012, Bambrick et al. 2008). Understanding the complex causal relationships and how they are likely to change in the future can inform policy with evidence-based recommendations.
Climate Change Implications

A complex relationship exists between climate and food-borne pathogens such as *Salmonella* (Cheng et al. 2013, Bentham et al. 2001, Zhang et al. 2008, Grjibovski & Kosbayeva 2012). The interplay of ambient air temperature and other climatic variables such as relative humidity, precipitation, and irregular climatic phenomenon like El Niño are not fully understood and published results are not consistent. Variability in geographical ecology makes generalizations difficult. Further complicating the relationship and the determination of causal pathways, climatic effects are often seen after a lag period following exposure. In the natural environment, *Salmonella* proliferates in its reservoirs, transcends the food chain, and incubates within the human body before the onset of signs and symptoms of infection (Kendrovski et al. 2011, Zhang et al. 2008, Grjibovski & Kosbayeva 2012, Kovats et al. 2004, Van Pent et al. 2004, Naumova et al. 2007, Pangloli et al. 2008). The effect of climatic exposure may be cumulative throughout or at various points of these levels, such as the effect of cumulative ambient temperature impacting proliferation of foodborne pathogens in natural environments (Ivanek et al. 2009). Human behavior, food preparation/consumption methods, and pathogen, reservoir, and host ecology contribute to this relationship. Predictable peak seasons of high risk are well documented (Pangloli et al. 2008, Bentham et al. 2001, Cheng et al. 2013, Kendrovski et al. 2011); these have been associated with weather trends in the summer months. Fewer cases are seen during winter months.

Aside from seasonal weather patterns, changes in climate can impact incidence and distribution of *Salmonella* (Tirado et al. 2010, Cheng et al. 2013, Naumova et al. 2007, Varga et al. 2013a & 2013b, D’Souza et al. 2004, Kovats & Lloyd 2010). Temperature correlates with functions of *Salmonella* growth rate (Kovats et al. 2004). Growth was observed between 7.5 and
48 degrees Celsius in culture, with optimal rates at 37 degrees Celsius (Smadi et al. 2012, Kovats et al. 2004). *Salmonella* serotypes are affected differently by ambient air temperatures, with the Enteriditis serotype being more resilient to temperature fluctuations than other serotypes. Further research is needed to understand the resiliency of individual serotypes to climate change, especially when serotypes have varying antibiotic resistance and virulence. The burden of disease may increase if climate change promotes the survival of serotypes with greater resistance and/or virulence (McMahon et al. 2007).

**Temperature Factors**

*Salmonella* infections were found to increase following exposure to increased ambient air temperatures in populations in the United States (Jiang et al. 2015, Cheng et al. 2013, Naumova et al. 2007). Between 2002 and 2012, extreme heat events were associated with increased risk of *Salmonella* infection in Maryland, particularly in coastal areas (Jiang et al. 2015). Risk was found to increase 4.1% for every degree Celsius increase in temperature. Similarly in Massachusetts, a 12.6% increase in infections was associated with each degree Celsius increase (Cheng et al. 2013), and daily incidence rates were associated with a 2-14 day lag period over a ten year period (Naumova et al. 2007).

Similar associations were found in other parts of the world (Tirado et al. 2010, Kendrovski et al. 2011, Zhang et al. 2008, Grijibovski & Kosbayeva et al. 2012, Kovats et al. 2004, Van Pelt et al. 2004, D’Souza et al. 2004, Britton et al. 2010), including studies of European populations. Increased temperature was positively associated with infections after a one week lag period, with the effect diminishing over a five week period in the Netherlands, as well as in England and Wales (Kovats et al. 2004, Van Pelt et al. 2004). In England and Wales, infections were positively associated with the mean weekly temperature of the preceding week.
Beyond a threshold of five degrees Celsius, a 10% increase in infections was associated with each degree Celsius increase. In Macedonia, a 5.2% increase in monthly infections was associated with each degree Celsius increase in temperature (Kendrovski et al. 2011). In northwest Russia, a positive linear relationship between monthly infections and mean temperature in the previous month was found, as well as a 1.84-2.32% increase in infections associated with each increase of one degree Celsius (Grjibovski & Kosbayeva 2012).

In Australia, infections were positively associated with the mean temperature of the previous month (Tirado et al. 2010, D’Souza et al. 2004). In another Australian study, there was a high correlation between maximum and minimum temperatures and infections after a two week lag period (Zhang et al. 2008). In New Zealand, a 15% increase in infections was positively associated with a one degree Celsius increase in mean temperature (Zhang et al. 2008, Britton et al. 2010).

**Precipitation Factors**

Mixed results or no associations were found when additional climatic variables such as precipitation were included in analyses. A warmer atmosphere stores more moisture, resulting in greater precipitation (Meehl et al. 2005); a significant association between precipitation and temperature may indicate that there is not an independent effect on *Salmonella* transmission, and may relate to local climate trends, which may not be generalized elsewhere. It is difficult to ascertain independent effects of precipitation and relative humidity, if any effect exists at all. Neither precipitation nor relative humidity had any significant association with *Salmonella* infections in one study in England (Kovats et al. 2004).

Some previous studies found temperature and precipitation levels to be positively associated with *Salmonella* infections: in Maryland, heavy precipitation events were positively
associated with *Salmonella* risk, with each event contributing a 5.6% increased risk of *Salmonella* infection; in northwest Russia, one of the three models tested in a retrospective time-series analysis found a significant association with precipitation, and each millimeter increase in precipitation was associated with a 0.24% increase in infections in the same month (Grjibovski & Kosbayeva 2012, Jiang et al. 2015, Cheng et al. 2013). Such positive associations may be due to contamination of drinking water.

Relative humidity was not significantly associated with *Salmonella* cases in two studies in Adelaide, South Australia (Jiang et al. 2015, Bi et al. 2008) and in another study of two different Australian cities, Brisbane and Townsville (Zhang et al. 2008, 2010). In Adelaide, a temperate city in South Australia, regression models of climate variables and cases were compared; between 1990 and 2004, 4,740 cases were recorded in the city, which had a population of 1.1 million in 2005. After controlling for seasonal variation, decreased precipitation (no lag period) was associated with increased cases in all models, possibly due to interactions with temperature or other aspects of the local environment. Relative humidity was not significant for any of the models. The seasonal autoregressive integrating moving average model had the best goodness of fit and forecasting abilities, which found the negative association between precipitation and cases significant at a 0.10 level (90% CI) but not at a 0.05 level (95% CI). Using a regression analysis for Brisbane and Townsville (both of which are further north and less temperate than Adelaide), the number of cases was significantly associated with increased precipitation and with maximum and minimum temperature. There was no significant association with relative humidity. Maximum and minimum temperature, relative humidity, and precipitation were positively correlated with monthly *Salmonella* cases in Townsville with a lag period of two months for each variable; in Brisbane, maximum and minimum temperature,
relative humidity, and precipitation were positively correlated with weekly cases with lag periods ranging from less than one week to two weeks. Relative humidity was only significant in the correlation analysis before controlling for autocorrelation, seasonality, and increases in cases over the study period. Study results may have been influenced by small sample sizes in one of the study regions; between 1990 and 2005, 5,294 cases were reported in Brisbane (a subtropical city with a population exceeding 1.6 million) compared to 1,170 cases in Townsville (a tropical city with a population less than 200,000).

**Outlook**

Future projections indicate increasing incidence and distribution of *Salmonella* infections, with the effect of ambient air temperature relatively consistent across a wide geographic range: in Australia, a one degree increase in weekly mean ambient air temperature is estimated to result in 5.8-8.8% increase in weekly infections, and a 4.1-10.2% increase in risk of infection (D’Souza et al. 2004, Zhang et al. 2010). In Ireland, local *Salmonella* incidence is predicted to increase by 2-3% by 2100 based on regional climate trends (Cullen et al. 2009), with similar predictions in Canada and Australia (D’Souza et al. 2004, Bi et al. 2008, Fleury et al. 2006). *Salmonella* morbidity rates are predicted to increase by 2050 based on modeled impacts of climate change on gastrointestinal illness (Bi et al. 2008, Zhang et al. 2010). Each one degree Celsius increase in mean weekly temperature is projected to increase the number of infections by 7% in South Australia and Brisbane. Years lost due to disability from *Salmonella* infection are projected to increase between 7-56% in South Australia and 60-106% in Brisbane by 2050 due to temperature alone.
METHODOLOGY

Preliminary Methodological Considerations

Building upon the preliminary literature review of *Salmonella* and climate change, there was a need to ascertain viable methodologic approaches for furthering study as elements are validated. During the formation of the dissertation methodology and its implementation, an inherent calibration to focus the scope was integrated throughout for improved alignment with changes in available resources to facilitate completion and with appropriate scope throughout exploration of study variables. Calibrated methodology was formed as an approach to encompass every high-caliber technical and analytical process involved to effectively link the deliverables to the formative strategy of the dissertation, produce high quality, evidence-based public health research with sufficient analytic depth appropriate to the dissertation scope and competencies. Furthermore, as described in the introduction, an enhancement as a result of the calibration was to formally develop the framework and use the project implementation as a tool; the cost-benefit was the exchange of resource-intensive analytics for a scope deemed too narrow, in favor of formalizing the framework and publishing the tool. This was enabled (and justified) by documenting the process and producing a formalized tool, for which this dissertation’s formative phase identified a gap in the knowledge base. Therefore, the exchange was worthwhile for the improved practicality and dissemination findings at the level of which there is maximum applicability and greater use. The value is for future public health practitioners addressing changing population-level disease dynamics as a result of climate change; the calibration enhances the dissertation by build in improved scaling of the drivers for gauging an appropriate public health response at a variety of levels (which better addresses the root cause of the problem
that this dissertation is focused on). Formalizing this method ensured enhanced portability and versatility of the framework that directly ties into the formative strategy, which was the foundation for the dissertation. The calibration improves contribution to generalizable knowledge and capacity building, and was agreed as the feasible solution for improved resource allocation and greater utility: researchers should be particularly inclined to implement a cost-effective tool, enabling resources to be allocated to priority areas. Successfully calibrating approaches accounting for external factors influencing implementation was demonstrable of problem-solving abilities and practicality; identifying feasible solutions reflect the realistic environment of working in public health.

**Systematic Literature Review**

To better understand the role of climate on *Salmonella*, the preliminary review of the literature supported further methodology to systematically identify, appraise, select, and synthesize all high quality, relevant research evidence and arguments to focus on the research question. One of the key elements differentiating the systematic review from a literature review is the review protocol (Kitchenham et al. 2006). This protocol is developed from a preliminary literature review and describes the research objective and methodology for the systematic review with a defined search strategy.

Systematically reviewing literature balances the evidence through mitigating information overload when there is an abundance of research on the topic (Petticrew & Roberts 2006). A systematic review is appropriate when there is a wide range of research on a topic but key elements are missing or there are potential gaps in the general knowledge, and is particularly useful in early stages of developing policy or planning research through developing a comprehensive, objective summary (Vins et al. 2015). Relying on the results of only one study
may produce an evidence foundation that is non-definitive, and adjusting exclusion and inclusion criteria gives the reviewer some power to mitigate this bias (Hess et al. 2014). Systematic reviews can direct future research by creating a general overview of the topic, based on existing evidence, and can contextualize past research, including research methodologies, for strategy and direction in research. If robust systematic review was already conducted on one specific area, the next step would be to systematically summarize or update the results using the search strategy. Ultimately, the question being addressed must be refined with consideration to the context, including the population, the exposure, and the outcome. In turn, this can be used as a tool to answer questions on etiology.

There are seven steps to systematically reviewing the literature: 1) clearly and concisely define the appropriate question or hypothesis that the review will test, 2) decide on the criteria for inclusion and exclusion of types of studies, 3) carry out a search strategy, 4) screen the search results, 5) appraise the quality and relevance of qualitative and quantitative studies that are included, 6) synthesize the studies and assess the heterogeneity of findings, and 7) disseminate results (Petticrew et al. 2006).

The appropriate research question answered by the systematic review is identified in the review protocol and is a result of identifying a need and then assessing background information (Vins et al. 2015). Sources of data are identified, and determining appropriate inclusion and exclusion criteria based on study design can be used as proxy to control the methodological quality of included studies to better formulate the final answer. These criteria, as well as techniques for data extraction, must be determined prior to starting the systematic review (Sheuly et al. 2013). Inclusion and exclusion criteria for studies are decided by the reviewer, and quality assessments of individual studies should be carried out. The hierarchy of quality in study design
is (from highest to lowest): systematic reviews and meta-analyses, randomized controlled trials with definitive results, randomized controlled trials with non-definitive results, cohort studies, case-control studies, cross-sectional surveys, and case reports (Guyatt 1995 & 2000, Petticrew et al. 2006). Alternatively, evidence typologies can be emphasized to conceptualize strengths of methodological approaches in terms of specific research questions (Petticrew et al. 2006, Vins et al. 2015). Decisions within the process are a function of the review question, application of theory, and how the results are used, and are not an inherent feature of systematic review methodology.

Once the protocol is accepted, the search process phase of the systematic review can be implemented. Ideally, a search strategy will have high sensitivity (retrieves a high proportion of the relevant studies) and high specificity (retrieves a low proportion of irrelevant studies). The design of the search strategy is database-specific and relates key terminology and definitions with Boolean operators and truncation for electronic databases, with the aim of identifying all relevant literature (Kitchenham et al. 2007). To mitigate publication bias, positive, negative and null results of studies should be assessed (Sheuly et al. 2013). The search strategy and results are documented for reference.

Studies are selected based on the inclusion and exclusion criteria, as well as practicality (e.g. English language, date, level of evidence, and other aspects; Sheuly et al. 2013, Petticrew et al. 2006). Studies are evaluated through use of tools, which can be developed or adapted from previous evaluations to measure quality. Data is extracted and synthesized using defined information management applications. Preliminary analyses of the search results will contribute to filtering information. A secondary analysis will synthesize the study data by summarizing and synthesizing the results in a manner that answers the research question. The flow of information
through the systematic review process can be mapped out with a flow diagram, displaying the number of studies identified by the search strategy, and reasoning for inclusion or exclusion (Vins et al. 2015). All results are reported accurately. The resulting evidence from the search strategy, as well as the process itself, is discussed in the context of how the research question was answered.

**Strengths of Associations**

A second approach which utilized for this dissertation is the study of environmental exposures and health outcomes, specifically heat (Nuckels et al. 2004). Chapter 3 will describe the specific methods chosen for the NYS *Salmonella* study based on this preliminary review of the literature and the final systematic literature review outlined in Chapter 2. The relationship between the outcome (dependent variable) and one or more exposures (independent variables) can be statistically estimated. Measuring this relationship can be done by interpreting the change in the value of the dependent variable when any one of the independent variables are changed while holding the other independent variables fixed. Studies can integrate environmental monitoring data into the analysis of health outcomes, and the spatial and temporal context can be explored to understand patterns in disease distribution and frequency.

Methods for studying the environmental associations with food- and water-borne disease are well established. Disease outcome variables include laboratory-confirmed case reports with associated demographic information such as age, gender, location, and time of disease onset (Chen et al. 2012, Constantin de Magny et al, 2008, Lake et al. 2009, Lal et al. 2015), weekly counts of disease-related hospital visits (Davies et al. 2014, Harper et al. 2011), laboratory testing of environmental samples from sites with high human and/or livestock population densities (Harper et al. 2011, Bi et al. 2009), inferences from weekly government health bulletins
(Bi et al. 2009, Simental et al. 2008), aggregate outbreak reports (Curriero et al. 2001) and household surveys (Benjamin et al. 2013).

Climate is often used as the exposure variable in exploring disease outcomes as they relate to changes in the environment. Common climatic variables used in past studies include ambient air temperature (Jiang et al. 2015, Constantin de Magny 2008, Lake et al. 2009, Lal et al. 2015, Davies et al. 2014, Harper et al. 2011, Bi et al. 2009, Simental et al. 2008, Benjamin et al. 2013), precipitation (Jiang et al. 2015, Chen et al. 2012, Constantin de Magny 2008, Lal et al. 2015, Davies et al. 2014, Bi et al. 2009, Simental et al. 2008, Curriero et al. 2001, Carlton et al. 2014, Benjamin et al. 2013), and relative humidity (Bi et al. 2009, Phung et al. 2015). Additional climate data include wind speed, daily hours of sunshine, atmospheric pressure, sea surface temperature, and solar radiation levels (Constantin de Magny et al. 2008, Simental et al. 2008, Benjamin et al. 2013). Statistical models can be developed to assess the association between the environment and disease through correlation and regression analyses (Strachan et al. 2006, Nygard et al. 2004, Padilla et al. 2013). Exposure metrics can be developed related to selected independent variables of concern and then linked to disease outcome at a selected spatial-level and/or assessed over time. Differences in case frequencies between areas and periods can be evaluated by chi-square and Fisher's exact tests (Simental et al. 2008, Curriero et al. 2001). The correlation between disease incidence and climate variables can be assessed with Spearman's rho, a nonparametric measure of statistical dependence (Wang et al. 2012, Julia et al. 2013, Sasaki et al. 2009). Pearson product-moment correlation analyses can assess the specific lag effects between case frequency and direct unit measures of climate (e.g. degrees of ambient air temperature; Chen et al. 2012).
Poisson regression or other types of count model regression can be used to investigate the role of changes in climatic variables in explaining disease frequency variation (Yang et al. 2012, Vollaard et al. 2004, Kelly-Hope et al. 2007, Teschke et al. 2010, Louis et al. 2005, Guzman et al. 2015, Singh et al. 2001) which can be adapted for time-series data to examine any short-term temporal patterns (White et al. 2009, El-Fadel et al. 2012, Mladenova et al. 2015, Tornevi et al. 2013, Hashizume et al. 2007). The regression can be adjusted for over-dispersion using quasi-Poisson regression to estimate additional dispersion parameters (Guzman et al. 2015, Davies et al. 2014) or through negative binomial regression (Jiang et al. 2015, Miller et al. 2007, Benjamin et al. 2013, Guzman et al. 2015, Hedlund et al. 2014). A time series analysis under quasi-Poisson distribution can be applied to evaluate the association between environment and disease incidence over a period of time to determine significant indicators associated with increasing disease (Constantin de Magny et al. 2008, Davies et al. 2014, Eisenberg et al. 2013). Zero-inflated Poisson regression can adjust for case counts of zero (Harper et al. 2011, Yang et al. 2012).

possible delayed effects of climate indicators on disease (Phung et al. 2015). Poisson regression using a generalized additive mixed model can be used to evaluate the multiple-lag effects of stratified climate indicators on disease. Models can be adjusted for multiple-lag effects of various variables for evaluating the associations between categorized climate indicators and disease, with further trend tests to examine linear associations.

**Case-crossover Approach**

A time-stratified case-crossover approach is one of the most common analytical methods used to assess the relationship between climatic variables and food- and water-borne diseases (Guzman et al. 2015, White et al. 2009, Zenner et al. 2014, Nichols et al. 2009). When evaluating transient exposures such as ambient air temperature, a case can be self-matched as its own control by looking at the time spent without disease (control window) before and/or after the time spent as a case (case window; Maclure 1991). Using conditional logistic regression, exposure is compared between the control window and the case window. Although there is the possibility of information bias, this can be mitigated by careful selection of the case and control window period length and timing and is an efficient approach through self-matching and through using case reports (as no control groups are reported through a surveillance system). Seasonal and geographic differences that do not vary over time are inherently controlled by this design. The model can be adjusted to help control for unknown spatially or temporally dependent covariates (Recuenco et al. 2007).

Methodologically, next steps should involve further identifying vulnerable populations. Health policy decisions should be made in context of unique combinations of factors influencing population and sub-groups vulnerability. Identifying vulnerabilities can be adapted to encompass indicators relevant to the research topic (Hartsig 2015). Identifying vulnerable populations can
direct research and policy through tailoring recommendations, targeting monitoring and evaluation efforts, and planning activities and resource allocation for intervention. Once the significant indicators of disease and group vulnerability are identified, the identification of patterns in time and space can be used to inform policy and guide decision-making (Buck 2014, Cutter et al. 2003).

Mapping approaches can be used to summarize and display information about vulnerable populations. Spatial epidemiology is a subfield of health geography and is used to examine geographic variations in disease distribution in the context of demographic, environmental, behavioral, socioeconomic, genetic, and infections risk factors (Rajabi et al. 2015). One of the most useful approaches in spatial epidemiology is disease mapping, which provides visual representations of intricate geographic data to provide a general overview of the subject matter used for explanatory purposes. Further approaches include studies of geographic correlation, clustering, and surveillance. Disease maps are a useful tool to survey high-risk areas to inform policy and direct resource allocation within mapped areas. Methods for mapping and analysis of spatial and temporal distribution of disease are well established using food-borne disease case reports and hospital records, as well as vector sampling for zoonotic diseases (Kistemann et al. 2004, Odoi et al. 2003, Mor et al. 2014, Berke et al. 2001, Ducrot et al. 2005).

Mandatory notifiable disease reporting provides a relatively complete database enabling access to demographic and disease-specific information for laboratory-confirmed cases (Bi et al. 2009). Many studies have extracted geographic information from governmental health authority surveillance systems for mapping purposes (Strachan et al. 2006, Nygard et al. 2004, Kistemann et al. 2004, Odoi et al. 2003, Mor et al. 2014, Weisent et al. 2011, Pardhan-Ali et al. 2012). Data on human cases is protected and previous studies take steps to protect case confidentiality by
using only the minimal resolution of the spatial location indicator. The optimal spatial-level location indicator, or a combination of indicators, are selected based on the objectives of the study and are then geo-matched to corresponding latitude and longitude coordinates, and overlaid with information from census data. Census data is used for population size determination at given spatial levels, including population denominator data in calculating spatial level-specific incidence rates and linear interpolation of population between census years (Johnson et al. 2005, Mor et al. 2014, Weisent et al. 2011). Census data can also be used for determining statistical geographic entities and their boundaries, because census-based county subdivision levels are considered to be relatively homogenous socially, demographically, and economically.

Multiple layers of information overlaid on maps can provide a tool for visual assessment. Dot maps, choropleth maps, and probability mapping are used for cartographic display (Nygard et al. 2004, Kistemann et al. 2004). Overlaid levels of information may be risk-related environmental data or applied to direct analyses; for example, if temperature data is on a bigger scale, geo-processing can link the spatial levels to the closest weather stations across the study area (Strachan et al. 2006). Correlation and regression analyses can statistically describe relationships visualized in mapping. Analyzing geographical correlations describes exposures in relation to outcomes on a geographic scale (Elliot et al. 2004). The health-related outcome may be mapped cases, and statistically correlated with overlaid levels of information, such as proximal social and environmental risk factors (Nygard at et. 2004, Padilla et al. 2014). Spatial statistics use the location indicator data directly in the analysis, and identify spatial and temporal clusters of disease by comparing the differences in frequency and distribution between two or more defined areas (Elliot et al. 2004, Pfeiffer et al. 2004). These statistics have been applied in

**Systematic Literature Review to Develop Specifications**

**Materials and Methods**

These methods describe a systematic review of the climate and Salmonella literature, including the protocol for the three key stages of the systematic review: 1. planning, 2. implementation, and 3. reporting. These methods were used in the research for the systematic review chapter in this dissertation (Chapter 2), submitted to a peer-reviewed journal for publication. The process was based on established guidelines for performing systematic reviews to understand potential knowledge gaps and the indirect health consequences of climate change, specifically the implications on Salmonella via pathways that have not been extensively studied. The causal processes diagramed through the synthesis of contemporary literature were developed with the intent to model the complexities of the pathways linking climate change to Salmonella.
The planning stage was the first of three key stages of the systematic review. Aspects of the planning phase of the systematic review were guided by an initial and informal preliminary literature review of climate and *Salmonella* reported earlier in this Chapter. From this, a need for a formal, systematic review was identified. A protocol was developed based on this need and guided by findings from the preliminary literature review. The planning phase built on earlier reports of this Chapter by defining clear and concise research questions to be answered, deciding on the inclusion and exclusion criteria, and how the information is sought, appraised, synthesized, and assessed. The need for the systematic review was determined and agreed upon by the dissertation committee upon review of the overview on climate change, climate change and human health, climate change in NYS, *Salmonella*, and climate and *Salmonella*, corresponding to the earlier reports of this Chapter, as well. Consultation with the dissertation committee about the findings in the preliminary literature review lead to the development of the following research questions:

1. Does climate change impact the environment of NYS?
2. What is the effect of climate change on *Salmonella* in NYS?
3. What factors contribute to *Salmonella* vulnerability in humans?
4. What aspects of climate change and *Salmonella* necessitate further research?

The first three research questions address pathways of specific interest; the fourth research question incorporates specific next steps in research on the aforementioned identified pathways, as well as evidence for potential gaps in the literature or other unknown factors. Information used to answer the above questions was systematically included or excluded based on selection criteria. Studies selected for inclusion were research in the form of peer-reviewed journal articles with full text available. Additional library resources were accessed when full text
is not immediately available online, through use of ILLiad, a software provided by the University Libraries for Interlibrary Loan and UA Delivery Services. The information was relevant to the research questions, and was used to answer the questions directly or provide supporting evidence for an answer. Studies were excluded if they are duplicatory, not peer-reviewed, published in a language other than English, or published prior to 2006 (this time frame synthesizes contemporary information, appropriate for assuring relevancy of selected articles in this systematic review).

The implementation stage was the second of the three key stages of the systematic review. In accordance with the established guidelines, the actual search was not implemented nor results reported until the systematic review protocol was approved through the acceptance of the dissertation proposal (which was approved in August 2016), thus validating the protocol for the systematic review phases.

The systematic review search strategy incorporated information from the preliminary literature review to guide understanding of the quantity and quality of information pertaining to the research questions and guide the search strategy development. Resources and keywords used in the preliminary literature review were refined. Electronic databases used in the initial identification of articles for Chapter 1, and used in the systematic review, include (in order of which searches are conducted):

2. Web of Science (http://ips science.thomsonreuters.com/product/web-of-science/)
4. Google Scholar (http://scholar.google.com)
In order to maximize the robustness of the search, databases incorporating relevant fields to the research questions were used. These electronic databases are frequently used by researchers in the fields of public health and atmospheric sciences, and can be used to explore the intersection of these fields in order to answer the research questions. Search criteria were entered into electronic databases or manually programmed during the process. A search algorithm was constructed with Boolean logic applied to relevant keywords.

The results of the search algorithm were firstly be screened by article title, secondly by article abstract, and thirdly by article full text. If the title denoted potential relevancy to the research questions and meeting of selection criteria, the hyperlink to the selected article was deposited into a title bank for further review. Upon completion of reviewing the titles, selected titles were revisited to review the associated abstract. If the abstract denoted potential relevancy to the research questions and meeting of selection criteria, the full text article was downloaded and stored into an article bank for further review. Upon completion of reviewing all the abstracts of selected titles, the selected full text articles were read for ensured relevancy to the research questions and meeting of selection criteria. Outcome of screening was documented for each level.

For selected articles, information was extracted and entered into an Excel spreadsheet. Each row represented an individual selected article, and each column denotes topics of information extracted from the selected articles. Topics include general and specific information about the article introduction, methods, results, and conclusions. Information pertaining to the article's relevance in the systematic review was determined by the author. Column headings were as follows:

- Article author/year/title
Individual articles were frequently selected which addressed more than one research question. In addition, the search captured the same article on more than one electronic database using various search algorithms.

The reporting stage was the third of the three key stages of the systematic review. Causal process modeling was the primary mechanism; qualitative synthesis was performed on the information extracted from the selected articles. The nature of the synthesis was dependent on the results of the search, and applied logic and evidence-based modeling to explore risk and protective factors associated with climate change and Salmonella outcomes. A causal process diagram was created to demonstrate complex pathways between the environment and health outcomes through systematic review output. A causal process diagram is a robust tool to logically organize and synthesize interdisciplinary research and will guide further research conducted in this dissertation, and adapts established frameworks developed by researchers exploring complex relationships between the changing environment, policy, and public health (Vins et al. 2015, Berry et al, 2010, Joffe & Mindel 2006)
Documentation of outcomes is in terms of answering the research questions through explaining and justifying the model building and synthesis process (illustrated by a flow chart of selection outcomes), tabulated characteristics of selected articles, and conclusions drawn from a discussion of results of the synthesis, illustrated by the causal process diagram.

Measuring the Localized Effect of Temperature Exposure on Salmonella Outcomes

These methods describe the quantification of the relationship between *Salmonella* and the selected climate variable, based on findings from the literature. The objective was to describe the strength of this relationship through statistical testing, which was reported to NYSDOH to generate insight into the genesis, development, and spread of *Salmonella* in the context of climate change. This information contributes to the understanding of complex causal relationships, guide future research on forecasting the dynamics of disease, and can be used by NYSDOH to develop evidence-based policy and recommendations. The methods described in this section of the dissertation are used in the research for Chapter 3 of the dissertation, for submission to a peer-reviewed journal for publication. The methods were selected following a review of relevant and contrasting methodologies in peer-reviewed research publications, and adjusted for optimization when the project was calibrated.

Materials and Methods

Epidemiologic and demographic data were used for study of outcomes. The NYS Department of Health communicable disease registry data was utilized for sourcing confirmed *Salmonella* cases residing in NYS with diagnosis dates between 2002 and 2012. *Salmonella* case data was provided by the NYSDOH Emerging Infections Program (EIP) within the Bureau of Communicable Disease Control (BCDC). *Salmonella* cases are reported to the NYSDOH via the
Communicable Disease Electronic Surveillance System (CDESS) using the Electronic Clinical Laboratory Reporting System (ECLRS). This system provides laboratories with a single electronic system for secure and rapid transmission of reportable disease information to NYSDOH. ECLRS data is directly deposited in a database by the reporting laboratory. Reporting is mandated for all confirmed *Salmonella* cases.

A case of *Salmonella* was defined as a reported *Salmonella* case meeting the criteria for a confirmed diagnosis. This study used only confirmed cases, for which reporting is mandated after meeting the laboratory criteria for diagnosis once *Salmonella* is isolated from a clinical specimen (both asymptomatic infections and infections at sites other than the gastrointestinal tract are reported if laboratory criteria for diagnosis were met).

Case data for this study included pre-geocoded case residence location, age, and gender. Additionally, onset dates, culture date, diagnosis date, serotype, and information related to outbreak and travel history were included information from case reports. For some variables with missing information, such as geocoded case residence locations, cases were excluded or raw CDESS data was explored, at the discretion of and with oversight from BCDC, to determine if cleaning was a viable resolution. All data in CDESS is geocoded automatically by MapInfo. Onset dates for cases with missing onset dates were estimated by using the average time between onset and culture collection for cases with known onset dates. The potential effect on the power of the analysis from using these estimations was addressed in the discussion section. CDESS was overhauled in 2009 into a relational database (Oracle); blank fields may indicate added variables following the overhaul.

Cases were pre-excluded from the dataset provided by BCDC if residence is any other state or country. Exclusion criteria were applied in the following order: missing residence, travel
outside of the state or country in the seven days preceding onset, outbreak-related, or duplicate case (two or more reports for the same individual within 180 days with the same serotype). To consider misclassification, the following inclusion criteria were applied and compared to the outcome of the exclusion criteria: non-missing residence, non-travel-related, sporadic or cluster-related, and unique case (no reports for the same individual within 180 days with the same serotype).

Demographic data for the study area was obtained from the US Census Bureau to provide denominators for calculation of incidence rates at the census tract level. Geocoded case residence location was assigned to the corresponding census tract.

This study received NYSDOH Institutional Review Board approval after weighing benefits and risks. The key human subjects issue for this project was the incremental risks of linking confidential social-spatial data to precise information about cases due to the potential risk of discovery of additional information about an individual without permission by linking geocoded information from other sources. To address this risk, the database provided by BCDC did not include key personal identifying information such as name, address, and date of birth. Because the database will include geocoded residence location, age, and gender, the database was protected by the following steps:

1. The original database was maintained on secure NYSDOH computer drives in the NYS cloud (i.e., not on computer hard drives);
2. No potentially identifiable data was maintained on any student laptop or home computer;
3. All presentations and written reports associated with this project were approved by the study co-investigators and NYSDOH before submission for publication in scholarly journals or disseminated for public access or use.
4. Any printouts of study materials that include information from the database that could be used to identify individual cases or their locations were maintained in locked file cabinets within NYSDOH.

The study also used climate data for assignment of exposure. Climate data on daily heat metrics, e.g. maximum and minimum ambient air temperatures, and a daily maximum heat index (a measure of combined effect of heat and humidity) were provided by the NYSDOH Center for Environmental Health (CEH). This NASA satellite data consists of historical meteorological data compiled from the North America Land Data Assimilation System (NLDAS). The North American Regional Reanalysis (NARR) is the source of non-precipitation land-surface fields, and is spatially interpolated into a 1/8\(^{th}\)-degree grid composed of 12 x 12 kilometer cells and temporally disaggregated to an hourly frequency. This database has an advantage over ground-based weather station data used in previous studies which had been limited to using climate data from the National Center for Atmospheric Research from airport weather stations (fourteen relatively homogenous weather and ozone exposure regions, well-covered by weather stations, were used as the typical spatial unit of analysis; with the NASA data, a greater number of data points allows for more localized associations with \textit{Salmonella} cases).

This study will use this data to compute weekly mean ambient air temperatures and a cumulative temperature variable in NYS, between 2002 and 2012 for each cell. The creation of the cumulative temperature variable adapts methodology utilized in previous studies looking at relevant effects of climatic variables, specifically ambient air temperatures. The cumulative effects of temperature can be interpreted as the total effect of a difference in daily temperature over the selected lag periods. For missing data, gaps were excluded and the denominator updated to maintain an accurate aggregate temperature variable. Exposure data was linked with cases by
assigning the geocoded locations for case residence addresses to a cell. The map of geocoded addresses was overlaid on the map of climate data using ArcGIS (version 10.3, 2014).

The literature review summarized in Chapter 1 of this dissertation indicated an unclear association between other meteorological indicators such as precipitation and humidity with Salmonella cases. In addition, the NASA dataset is not a good source of this indicator data, and other sources would have methodologic limitations. Thus this analysis will focus on the association with temperature.

For the statistical analysis, conditional Poisson regression using Statistical Analysis System (v9.3, 2012) will determine the strength of association between ambient air temperature and Salmonella risk using weekly counts of cases for each of the climate grids. A case-crossover approach was utilized with bi-directional control selection. Cases were self-matched as their own control by looking at the time spent without disease (10 controls) before and after the case occurrence. Every case and its controls were linked to the corresponding temperature variables. Control windows will occur on the same day of the week at one, two, three, four, and eight weeks preceding and following the case to examine the effect of different lag periods. Using both preceding and following control windows will control for seasonality, and matching at the eighth week can be used to show there is no significant lag effect at this extent.

Data was organized by creating a new dataset, through expanding the existing case dataset and adding multiple rows, and then linking controls with cases through strata assignments. The cumulative effect of temperature was estimated by summing the log scale regression coefficients of lagged effects. To distinguish between short-term temperature effects in regard to seasonal temperature effects, the mean weekly temperature effect was compared to
the estimate of the cumulative effect over all lag periods, as obtained by summing the lags. Statistical significance was assessed at p-value <0.05.

Demographic analyses of the collected data and the statistical techniques which were utilized and calibrated for optimization for the current study as a tool in a portable framework. In order to organize and analyze epidemiological data to understand variation in disease frequency geographically and over time, we describe variation in terms of case characteristics using surveillance data and presented as rates in a manner that be operationalized in additional contexts.

The epidemiology of *Salmonella* was described in this study through group comparisons, based on relevant and comparable selections for food-/water-borne disease research and variables inherent to the data sources used. Population-based analyses will use will data obtained from the US Census Bureau (at the tract level, which are defined as significantly homogeneous across population characteristics) to provide denominators for incidence calculations. Multi-year projection data was used and linked with case and climate data.

For the cumulative temperature variable, methodology utilized in previous studies looking at relevant effects of climatic variables, specifically ambient air temperatures was adapted; the cumulative effect is interpreted as the total effect of a difference in daily temperature over a one week lag period. For missing data, the gap was excluded and the denominator changed to maintain an accurate aggregate temperature variable. Using the culture date, date characteristics were used to identify the year of infection. Results were presented in frequency tables and map figures (to represent geographically based differences in rates). Secondary analyses were proposed based upon review of preliminary analyses.
Framework for Communicable Disease Response to Climate Change

The mixed-methodology for this dissertation was formalized into a framework with four integral steps: scope, measure, analyze, and calibrate (SMAC; Chapter 4).

Materials and Methods

Our formative processes resulted in a specialized purpose, which was to produce a valid and reliable means for monitoring, evaluating, and reporting change in terms of specific disease outcomes affected by climatic change. Finding the framework to be effective and the deliverables to be valuable, our intent was to make our methods and findings accessible to all. Our SMAC framework validates outputs at each step, to allay concerns of bias as a result of indirect linkages inherent to the exposure and outcome. Our measurements were subject to the dimensionality and interplay of contributing factors, completeness and availability of data, and misclassification, which we strategically worked around through calibrating processes at each step. For limitations we identified, we were then able to address using our framework by supporting improvement processes and developing recommendations for subsequent analyses using the SMAC framework with an even more narrow scope. This included the recommendation for improving the quality of serotype data to support study of differential serotype associations with ambient air temperatures. Some serotypes manifest differently and there could be serotype-related clinical implications (D’Souza et al. 2004; Zhang et al. 2010). Furthermore, in-depth lagged effects, based on the hypotheses we tested with our case-crossover design, would be of interest for subsequent study.

Technical and analytical resources were found to be an integral to this implementation. The overall duration and resource-intensiveness of activities is important to gauge, in consideration of the age of data used in the quantitative components as well as how the implementation timeframe can impact human resources (in our case, the key scientific and
professional contributors). We quantified and strategically allocated our limited resources to ensure timely implementation and the production of meaningful results. Interim assessments demonstrated the extent of resources put into the high-caliber work involved in the analytical and technical processes. We recommend an approach which standardizes the robustness of these processes, and which functions to make adjustments to SMAC, between and among steps, to strengthen linkages with the formative strategy. To mitigate interruption of implementation as a result of resource reduction, we calibrated processes during implementation by conducting a cost-benefit analysis to ensure appropriate scale of the methodology for an actionable public health response. We recommend maintaining a level of analytic depth, which can at minimum be used as a validation step to demonstrate efficacy and value of the framework, and to be used as the evidence basis for continued research or public health practice.

Integral methods identifying patterns in distribution and frequency while differentiating between systemic and random fluctuations involve matching spatiotemporal data to the exposure and outcome; subsequent study could forecast outcomes to provide early warnings. Aggregate disease data, as our framework had used with *Salmonella*, can be done cost-effectively through use of administrative data to enable the SMAC framework to be cyclically applied, using continuously calibrated outputs for highly specific and purposeful allocation of resources and context-specific best practices.

Our implementation of the SMAC framework presents feasible solutions for improved resource allocation and greater utility of public health research and practice to mitigate adverse communicable disease outcomes related to climate change. Researchers should be particularly inclined to implement a cost-effective framework, enabling resources to be allocated to priority areas. This framework encourages calibrated implementation in real time, to strategically
incorporate resource limitations as a barrier to resolving the overarching public health problem, and this feedback loop optimizes outputs for enhanced public health response. This is an adaptation for realistic implementation of the framework in this context; an inherent instability is introduced when inputs are multi-disciplinary in nature, and barriers are unpredictability and may be attributed changing politics.

Building upon the SMAC implementation, we were able to recommend direction of future research. To ascertain scope, we reviewed the methodological approaches to the premise of these directions, as well as content-specific areas.

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Chapter 2. *Salmonella* and the Changing Environment: Systematic Review using NYS as a Model

**INTRODUCTION**

Salmonellosis is the costliest foodborne illness for Americans (USDA 2016), affecting an estimated 1.2 million people each year in the United States and causing nearly 400 deaths. In 2013, the cost of the disease exceeded $3.6 billion, accounting for nearly a quarter of the total economic burden of foodborne disease to the United States ($15.5 billion). There has been an increased focus on preventing salmonellosis, through evidence-based interventions and understanding the role of the environment (which broadly includes climate, ecology, and how these interact with the host and the agent). Climate change, which is the sustained change in weather patterns, including change in ambient air temperature, may impact salmonellosis. Comprehensive and effective approaches to combating the disease should encompass impacts of climate change; however, the impacts of climate change on salmonellosis were not well understood. Future changes to the epidemiologic profile of salmonellosis were difficult to predict because of the complex nature and multifaceted influences of host–agent–environment interactions and relationships which are highly sensitive to climate change. This is exemplified by *Salmonella*, the organism causing the disease, proliferating in warmer ambient air temperatures. Furthermore, human behaviors are contingent on environmental factors, and in turn, changing behaviors impact health (Bradley et al. 2005). Changes in the ecosystem may shift or expand the range of infectious agents and associated organisms, potentially exposing immunologically naive human or reservoir populations.
In the natural environment, *Salmonella* proliferates in its reservoirs, transcends the food chain, and incubates within the human body before the onset of signs and symptoms of infection (Kovats & Lloyd 2010; Van Pelt et al. 2004; Kendrovski et al. 2011; Naumova et al. 2007; Pangloli et al. 2008; Zhang et al. 2008; Ivanek et al. 2009; Grjibovski & Kosbayeva 2012). Human behavior, food preparation/consumption methods, and pathogen, reservoir, and host ecology contribute to this relationship, even when accounting for predictable peak seasons of high risk. These predictable peaks are well documented and associated with weather trends in the summer months, and fewer cases occurring during winter months (Bentham & Langford 2001; Kendrovski et al. 2011; Pangloli et al. 2008; Cheng et al. 2013). Aside from seasonal weather patterns, changes in climate can impact incidence and distribution of *Salmonella* (D’Souza et al. 2004; Naumova et al. 2007; Kovats & Lloyd 2010; Tirado et al. 2010; Cheng et al. 2013; Varga et al. 2013a, 2013b). The effect of climatic exposure may be cumulative throughout or at various points in the aforementioned domains, such as the effect of cumulative ambient temperature impacting proliferation of foodborne pathogens in natural environments.

Ambient air temperature has been identified to have a role in *Salmonella* occurrence. *Salmonella* infections were found to increase following exposure to increased ambient air temperatures in populations in the United States (Naumova et al. 2007; Cheng et al. 2013; Jiang et al. 2015). Between 2002 and 2012, extreme heat events were associated with increased risk of *Salmonella* infection in Maryland, particularly in coastal areas (Jiang et al. 2015). Risk of infection was found to increase 4.1% for every degree Celsius increase in temperature. Similarly, two studies in Massachusetts found that a 12.6% increase in infections was associated with each degree Celsius increase (Cheng et al. 2013), and that between 1992 and 2001, peak in daily incidence of *Salmonella* closely followed the peak of ambient air
temperatures with a 2–14 day lag period (Naumova et al. 2007). Similar associations were found in various localities, although generalizability may be limited or indeterminable (D'Souza et al. 2004; Kovats & Lloyd 2010; Van Pelt et al. 2004; Zhang et al. 2008; Britton et al. 2010; Tirado et al. 2010; Kendrovski et al. 2011; Grjibovski & Kosbayeva 2012). Future projections indicate increasing incidence and distribution of *Salmonella* infections (across all serotypes), with the effect of ambient air temperature on projected infections being relatively consistent across a wide geographic range (D'Souza et al. 2004; Zhang et al. 2010). However, studies of individual *Salmonella* serotypes found differential relationships with ambient air temperatures; this is of particular concern due to certain serotypes being associated with more severe disease.

Aside from ambient air temperature, mixed results or no associations were found between occurrence of *Salmonella* and other climatic variables used in previous studies, which were primarily precipitation and humidity (Meehl et al. 2005; Grjibovski & Kosbayeva 2012; Cheng et al. 2013; Jiang et al. 2015). A few previous studies found temperature and precipitation levels to be positively associated with *Salmonella* infections (Grjibovski & Kosbayeva 2012; Cheng et al. 2013; Jiang et al. 2015); however, it is difficult to ascertain independent effects of precipitation and relative humidity, if any effect exists at all. A significant association between precipitation and temperature may indicate that there is not an independent effect on *Salmonella* transmission (a warmer atmosphere is able to store more moisture, which can result in greater precipitation); the extent of this may be dependent on local climate trends, limiting generalizability to other localities.

The purpose of this study is to logically organize and synthesize the evidence for associations between *Salmonella* and the environment, specifically to understand the impact of
climate change. By doing so, further research on theorized associations can validate application of in-depth quantitative analyses to determine strengths of association and investigate the effects of changing ambient air temperature as well as other pertinent climatic and ecological factors.

This study has two aims: to produce meaningful findings which are generalizable and applicable to various settings and simultaneously, produce these findings specifically for the setting of New York State (NYS). This is justified as NYS is a geographically large and populous northeast state with excellent data systems and prior applicable research. NYS has a humid continental climate across its diverse topography, which includes highlands, mountains, and plateaus, as well as a large metropolitan area that is significantly warmer than surrounding areas due to anthropogenic activities (NCDC 2015). NYS has experienced the effects of climate change, with indications that, on average, the climate has been and will continue to become wetter and warmer (Karl et al. 2009; Melillo et al. 2014). Due to diverse topography and geography of NYS, the climate is inherently diverse, and climate change affects NYS to a variable extent and magnitude (Insaf et al. 2013). Regional differences in climate reflect this: the changes in meteorological variables are not necessarily the same across the entire state, and may reflect areas of NYS (as well as settings outside of NYS) that are more or less impacted by climate changes.

Based on these characteristics of NYS (which were disparately sourced from various scientific fields), the following was unclear: (1) if all factors relevant to understanding the impact of climate change on the NYS environment were sufficiently and comprehensively identified and described, as would be necessary for contextualizing a valid epidemiologic profile of *Salmonella* in light of a changing environment, and (2) the roles of specific environmental factors, in terms of effects on *Salmonella* occurrence in NYS. These uncertainties lead to the development of two NYS-specific research questions (RQs). Framed by these two RQs, two more RQs were
developed, as the following areas were also unclear: (3) if *Salmonella* vulnerability was sufficiently characterized in the context of climate change, and (4) what further research is necessitated on aspects of climate change and *Salmonella*. The latter two questions were inherently broader and not confined to the setting of NYS, as their implications are relevant in any setting, and there was limited information specific to NYS. These four questions are described further in the study methodology.

**METHODS**

The study design was a systematic review of the literature, which was developed based on established guidelines to identify and understand potential knowledge gaps and the indirect health consequences of climate change, specifically the implications on *Salmonella* via pathways that have not been extensively studied (Petticrew & Roberts 2006; Kitchenham & Charters 2007; CRD 2008; Sheuly 2013; Vins et al. 2015). From what is known about *Salmonella*, the complex interplay of the host, agent, and environment, and the extent of unknowns involved in gauging the causes and trajectory of the disease, a systematic review ascertains the existence of causal processes, which is a useful design for the early stages of developing policy or planning research through developing a comprehensive, objective summary (Petticrew & Roberts 2006; Vins et al. 2015). Systematically reviewing the literature balances the evidence through mitigating information overload when there is an abundance of research on the topic (Petticrew & Roberts 2006), as well as when there is a wide range of research on a topic but key elements are missing or there are potential gaps in overall knowledge. The systematic review tool was further developed through incorporating findings from the preliminary literature review, which
were used for narrowing the scope and to develop the RQs introduced in the prior section, as per the established guidelines. The following RQs were developed:

1. Does climate change impact the environment of NYS?
2. What is the effect of climate change on *Salmonella* in NYS?
3. What factors contribute to *Salmonella* vulnerability in humans?
4. What aspects of climate change and *Salmonella* necessitate further research?

Information was systematically included or excluded based on selection criteria. Articles were excluded if duplicatory, not peer-reviewed, nor published in a language other than English. Articles published prior to 2006 were excluded based on guidelines for synthesizing contemporary information (Meline 2006), appropriate for assuring relevancy of selected articles. To focus the geographic scope for the first two RQs, articles with a setting outside of NYS were excluded after the search was implemented.

Search algorithms were constructed by combining relevant keywords to frame the RQs. To maximize the robustness of the search, databases which include scientific fields and disciplines relevant to the RQs were used. These electronic databases are frequently used by researchers in the fields of public health and atmospheric sciences, and can be used to explore the intersection of these fields in order to answer the RQs. Electronic databases used in the systematic review include (in order of which the searches were conducted):

2. Web of Science (http://ipscience.thomsonreuters.com/product/web-of-science/)
4. Google Scholar (http://scholar.google.com)
The results of the search algorithm were first screened by article title, secondly by article abstract, and thirdly by article full text for relevancy to the RQs and meeting of selection criteria. For selected articles, information was abstracted and entered into an Excel spreadsheet, with each row representing an individual selected article, and each column denoting key elements abstracted from the selected articles. Topics included general and specific information about the article introduction, methods, results, and conclusions. For each article, the level of evidence was assessed using a level of evidence hierarchy (from highest to lowest: systematic reviews, followed by randomized controlled trials, cohort studies, case-control studies, case series/reports, and lastly, editorials/expert opinions). This was then used for limiting secondary reviews (i.e. inclusion criteria for additional relevant articles identified through the review of references of abstracted articles) as well as to assess the findings, identify limitations, and add credence to conclusions. Evidence of causal processes was synthesized through leveraging the level of evidence, equally weighting inter-level evidence.

Articles which were selected for abstraction through the systematic review's search methodology are tabulated in Appendix Table 3 and include each article’s citation as well as detailed information (note that the works cited for this study's background and methods appear in the References section). Information abstracted from the selected articles was used to answer each RQ. For each RQ, the Results section presented a critical lens for the articles identified to answer each corresponding RQ. Subsequently, RQ-level results were integrated to make inferences about risk and protective factors associated with climate change and Salmonella outcomes and a causal process diagram was developed to account for the varying specificity of the RQs. Guided by an established model to illustrate complex pathways between the environment and health outcomes through systematic review output (Perry 1983; Joffe &
Mindell et al. 2006; Berry et al. 2010; Vins et al. 2015), a causal process diagram was created. A causal process diagram is a robust tool to logically organize and synthesize interdisciplinary research. The model adapts established frameworks developed by researchers exploring complex relationships between the changing environment, policy, and public health. In the Discussion section, integration of the background literature into a higher-level evaluation of the results across multiple RQs is framed by the preceding causal process diagram.

RESULTS

Screening Results

In the flowchart (Appendix Figure 3), 3923 articles were identified from searching the four electronic databases. Title screen was used to exclude 3576 of the 3923 articles (91%); 347 of the 3923 articles (9%) were not excluded based on the title screen, and were subsequently screened by the article abstract. Of the remaining 347 articles, 148 articles (4% of the total search results) were excluded based on the abstract screen, and 108 articles (3% of the total search results) were excluded based on the subsequent full article screen. The result was 91 articles (<1% of the total search results) that were not excluded by screening of the title, abstract, or full text.

Of the 3923 articles identified from searching the four electronic databases, Google Scholar identified the most (n = 2,324; 59%), followed by PubMed (n = 702; 18%), ScienceDirect (n = 470; 12%), and Web of Science (n = 427, 11%). Across all four electronic databases, 3832 articles (98%) did not meet criteria and were excluded. Of the 91 articles selected for abstraction, PubMed identified the most articles selected for abstraction (n = 34;
37%), followed by Google Scholar (n= 31; 34%), Web of Science (n = 19, 21%) and ScienceDirect (n = 7; 8%).

Of the 3923 articles identified from searching the algorithms constructed to answer the RQs, RQ4 had the most (n = 2,070; 53%), followed by RQ1 (n = 970; 25%), RQ3 (n = 866; 22%), and RQ2 (n = 17; <1%). Across all four RQs, 3832 articles (98%) did not meet criteria and were excluded. Of the 91 articles selected for abstraction, RQ3 had the most (n = 35; 38%), followed by RQ1 (n = 30; 33%), RQ4 (n = 22; 24%), and RQ2 (n = 4; 4%).

A total of 12 systematic literature reviews were re-reviewed for candidate articles contained within. A title and abstract screen was conducted primarily. The following criteria were used for these secondary articles: articles were excluded if they were published prior to 2006, if they were deemed level V or below for level of evidence, and/or if they were outside the scope of the original RQ corresponding to the parent systematic literature review. A total of 21 articles met this criteria and were identified as candidates; these underwent full-text screening. Two articles were found to meet the criteria and were selected for abstraction.

**Characteristics of Articles Selected for Abstraction**

About half of the articles (n = 39; 43%) were published before 2011, the midpoint of the review period. One article (1%) was published in the latest year of the review period (2017), though the latest year may be an incomplete representation as the electronic databases are continually updated. To broadly assess the evidence relating to the topic, of the 91 articles, the most frequent study design was case–control (n = 34; 37%), followed by case studies (n = 33; 36%), systematic reviews (n = 12; 13%), cohort studies (n = 5; 5%), randomized controlled trials
(n = 4; 4%), and expert opinions in the form of editorials; n = 3; 3%). **Appendix Figure 3** gives details of articles selected for abstraction.

**The Impact of Climate Change on the Environment of NYS (RQ1)**

For RQ1 (Does climate change impact the environment of NYS?), 30 articles were identified; see **Appendix Table 3** for details of individual articles selected for abstraction to answer this RQ. For study design, 26 of 30 articles (87%) were retrospective study design, including one article of the 30 (3%) which was a systematic literature review; a prospective study design was used in four of the 30 articles (17%). Approximately half of the articles were published before 2011.


The study designs of the articles included (from highest to lowest in the hierarchy of evidence): one systematic review, two randomized controlled trials, thirteen case control studies, twelve case studies, and two expert opinions in the form of editorials. The strongest evidence relevant to this RQ was information on how NYS responded to climate change using the
ClimeAID integrated assessment for effective climate change adaptation (Rosenzweig 2011). Furthermore, among the other articles included for this RQ, relevant findings were similar or complimentary to the ClimeAID integrated assessment (to various extents) and the ClimeAID integrated assessment was directly referenced in one other RQ1 article (Burns et al. 2007).

Across the 29 other articles, it was noted that as each study design indicated stronger evidence (as a higher level in the hierarchy of evidence), a greater extent of similarity of findings was reflected when compared to the ClimeAID integrated assessment. Relevant studies and supporting evidence additionally identified by this study's search algorithms of this RQ were appraised and analyzed to identify and assess vulnerabilities and adaptation strategies to describe the trends in climate. Eight sectors (water resources, coastal zones, ecosystems, agriculture, energy, transportation, telecommunications, and public health) were focused on, and linkages between climate vulnerabilities, risks, adaptations, and monitoring gaps were applied to seven regions across NYS. Trends and statistical significance were calculated for the relevant observations and models. Observed climate trend analyses determined that: since 1970, average temperatures in NYS were increasing by approximately 0.6 degrees Fahrenheit per decade, and average winter temperatures were increasing at a rate of over 1.1 degrees Fahrenheit per decade. Since 1900, the variation in precipitation trends increased year-to-year and decade-to-decade, with heavier precipitation events becoming more prevalent in recent decades; sea levels have also risen by approximately one foot over this same period.

Furthermore, strong evidence reflected the assessment of the impact of climate change on the environment of NYS to develop future climate projections (Burns et al. 2007; Frei & Gruber 2010; Rozell & Wong 2010; Rosenzweig 2011; Insaf et al.2012). Changes in mean temperature were projected to be likely, with an increase across NYS up to 9.0 degrees Fahrenheit by the
2080s (Burns et al. 2007; Rosenzweig 2011). Precipitation changes were also projected to occur, with the largest increases to occur in winter. Changes in extreme climate events were predicted throughout NYS, with increases in extreme heat events, intense bouts of precipitation, and coastal flooding. North-to-south shifts in ecoregions, exacerbated by the above factors, will continue, resulting in challenges for the sectors under study, including public health, with predictions of disease occurrences previously not widely seen. These factors, indicative of climate change in NYS, provide evidence of impacts on the environment across sectors in NYS.

The Effect of Climate Change on Salmonella in NYS (RQ2)

For RQ2 (What is the effect of climate change on Salmonella in NYS?), five articles were identified; see Appendix Table 3 for details of individual articles selected for abstraction to answer this RQ. The study design in three of the five (60%) articles was prospective and in two of five (40%) was retrospective, and the articles were all published in the second half of the review period. Three articles, using the farm environment, characterized the prevalence, persistence, and diversity of foodborne pathogens, including Salmonella (Strawn et al. 2013, 2014; Weller et al. 2015). One article investigated the effects of climate on hospitalizations due to gastrointestinal infection, including Salmonella (Lin et al. 2012). One article investigated surface water, weather factors, and presence of Salmonella (Jones et al. 2014). All five articles established a linkage between climate or the environment, and Salmonella.

The study designs of the articles included (from highest to lowest in the hierarchy of evidence): one randomized controlled trial, one case control study, and three case studies. Hierarchically, the strongest evidence relevant to this RQ included the quantification
of *Salmonella* diversity, to aid in the identification of *Salmonella* contamination sources (Strawn et al. 2014). *Salmonella* isolates from 33 NYS produce farms were subjected to a regional comparison to determine serotype uniqueness, and distinct differences between *Salmonella* subtypes isolated between the two regions were identified, confirming that regional characteristics (landscapes, local climates, and/or wildlife populations; all of which are impacted by climate change, as per aforementioned findings relevant to RQ1) influence the *Salmonella* subtype diversity found in different produce production environments. Furthermore, time-series analyses established the linkage between weather factors and increased risk of *Salmonella* hospitalizations, manifested as gastrointestinal infections (Lin et al. 2016). Between 1991 and 2004 in NYS, temperature, extreme heat, and precipitation were associated with the cases, accounting for lag (of up to 10 days) and seasonality. Stratified analyses identified greater impacts on subpopulations (Hispanics, blacks, and females) in regards to vulnerability as a result of heat effects. The generalizability of these results may be constrained by time and space. The case studies contextualized the results, as these additionally confirmed the presence of *Salmonella* in NYS irrigation and farming settings (Strawna et al. 2013; Weller et al. 2015), with increased presence linked to periods of rainfall of less than 0.64 cm (3 days before sampling), when growers are more likely to use water for irrigation (Jones et al. 2014). The lowest levels of *Salmonella* were associated with heavy rainfall amounts; the study confirms inconsistencies with the correlation of *Salmonella* levels and precipitation, as previously reported, and that other factors likely influence the association of precipitation and *Salmonella* in these settings.
Factors Contributing to Salmonella Vulnerability in Humans (RQ3)

For RQ3 (What factors contribute to Salmonella vulnerability in humans?), 33 articles were identified; see Appendix Table 3 for details of individual articles selected for abstraction to answer this RQ. The United States represented the largest proportion of the studies for locale (7/33; 21%), followed by China and Australia with four articles (12%) each (Appendix Table 1). Additional countries contributed 1–3 articles each. For study design, 29 articles (88%) of the 33 were retrospective, including two articles (6%) of the 33 which were systematic literature reviews (6%); four articles (12%) of the 33 were prospective study design. Two-thirds of the articles were published in the second half of the review period.

The significant findings of the studies from the articles included identifying risk factors, such as exposure pathways (meat products, pets, attendance at children's day care, infected family members, nosocomial) (Bellido-Blasco et al. 2007; Oggioni et al. 2010; Vanhoof et al. 2012; Thompson et al. 2013; Varga et al. 2013a, 2013b; Middletown et al. 2014; Yang et al. 2015; Folster et al. 2015; Chen et al. 2016) and health behaviors (hand-washing, food preparation) (Chen et al. 2012; Quinlan 2013; Middletown et al. 2014; Bassal et al. 2014; Yang et al. 2015). Several studies described significant associations of case demographics with: severe/chronic infection (Doorduyn et al. 2008); prevalent serotypes (Hendriksen et al. 2009; Folster et al. 2015) and serotype virulence (Andino & Hanning 2015; Jokinen et al. 2015), multi-drug resistance (Dionisi et al. 2011; Graziani et al. 2011; Ran et al. 2011; Tabu et al. 2012; Vanhoof et al. 2012; Afema et al. 2014; Yang et al. 2015; Folster et al. 2015; Jokinen et al. 2015; Liang et al. 2015) and, comorbidity with other endemic diseases (Tabu et al. 2012). Several studies quantified the relationship between climate variations and cases of Salmonella infection, describing in terms of seasonality, extreme events, and ambient air.

The study designs of the articles included (from highest to lowest in the hierarchy of evidence): two systematic reviews, one randomized controlled trial, five cohort studies, thirteen case-control studies, and twelve case studies. The strongest evidence from systematic reviews provided insight into human vulnerabilities from a temporal and spatial lens. From research in NYS, a synthesis of 86 studies of human zoonotic enteric diseases were used to identify patterns in Salmonella occurrence, confirming ubiquitous seasonal variation across transnational boundaries with regional variations highlighting complex environment–pathogen–host interactions, and Salmonella having a distinct summer peak similar to other bacterial diseases included in the study (Lal et al. 2012; Hellberg & Chu 2016).

The findings support important direct and indirect consequences for future enteric disease risk as a result of distal, long-term climatic variability, and proximal environmental influences and host population dynamics. Additionally, the assessment and prediction of enteric disease burden in temperate, developed countries across the globe were focuses of another methodologically robust synthesis of studies, the findings of which support consideration for public health interventions and further research by targeting specific populations. The effects of climate change on the persistence and dispersal of foodborne bacterial pathogens, including Salmonella, were identified; relationships with temperature, rainfall, drought, and wind were systematically identified and used to predict how projected changes in climate will impact Salmonella in the environment. In terms of the RQ, the findings are evidence of the
concerted influence of a variety of factors influencing *Salmonella* etiology and linkages to impacts on specific populations who can then be characterized as vulnerable.

Vulnerability was also considered from the clinical perspective. Drug resistance is increasingly of concern and was the focus of several studies identified in the search algorithm for this RQ. From studies in Italy, multi-drug resistance and virulence of *Salmonella* serotypes were characterized from human, animal, and environmental sources to bolster understanding of the molecular basis of the drug resistance and evaluate the origins of serotypes isolated from different sources, and how this facilitates the spread of hard-to-treat disease (Dionisi et al. 2011; Graziani et al. 2011; Afema et al. 2014).

The transmission dynamics of drug resistance was also the focus of a United States-based study, confirming prior evidence that cattle are a source of exposure to drug resistant serotypes of *Salmonella*, thus identifying groups of humans subject to greater risk of exposure. However, the diversity of the profiles of the serotypes indicates *Salmonella* and associated resistance from humans and cattle may not be entirely derived from a common population, which adds a layer of complexity. Cohort studies also contributed to characterizing those at risk of *Salmonella* infection, including human behavior, such as chicken consumption which remains a significant risk factor for *Salmonella* infection. In Australia, 333 adults had laboratory-confirmed *Salmonella* infection and 101 were hospitalized (over a total follow-up of 1,120,242 person-years). The risk of *Salmonella* infection notification was not found to differ by age, but risk of hospitalization increased with age. Elderly males had the highest risk of infection-related hospitalization. The risk was 70% higher for those living in rural or remote areas, those taking proton pump inhibitors, and those reporting chicken/poultry intake at least seven times per week.
This finding highlights the importance of reducing contamination of poultry and improving food safety advice and case management for older people.

Aspects of Climate Change and *Salmonella* Necessitating Further Research (RQ4)

For RQ4 (What aspects of climate change and *Salmonella* necessitate further research?), 28 articles were identified; see Appendix Table 3 for details of individual articles selected for abstraction to answer this RQ. The United States represented the largest proportion of articles on locale (5/28; 18%), followed by Australia and the Netherlands (each with 4/28; 14%) with additional countries contributing one article each (Appendix Table 2). All of the 28 articles (100%) were retrospective studies, including 10 of the 28 (36%) which were systematic literature reviews. Approximately 54% were published in the latter half of the review period.

Further research is needed on serotype-specific risk factors and the role of the environment (Marcus et al. 2007; Kumar et al. 2009; Michan et al. 2012; Andrews & Ryan 2015), including serotype resiliency and contribution to salmonellosis outcomes (Kovats & Lloyd, 2010); serotypes Enteritidis and Typhimurium are the most common in the United States, and the Enteritidis serotype was been found to be more resilient to temperature fluctuations than other serotypes. Additionally, further research should include robust incorporation of source of infection into study methodology (Mughini-Gras et al. 2008, 2014) as well as treatment implications (Zali et al. 2011), food safety issues related to climate change (Miraglia et al. 2009; Tromp et al. 2010; Bassal et al. 2011; Lake et al. 2012), associations with health hazards in terms of migration and climate adaptation (Kjellstrom & Weaver 2009); salmonellosis and health expenditures as a result of climate change (Markandya & Chiabai 2009; Maertens de Noordhout et al. 2015); improved monitoring and resolution of temperature variables associated

The study designs of the articles included (from highest to lowest in the hierarchy of evidence): eleven systematic reviews, nine case control studies, seven case studies, and one expert opinion in the form of an editorial. The strongest evidence relevant to aspects of climate change and *Salmonella* necessitating further research are from the systematic reviews, at the top of the hierarchy of evidence, due to the inherent design of this methodology to uncover gaps in the knowledge base upon synthesizing disparate sources of information. Aspects necessitating further research on the interplay of *Salmonella* and climate change were found to have several common themes throughout these articles: measurement capacities, cross-sector and extra-sector study scope, and generalizability of results.

Measurement capacity is an aspect of methodological consideration of studying climate change and *Salmonella*; frequently there was a lack of sufficient quantification to understand, articulate, and frame findings, inferred from the systematic reviews' meta-analyses (and the corresponding limitations reported in the discussions and conclusions). This contributes to gaps in reporting on magnitude and specification of effects. Cross-sector and extra-sector study scope need further development to accurately reflect the multi-disciplinary approaches and reaches in public health, and the very nature of the topic. This primarily pertains to in-depth inclusion of sector-specific intermediary drivers (and to a lesser extent exposures and outcomes) throughout the epidemiologic triad. Additionally, there is a need to incorporate information identified from
the synthesis of disparate information sources. Enhanced measurement capacity and appropriate scope of study are important considerations of generalizability. When applying existing research in novel situations, the limitations of generalizability are especially important to account for. Changing climates and environments are constrained by time and space; studies with a specific spatial or temporal context should avoid ecologically fallacious interpretations and attempt to account for the complexity of the variables at play.

Previous *Salmonella* research on seasonality in human zoonotic enteric diseases in NYS identified the need to understand the concerted influence of proximal environmental influences, climate variability, and host population dynamics (Lal et al. 2012). This was concluded as imperative to improving assessment and prediction of *Salmonella* burden in temperate, developed countries. Longer-term climate variability was found to have direct and indirect consequences for future enteric disease risk (Lal et al. 2012; Hellberg & Chu 2016). Similar findings were systematically identified through study of the effects of climate change on the persistence and dispersal of *Salmonella* in the environment (Hellberg & Chu 2016), which also highlighted the importance of understanding changing transmission dynamics from animal hosts.

The scope of food safety, security, and nutrition was the focus of a review of adaptation in developed countries. Complex structures are in place or being developed to support adaptation to the food safety consequences of climate change, although their effectiveness will vary between countries, and the ability to respond to nutritional challenges is less certain (Lake et al. 2012). Uncertain health consequences in developed countries were linked to the key global food sector indicators, which are impacted by climate change. The authors identified the need to study the relationships at greater resolution and with greater accuracy in measurement to validate the theorized propagation of foodborne diseases, including *Salmonella*. The projection modeling
ultimately leads to a significant degree of uncertainty about future impacts. In conjunction with evidence that climate change may lead to more variable food quality, this reinforces the need to maintain and strengthen existing structures, interventions, and policies surrounding the global food and agricultural sectors.

**Causal Process Diagram**

Common themes qualifying as key drivers were identified from the abstracted articles in the systematic literature review. These were organized to demonstrate the complex interplay, and presented as a causal process diagram (Appendix Figure 2). As an analytical tool to mitigate potential bias magnification as a result of variances in specificity of the RQs, the processes were identified and evaluated from the preceding RQ-level results and strategically organized into the diagram to ascertain exposures, intermediaries, and outcomes. Exposures and outcomes were identified, as well as intermediary factors which interface between exposures and the outcomes; these were categorized and assigned predominant directionality in regard to cause and effect.

Exposures were identified and categorized as climatic factors (climate change, temperature, precipitation, extreme weather events, and seasonality) and ecological factors (natural environment, reservoir characteristics, food chain/cold chain). Intermediaries were identified as *Salmonella* biology (range, reproduction, proliferation, ability to survive/adapt, serotype fitness, transmissibility) and population factors (human behavior, travel, migration, socio-demographics, economics, sanitation, and hygiene). The outcome was identified as salmonellosis (incidence, risk, rate of exposure, serotypology, virulence, treatment resistance, clinical manifestation, immune system and co-infections, and reporting constraints). Unidirectional relationships were identified to gauge the interplay. Climatic factors
predominantly affected other exposures that were ecological, intermediary factors of *Salmonella* biology and population factors, and the outcome of salmonellosis as well. Intermediaries were affected by both climate and ecological exposures, and intermediaries also affected salmonellosis outcomes; however, there was limited interaction between the two intermediary categories.

**DISCUSSION**

Climate change is identified as a concern for NYS, so strategies to mitigate salmonellosis outcomes should account for effects of a changing climate impacting the local environment, and changing the parameters of disease occurrence through a variety of mechanisms. With the environmental factors framed as the key drivers, changing climatic factors may induce changes throughout the model, through various pathways and upon multiple levels. Climate change independently impacts these intermediary factors that complicate the association between environmental exposure and salmonellosis; for example, changed climatic conditions may promote highly virulent serotypes to thrive in an expanded range, resulting in poorer salmonellosis prognoses for the population also living in that range. The key findings of this study are logically organized and synthesized evidence for understanding associations between *Salmonella* and the environment, which may enable researchers to understand the impact of climate change on disease, and operationalize targeted approaches for mitigation and prevention through public health measures. Further research on theorized associations validate the application of in-depth quantitative analyses to determine strengths of associations, especially effects of changing ambient air temperatures, as well as other pertinent climatic and ecological factors.
The primary objectives of this study were to determine the following: the impact of climate change on the environment of NYS, the effect of climate change on Salmonella in NYS, factors that contribute to Salmonella vulnerability in humans, and aspects of climate change and Salmonella which necessitate further research. The RQs are designed to ascertain the factors (particularly in terms of an environment undergoing climate change) that drive salmonellosis outcomes, applicable to NYS where climate change is a concern. A total of 91 articles were recently published on the topic of climate change and Salmonella, which were synthesized to provide a comprehensive understanding of the topic, in terms of the primary objectives. The answers to each of the four RQs are summarized holistically in the following paragraphs.

To answer RQ1 (Does climate change impact the environment of NYS?), this systematic review consistently identified articles that contributed evidence that the environment of NYS is impacted by climate change. All of the articles that were relevant to answering RQ1 indicated climate change was impacting the environment of NYS, in a myriad of ways. Although there was minimal published evidence identified on the effects of climate change on Salmonella specifically in NYS, all of the articles identified for this RQ established a linkage between climate change and Salmonella. This was reinforced by articles identified by RQ2. Additionally, there was evidence which identified and supported the existence of factors that contribute to human vulnerability and susceptibility to Salmonella. These factors spanned the social, economic, demographic, and clinical (physical and behavioral) domains. As evidenced by the synthesis of the results of the studies from the abstracted articles as well as the development of the causal process model, the relationships involved are complex, dynamic, and have dimensionality. Furthermore, cross-disciplinary scientific and medical fields contribute to the knowledge base in incremental steps, often with mixed and conflicting findings. As a result,
there are gaps in the understanding of these relationships, as well as limited capabilities to measure and quantify the various elements involved to validate conclusions.

To answer RQ2 (What is the effect of climate change on *Salmonella* in NYS?), this systematic review identified articles that contributed evidence of a complex relationship between climate and *Salmonella*. Due to the commonalities of the interplay between the environment, the host, and the agent, such complexity is likely extended to other food- and waterborne diseases as well. The influence of climate change on the proliferation of associated pathogens is an important aspect of public health research. Due to the complex mechanisms involved, negative health outcomes as a result of climate change impacting food and waterborne pathogens are challenging to combat due to limited information and theoretical models predicting diverse outcomes. This review identified the linkages to help understand the causal pathways, and identified gaps in knowledge.

To answer RQ3 (What factors contribute to *Salmonella* vulnerability in humans?), this systematic review identified articles that contributed information on risk factors based on characteristics of exposure pathways (such as handling or consuming meat products, owning pets, attending children's day care, as well as an exposure from an infected family member or while hospitalized). Health behaviors can have protective effects, such as hand-washing and following guidelines for food preparation. Demographic groups that are resistant to changing behavior may become vulnerable to infection. Cases that were severe or chronic infections were linked to serotype prevalence, virulence, drug resistance, and comorbidity with other diseases, thus vulnerability to *Salmonella* may be greater in a specific subpopulation as a result of these variables. The relationship between climate variations and vulnerability to *Salmonella* infection
is therefore through the impacts on intermediary drivers, exacerbated by seasonality, extreme weather events, and maladaptation to a changing environment.

To answer RQ4 (What aspects of climate change and *Salmonella* necessitate further research?), this systematic review identified articles that provided information on aspects necessitating further research on the interplay of *Salmonella* and climate change. This included three inter-related domains: improved measuring and specificity of key elements under investigation for better quantification of relationships, expanding scope of research to include factors linked to sectors not immediately associated with the exposure and outcome, and improved capacity in research to ensure valid application in a variety of settings. Environmental changes on specific risk factors, such as infection sources and serotypes, were cited in the literature. Also included were expanding study into treatment implications, food safety and security, health hazards in terms of migration and vulnerability to disease, resource allocation, and improved monitoring and resolution of temperature variables associated with *Salmonella* as well as other key indicators and proxies for in-depth understanding of trends and health-related outcomes.

This systematic review, through the synthesis of disparate sources of information, hierarchical organization of key findings, and mitigation of methodological flaws, is a viable tool for the identification of problem areas and to answer the specific RQs which are strategically developed. A limitation of this systematic review methodology is that studies low on the hierarchy of evidence, or deemed to be of insufficient relevance to the RQs, may in reality be serving as a starting point for resource-limited locales, which may now be omitted from the focus of this critical analysis. Since climate is linked to location, and location is factored into our study with its focus on NYS, this review may be eliminating knowledge as a result of cost-effective
research or starting points for novel approaches, which can provide some valuable insight (and perhaps the only insight) into a location or domain when other types of research are not feasible or not yet published.

In this paper, the evidence of causal processes is presented with an equal weighting schema across the exposure, intermediary, and outcome levels. The full extent of the dimensionality of the relationships (e.g., short vs. long term associations) is beyond the scope of this study. Thus the limited assessment of dimensionality should be considered when interpreting the role of exposures that are contextualized with a timeframe, such as seasonality (predictable change or pattern of conditions which recur or repeat over a one-year period), weather (conditions in the short term or as an event), and climate (conditions in the long-term or sustained patterns). However, these results can serve to validate the selection of variables in a subsequent study, using more specific and appropriate methodology, to ascertain the strengths of association to better understand dimensionality of the relationships. A valid approach would be to explore strengths of association between exposures, specifically temperature and temperature-related indicators (such as cumulative effects of temperature) with consideration of lag between exposure and salmonellosis outcomes. Furthermore, a valid study design would address dimensionality of these relationships by focusing on target populations and timeframes for which there is available and appropriate data. Based on the causal process diagram, intermediary drivers may contribute to resource-lacking countries having different (and likely more severe) outcomes through inability to adapt, vulnerabilities, impoverishment, and lack of resources, as well as other barriers.
CONCLUSION

This systematic review bolsters understanding of the interplay of *Salmonella* and the changing environment, and how climate trends in NYS impact *Salmonella* outcomes. The study was conducted with consideration of the local environment of NYS and develops rationale for evidence-based public health solution for this location through synthesis of existing research. Further research on the topic within this specified locale is justifiable, to further focus understanding of the context-specific causes and effects pertaining to climate change and *Salmonella* for various public health applications. State-level climate trends are increasingly studied at finer resolution and such specifics can be applied to understand local climate history and forecast trends with increased accuracy, and account for intermediary influences. Local serotypes can be included in the equation; resiliency of individual serotypes (which may be more or less prevalent) to local climate change, especially when serotypes have varying antibiotic resistance and virulence, are potential barriers to efficacious intervention. The burden of disease may increase if climate change differentially affects other environmental exposures related to disease, as well as identified intermediaries, such as the survival of serotypes with greater resistance and/or virulence, as this study identified the importance of further study of serotyping trends in this regard.

These findings can be used to direct future research through development of a comprehensive and dynamic purview of *Salmonella* in light of climate change, based on existing evidence and contextualizing past research and incorporating epistemological considerations effectively strategize and operationalize, with enhanced rigor, subsequent research studies and public health intervention. Further research should take into account past trends in climate and epidemiological data, as well as present effects of climate change on the presence of *Salmonella.*
Existing data applied to evidence-based models can confirm and extrapolate disease patterns based on various climate change scenarios. A robust understanding of the effects of climate change on human health can lead to improved public health planning and preparedness, and enable adaptation in a changing environment.

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Chapter 3. Spatiotemporal Salmonellosis Risk and Ambient Air Temperature: A Case-Crossover Study

INTRODUCTION

Salmonellosis is the costliest foodborne illness for Americans (USDA 2016), affecting an estimated 1.2 million people each year in the U.S. and causing nearly 400 deaths annually. In 2013, the cost of the disease exceeded $3.6 billion, accounting for nearly a quarter of the total economic burden of foodborne disease to the U.S. ($15.5 billion). There has been an increased focus on understanding the role of the environment (which broadly includes climate, ecology, and their interactions with the host and agent) when formulating evidence-based interventions aimed at preventing salmonellosis. Comprehensive and effective approaches to combating the disease should encompass impacts of climate change, which is the sustained changes in weather patterns, including change in ambient air temperature. While climate change may affect the incidence of salmonellosis in a number of ways, these impacts are not well understood. Future changes to the epidemiologic profile of salmonellosis are difficult to predict because of the complex nature and multifaceted influences of host-agent-environment interactions and relationships which are highly sensitive to climate change. This is exemplified by Salmonella, the organism causing the disease, proliferating in warmer ambient air temperatures. Furthermore, human behaviors are contingent on environmental factors, and in turn, changing behaviors impact health (Bradley et al. 2005). Changes in the ecosystem may shift or expand the range of infectious agents and associated organisms, potentially exposing immunologically naive human or reservoir populations.
In the natural environment, *Salmonella* proliferates in its reservoirs, travels through the food chain, incubates within the human body, and presents as a sporadic case (not outbreak-related). Following an incubation period of approximately 12-72 hours, clinical signs and symptoms of *Salmonella* infection include fever, which is almost always present, as well as sudden onset of diarrhea and abdominal cramps; less frequent signs and symptoms include hematochezia (blood in stool), nausea, vomiting, and headache (Cummings et al. 2012; Krueger et al. 2014; Acheson 2001). Human behavior, food preparation and consumption methods, and pathogen, reservoir, and host ecology modulate transmission, even when accounting for predictable peak seasons of high risk. These predictable peaks have been well documented and associated with weather trends, with incidence peaking in the summer months, and fewer cases occurring during winter months; however, climatic factors were found to have variable effects on localized disease incidence and distribution, including for *Salmonella* (Kendrovski et al. 2011; Pangloli et al. 2008; Naumova et al. 2007; Cheng et al. 2013; Tirado et al. 2010; Varga et al. 2013; D’Souza et al. 2004; Kovats and Lloyd 2010).

Using NYS as a model, causal processes of *Salmonella* and the changing environment were systematically identified (Welch et al. 2018). Three inter-related considerations were identified: measurement and specification of key elements for accurate quantification of relationships, expansion of study scope to include factors linked to sectors not immediately associated with the exposure and outcome, and research capacity to ensure valid application in a variety of settings. Evidence-based models applying climate and epidemiological data confirm and extrapolate disease patterns based on various climate change scenarios. A robust understanding of the effects of climate change on human health can lead to improved public health planning and preparedness, and enable adaptation in a changing environment. To ensure
specifications in this study use valid exposure and outcome metrics, we incorporated the findings from the Welch et al. 2018 review, and followed causal pathways that were specific to NYS. The objective of this study was to quantify risk of *Salmonella* associated with climate change, using a case-crossover study design. We specifically evaluated case characteristics and ascertained the extent that case outcomes were more likely to occur as a result of time and location of higher ambient air temperatures.

**METHODS**

**Epidemiological Data Sources and Indicators**

This case-crossover study was conducted by the New York State Department of Health’s (NYSDOH) Office of Public Health Practice (OPHP). We used culture confirmed human salmonellosis cases provided by the NYSDOH Bureau of Communicable Disease Control (BCDC). Laboratories and patient care providers in NYS are required to report all salmonellosis cases to county health departments and to submit isolates to the NYSDOH laboratory for diagnostic confirmation and speciation; county health departments then securely transfer all case data to NYSDOH via the Communicable Disease Surveillance System (CDSS; Cummings et al. 2012). CDSS data was used by BCDC to identify eligible cases for NYS between January 1, 2002 and December 31, 2012. BCDC also houses the Emerging Infections Program (EIP), through which supplemental data was accessed. EIP is funded by the Centers for Disease Control and Prevention (CDC) to enhance surveillance through collaboration between the CDC, health departments, and academic centers in ten states; supplemental laboratory data for identified cases was sourced from the Foodborne Diseases Active Surveillance Network (FoodNet; a reliable,
active population-based surveillance and research platform for validated data on enteric diseases, including salmonellosis; CDC, 2016). BCDC enhanced the final dataset by combining CDSS and FoodNet patient and laboratory data, and provided the epidemiological data for our specified variables of interest, including residence location, age, gender, dates for symptom onset, culture collection, laboratory-confirmed diagnosis, serotype, and information related to outbreak and travel history. Demographic data was obtained from the US Census Bureau [American Community Survey (ACS 2012)], which was used for calculating incidence.

Temperature Data Sources and Indicators

Climate data on daily heat metrics was provided by the NYSDOH Center for Environmental Health (CEH). The dataset is comprised of NASA satellite data which consisted of historical meteorological data compiled from the North America Land Data Assimilation System (NLDAS). The North American Regional Reanalysis (NARR) is the source of non- precipitation land-surface fields, spatially interpolated into a 1/8th-degree grid composed of cells, each with an area of 12 km², and temporally disaggregated to an hourly frequency. This database was advantageous over ground-based weather station data used in previous studies (Hsu et al. 2016; Lin et al. 2012; Climate and Health Profile 2015), which were limited to using climate data from the National Center for Atmospheric Research from airport weather stations (fourteen relatively homogenous weather and ozone exposure regions, well-covered by weather stations, were then used as the typical spatial unit of analysis). With the NASA data, a greater number of data points allows for more localized associations with Salmonella cases. This study used the data to compute weekly mean ambient air temperatures in NYS between 2002 and 2012 for each cell.
Study Design

We used a time-stratified case-crossover design. Counts of cases per calendar week during the study period were used; for each day that a culture collection occurred, the exposure variable was the weekly mean ambient temperature for the calendar week that of that day of culture collection. For the control, we used the same day of the week one, two, three, four and eight weeks before and after the day of culture collection (and the exposure variable for each control was the weekly mean ambient temperature for the corresponding week). A time-stratified case-crossover study design is a statistical technique appropriate for examining short-term exposures with relatively acute outcomes (Basu et al. 2012).

The approach is a modification of the matched case-control study where each case serves as its own control, so that known and unknown time-invariant confounders are inherently adjusted for by study design. This enabled comparison of cases’ weekly mean ambient air temperature with the ten strategically selected control periods to control for the time trends (seasonality). Controls reflected the derivative case’s characteristics, with the exception that each control’s temporal data was adjusted along an ordered timeline (from the same day of the week as the derivative case: one, two, three, four, and eight weeks before and after the case’s week of culture collection date to assign ten defining bi-directional control windows); in tandem, control exposure (weekly mean ambient air temperature) assignment corresponded to the control’s adjusted week. The model used the following: for the survival factor, a continuous time variable was assigned to each subject (case time = 0 and control time = number of weeks between control window date and the case date). A censoring dichotomous variable was created (0=case,
control); censorship was on the value of 1. The explanatory variable was the assigned weekly mean ambient air temperature. Strata were assigned by case serial number; in each stratum, the case had the same serial number as the ten controls. The rationale for using the set of bi-directional control windows with the case-crossover design is because temperature is time and location specific, and *Salmonella* is likely associated with the local temperature. Because *Salmonella* occurrence has seasonal peaks, this enables us to control for confounding seasonality.

To implement our study design with robust methodology, we assessed data integrity for variables of interest during the study period to confirm study eligibility, and to identify and address inconsistencies between the disparate data sources. Since date variables and geographic information were integral to the study design, we prioritized validating these variables in the dataset by manually refining both the epidemiological and temperature data sources and indicators, as described below.

For the epidemiological data sources and indicators, we manually generated coordinates of case location and confirmed completeness of case dates (the FoodNet catchment area increased from 15 counties at the start of our study period to 34 counties at the end of the study period; at present, the NYS EIP catchment area includes metropolitan Albany, Buffalo, and Rochester, representing approximately 4.3 million residents; Cummings et al. 2012, CDC 2015). In collaboration with BCDC, study eligibility criteria were implemented. Records with residence outside of NYS were excluded, as well as those who reside in New York City (NYC) due to generalizability constraints (considerable urban heat island effects) and data limitations (different case reporting system from the rest of NYS). Aside from NYC, the other metropolitan areas of NYS are considerably smaller by area and population densities (lesser heating effects on fewer residents); for the purposes of our study, these were included to ensure power of our analysis and
the impact was considered negligible. Although NYC is geopolitically located within NYS, all subsequent references in this study to NYS imply exclusion of NYC.

In consideration of the spatial parameters of the exposure, we then reviewed selection outcomes and applied the following order of exclusion criteria for eligible records with indication of: missing residence, recent interstate or international travel, relation to an outbreak, or duplicate recording (i.e., two or more instances of the same individual and serotype within 180 days). To further validate, we reviewed date criterion in regard to the time-specific exposures and outcomes of interest in this study. In determining the most appropriate indicator for the date, the extent of missing temporal data for symptom onset, diagnosis, and culture collection was reviewed to validate case occurrence, accounting for indicator comparability and generalizability to other research and systematic variability between and among potential date indicators. Culture collection date was selected because it was used by most previous studies, it is a frequently recorded objective date compared to onset date, and it is recorded earlier than diagnosis date which is subject to laboratory variability. With the final exclusion of 1,287 records (10.1%) for missing culture date, the data set for the study consisted of 11,469 cases.

For temperature data sources and indicators, if data was missing, the gap was excluded and the denominator changed to maintain an accurate weekly mean temperature using only complete data. We excluded precipitation and humidity data; although NLDAS provides this additional climate data, previous studies found mixed results or no associations between precipitation and/or humidity with Salmonella (Meehl et al. 2005, Grjibovski & Kosbayeva 2012, Cheng et al. 2013; Jiang et al. 2015), and others found temperature and precipitation to be positively associated with Salmonella (Grjibovski & Kosbayeva 2012, Cheng et al. 2013; Jiang et al. 2015). A significant association between precipitation and temperature may indicate that
there is not an independent effect on *Salmonella* transmission (a warmer atmosphere is able to store more moisture, which can result in greater precipitation). Therefore, this study focused on temperature from the spatially interpolated and temporally disaggregated NARR dataset, which was suited for this study’s design. In regard to *Salmonella*, distinguishing between independent effects of precipitation and relative humidity were beyond the scope of this study, if any effect exists at all.

We linked the epidemiological and temperature data (by assigning the geocoded locations of cases and temperatures, occurring at the same time) to the corresponding grid cell using ArcGIS (version 10.3, 2014).

In accordance with NYSDOH Institutional Review Board approval requirement, this study addressed risks of using protected health information (PHI) by limiting access of CDSS and FoodNet data. Only records eligible for inclusion in this study were provided by BCDC, and were only accessible on secure NYSDOH servers.

**Statistical Analysis**

Descriptive analyses were performed to describe *Salmonella* cases and to generate annual counts of *Salmonella* cases and percentages of total study count. Univariate conditional logistic regressions were conducted using the PHREG procedure in SAS statistical software, using a continuous measure of weekly mean ambient air temperature as the predictor of interest, to obtain an effect estimate. Breslow's likelihood was used in modeling for handling of failure time; since this application uses case-control matching of one-to-multiple (1:k), the likelihood function for the conditional logistic regression is reduced to that of the Cox model for the continuous time scale.
The global null hypothesis was tested for all regression coefficients in the model equaling zero (β=0), which produced the likelihood ratio, score, and Wald test of individual explanatory variables to ascertain statistical significance for the maximum likelihood estimate of a subject being a case or a control with weekly mean ambient air temperature as the explanation. By exponentiating the parameter estimates (PE), which correspond to the degree Fahrenheit (°F) change, the hazard ratio (HR) was calculated for interpreting the statistically significant explanation of ambient air temperature. The probability of observing a chi-square statistic (Pr > χ²) as extreme as, or more so, than the observed one in the global null hypothesis, was compared using α = 0.05 to ascertain the hazard significance.

Based on biological plausibility, additional hypotheses were developed to account for temperature having an impact on risk of case occurrence prior to the culture collection date, considering latency and incubation and possible risk exacerbation as a result of cumulative temperature effects. Therefore, we tested a second hypothesis that factoring for lag between exposure and outcome may produce stronger associations. Based on our interpretation of the time differences between symptom onset and culture collection (mean 3.42 days, median 4 days), we determined a one-week lag period should be the specification. To test the impact of cumulative exposure effects contributing to increased risk, a third hypothesis was developed that factored the ambient air temperatures of the month preceding a case. We calculated a monthly temperature average as the ambient air temperature value for the preceding month’s control windows). Since the Cox model is not multiple linear regression (for which regression coefficients of independent predictor variables would be additive) and the hazard ratios are not the coefficients in the Cox model, to calculate the accumulated risk, coefficients of associations are multiplicative (since hazard ratios are obtained by exponentiating the Cox regression
coefficients). The results are scaled to represent a percent excess risk per 10°F change in temperature using the calculation: \((HR - 1) \times 100\%\). Statistical analyses were performed in SAS 9.4 (Cary, NC, USA).

RESULTS

Case Characteristics

A total of 11,469 cases occurred in NYS during the study years of 2002 through 2012. A profile of the 11,469 cases was tabulated; cases, as a percentage of the study sample, were contrasted with census-derived population frequencies (Appendix Table 3). By age group across all study years, the majority of cases occurred in the 18-64 years (adult) age group (50.35%), followed by the 5-17 years age group (21.2%), the < 5 years age group (15.07%), and the 65+ years age (elderly) group (13.08%); of the 11,469 cases, 0.30% were unable to be categorized into an age group. By sex across all study years, more cases were female (53.88%) and fewer were males (46.11%); of the 11,469 cases, one case (0.01%) was unable to be categorized by sex. Rate differences were apparent for age group and sex. Case frequencies were higher in the study sample compared to the population for those < 5 years old (15.07% vs. 5.65%), those 5-17 years old (21.20% vs. 17.05%) and females (53.88% vs. 50.94%, respectively). Case frequencies were lower in the study sample compared to the population for those 18-64 years (adult) age group (50.35% vs. 62.68%), those in the 65+ years (elderly) age group (13.08% vs. 14.62%), and males (46.11% vs. 49.06%).

By month, aggregate case counts ranged from a seasonal trough in February (4.80% of all cases) to a peak in August (13.51% of all cases); at the peak, *Salmonella* occurrence was 181%
greater than at the trough (Appendix Figure 4). The *Salmonella* case numbers, incidence, and proportion were also described by year of the study (Appendix Table 5). Using census data, we compared cases to the eligible population (n=11,198,904) for incidence calculations. The study year with the highest case count was 2002 (during which this year’s cases comprised 10.76% of all cases occurring between 2002 and 2012); this year also had the highest annual incidence (10.76 cases per 100,000 in 2002). The study year with the lowest case count was 2004 (during which this year’s cases comprised 8.20% of all cases occurring between 2002 and 2012; this year also had the lowest annual incidence (8.20 cases per 100,000 in 2004).

**Explanatory Ambient Air Temperature**

Using ambient air temperature to explain the likelihood of *Salmonella* case occurrence, case windows were compared to control windows for all three hypotheses. For modeling the independent and combined contributions, control windows were indexed using a case window as the week of the case culture date (Hypothesis 1; H₁), control windows were indexed using a case window as the week preceding the week of the case culture date (Hypothesis 2; H₂), and factored cumulative ambient air temperatures using a case window as the week of the culture date (Hypothesis 3; H₃). Since control windows are temporally spaced bi-directionally to and from the case window, there will always be at least two control windows (at least one prospective control window and at least one retrospective control window); therefore, contribution of the control windows’ effects are described in the corresponding number of Weeks. A hazard ratio of 1 would be indicative of the explanatory variable not contributing to differential likelihood of case versus control outcomes; the results presented below characterize hazard by the amount greater than 1 (i.e., a positive association), which is the excess risk.
We calculated the independent contribution by individual window of *Salmonella* risk from ambient air temperature (Appendix Table 6). When the case windows were compared to control windows, ambient air temperature was ubiquitously found to contribute excess risk of *Salmonella*, though not all positive associations were statistically significant. Excess risk increased with increased time between the bi-directional controls windows and the case window. For all three hypotheses, the independent contribution of the Weeks 1 timeframe was not statistically significant. For the Weeks 2 timeframe, the $\alpha$ of the two hypotheses which did not account for lag ($H_1$ and $H_3$) was greater than the $\alpha$ of the hypothesis which did account for lag ($H_2$), although the probability of observing a chi-square statistic ($Pr > \chi^2$) at least as extreme as the observed one in the global null hypothesis was sufficiently low indicating significant independent contribution.

We also calculated the combined effects of cumulative ambient air temperature contributing to *Salmonella* risk (Appendix Table 7). The combined effects, similar to the independent effects, demonstrated excess risk of *Salmonella* with increased cumulative ambient air temperature. The combined effects of cumulative ambient air temperature were greater than independent effects, when the control timeframes were the same, and excess risk trebled as the control timeframe doubled: cumulative temperature effects produced excess risk of 0.7 per 10°F within two weeks which increased to 2.1 per 10°F within four weeks.

**DISCUSSION**

The results of this study quantify risk of *Salmonella* as a result of climate change in NYS between 2002 and 2012, based on the distribution and characterization of the population. Cases were more frequently adults and more frequently female. Using meteorological definitions of
seasons, most cases in our study occurred in the summer (37.27% occurring June through August), followed by autumn (26.15% occurring September through November), the spring (20.80% occurring March through May), and winter (15.79% occurring December through February). In comparison to winter, the frequency of *Salmonella* cases was 136% greater during summer, though cases that did not occur during summer accounted for 62.73% of the total. For half of the year, from the end of spring through the middle of autumn, cases occurred nearly twice the rate in comparison to the other half of the year, from late autumn through the middle of the spring (i.e., 63.88% occurred May through October, in comparison to 34.12% occurred November through April); statewide, overall seasonal temperatures are typically colder in this latter half (Insaf et al. 2013). We found these general seasonal trends to be consistent with other studies (Kendrovski et al. 2011; Cheng et al. 2013; Bentham & Langford, 2001; Pangloli et al. 2008). Quantifying this seasonality, in terms of the volume of cases at given periods over the course of a year, can be used to focus targeted approaches; for example, a statewide health educational initiative on barbecue food preparation could initiate outreach efforts during the spring, preemptively scaling up to coincide with warmer weather (especially when warmer temperatures are sustained over relatively short-term periods, such as the preceding month), to offset the upward trend which peaks in August. Targeted approaches can be calibrated with greater specificity using measurements over extended periods of time with regard to local climate change; although the proportion of annual cases to the total differed by 2.56% from the highest year to the lower year, differences may be more pronounced by comparing annual frequencies by disaggregated season or month (not calculated for this study).

This is the first study to utilize a case-crossover approach to specifically assess the excess risk of increased temperatures during the week of and lagged weeks of sporadic *Salmonella*
cases. Thus the size of the excess risks from this study could not be directly compared to other studies published to date, but the findings provide insight nonetheless. Ambient air temperature was ubiquitously found to contribute excess risk of *Salmonella*, though there was no significant contribution within one week of the temperature exposure. Furthermore, we found that combined effects of cumulative ambient air temperatures were greater than independent effects when the control timeframes were the same, and excess risk trebled as the control timeframe doubled.

Generally, epidemiological trends were consistent with comparable studies. Because associations between occurrence of *Salmonella* and other climatic variables such as precipitation and humidity have been indeterminate in other studies (Meehl et al. 2005), other climatic variables were not a focus of this study. Both temperature and precipitation levels may be positively associated with *Salmonella* infections (Grijibovski and Kosbayeva 2012; Cheng et al. 2013; Jiang et al. 2015) and independent effects can be difficult to determine. A warmer atmosphere is able to store more moisture, which can result in greater precipitation, and this may be dependent on local climate trends, limiting generalizability to other localities. Therefore, we focused on ambient air temperature associations with *Salmonella* occurrence. Among populations in the United States, cases increased following exposure to increased ambient air temperatures (Naumova et al. 2008; Cheng et al. 2013; Jiang et al. 2015). Between 2002 and 2012 in a Maryland study, extreme heat events were associated with increased risk of *Salmonella* infection (Jiang et al. 2015). Following conditions of extreme temperature (defined in the study as exceeding the 95th percentile, as derived from the distribution of daily maximum temperatures over a 30-year period), a 4.1% increase in salmonellosis risk was reported following these extreme temperature conditions; this increase in risk was more pronounced in coastal areas (5.1%) compared to non-coastal areas (1.5%). In a Massachusetts study between 1992 and 2001,
significant findings included peaks of daily *Salmonella* case incidence closely following ambient air temperature peaks, with a 2-14 day lag period (Naumova et al. 2007). Additional studies in various localities also reflected similar associations, although generalizability may be limited or indeterminable (Kendrovski et al. 2011; Zhang et al. 2008; Grjibovski and Kosbayeva 2012; Kovats and Lloyd 2004; Van Pelt et al. 2004; Tirado et al. 2010; D’Souza et al. 2004; Britton et al. 2010). Research indicates increasing incidence and distribution of *Salmonella* infections (across all serotypes), with the effect of ambient air temperature on projected infections being relatively consistent across a wide geographic range (D’Souza et al. 2004; Zhang et al. 2010).

Additionally, several studies which characterized *Salmonella* risk through population-based laboratory surveillance noted some similarities in regard to the variability from spatiotemporal considerations and seasonality, including international and multinational cohort studies (Chen et al, 2016; Ternhag et al, 2006; Laupland et al, 2010). However, the cohort studies used different case criteria (including regional differences in mandatory reporting), were not based in the US, had a smaller populations in the catchment area, shorter study durations, or were a mix of these factors. Average annual incidence rates varied from our incidence calculation (e.g., Laupland et al. reported approximately nine times lower incidence than in our study, and also found increasing incidence over time and male gender as significant risk factors, in contrast to our study). Significant geographic differences in the cohort studies likely represent true differences that are specification dependent, and there is limited generalizability to our study. Where risk for *Salmonella* is influenced by age and gender, populations differing in demographic structure will then differ in crude incidence rates. Even when controlling for this, there are likely internally different rates of case ascertainment (identifying all culture-positive cases among residents) among the cohort. While in some cases ascertainment was expected to
approach or equal 100%, similar to NYS, this was not strictly the case. It is also likely that there are significant differences in the culturing practices among regions (e.g., more or less invasive or costly culture sampling depending on the frequency of already observing higher numbers of culture-positive cases). Lastly, the studies used different parameter estimates for the excess risk calculations, and none of these studies reported a useful comparable product of temperature change.

Case-crossover design is a novel, effective approach to mitigate misclassification bias with strategic selection of retrospective and prospective windows for controls, temporally ordered in relation to the case. The bi-directionality of measured effects controls for seasonality by design, which validate the associations which suggest risk of *Salmonella* occurrence increases upon proximal spatiotemporal exposure to higher ambient air temperature. This study tested three hypotheses, and factored the independent contribution of exposure timeframes, which enabled us to conceptualize excess risk over time, for given locations. Furthermore, for the cumulative model, we factored a combined risk contribution of cumulative ambient air temperatures for a comparison to the independent effects. Each hypothesis had invoked a parameter to assess validity of the calculated risks. The first additional hypothesis (H$_2$) factored lag into the exposure and outcome relationship, since our literature review identified the incubation period of *Salmonella* (12-72 hours) and our methodology accounted for the average time between the date of symptom onset and case culture (3.4-4.0 days); the second additional hypothesis (H$_3$) expanded on these concepts by factoring cumulative temperature effects over longer periods of time, as this may promote *Salmonella* to proliferate in the natural environment, which may increase the likelihood of transmission; this would translate to stronger associations
between this cumulative temperature factor and case occurrence, assuming more of the population encounters transmission pathways of *Salmonella*.

In our study, there were inherent challenges to validity that we addressed in our case-crossover methodology and statistical analysis. There is an indirect pathway between the temperature exposure and case occurrence, so the validity of the results are dependent on the extent of statistical noise that we successfully removed from the analysis, and controlled for confounding. Measurement in our study was subject to the dimensionality and interplay of contributing factors, completeness and availability of data, and misclassification.

As a preliminary approach, the methods for this study were strategically developed using evidence from the Welch et al. systemic review, as per established guidelines. In investigating *Salmonella* cases and temperatures, there is a confounding factor due to the seasonality of case occurrence and the higher seasonal temperatures. By including the bi-directional windows in the regression model, an extent of seasonality was accounted for, and the eight-week control windows separately modeled to report comparative effects. Our study suggested that risk contribution may also be occurring at timeframes outside of the four weeks prior to the case occurrence (based on the excess risk contribution at the Weeks 8 timeframe). This should be incorporated into further study by using additional and/or more robust methods to factor cumulative temperature effects, account for lag as a result of incubation and latent periods, and examining and comparing alternative control windows. Creation of an improved cumulative temperature variable should adapt methodology utilized in previous studies looking at relevant effects of climatic variables, specifically ambient air temperatures, and consideration should be given to models using alternate lag times, as well as incorporate the latest and finest resolution epidemiological and climate data. Subsequent analyses could add to the robustness of the
measurements by including an in-depth meta-analysis following conditional logistic regression to estimate effects and to use additional techniques for controlling for confounders.

For this study, culture collection date was used as the anchor date in the analysis instead of onset date or diagnosis date (with adjustments made to this date for the one-week lag effects). Although this study opted to use culture collection date to reduce misclassification (in exchange for a reduction in power of analyses due to exclusion of 10% of the cases with missing culture date), alternate dating methodology could be selected to compare and contrast findings with other studies using alternative dates which may encompass dimensions of exposures or outcomes that were not encompassed in this study. Estimates could be made by calculating the average time between either of these other date fields and culture date, and then applying the average to generate the estimate for the records with missing culture date. Any estimation could increase potential misclassification of the culture date, although this would be a more serious methodological problem if the misclassification was systematic (which cannot be determined with this dataset). Given that the analyses were critically related to time, it was deemed more important to reduce misclassification than increase study power. For that reason, the records with missing culture date were excluded.

The temperature data we used was collected from NASA satellites specifically for studying climate across a wide geographic area. The data we used is on a grid across the state, and each cell contains an area of 12 km². There is the possibility that temperature exposure would be incorrect for some of the cases in large zip codes, especially if the zip code includes multiple elevations. Thus, there would be some misclassification of exposure by using the zip code centroid. This study did not include in its analysis other climate indicators such as precipitation and humidity. In addition, the NASA dataset was not considered a good source of
precipitation and humidity indicator data, and other sources would have methodologic limitations. This analysis focused on the association with weekly mean ambient air temperature, and simultaneous consideration was noted for areas of further focused study on *Salmonella* and climate, e.g. through calculation of more complex temperature indicators to assess the effect of exposure and case occurrence, as well as cumulative temperature effects.

In our study, we were unable to rely on serotype data for all areas of NYS during the study period. Our data sources identified Enteritidis (18.85%) and Typhimirium (12.65%) to consistently be the most reported serotypes during the study period; however, there were limitations to incorporating serotype data from disparate data sources. The largest proportion of cases (36.73%) was classified as “other/unknown”. Although it was evident that some serotype data had been validated (i.e., in FoodNet counties), the timeframes and extents were unknown, and mixed methods of back-end grouping by antigenic relationships or other commonalities limited our ability to analyze by serotype. Complete validation of serotype data for this study’s spatiotemporal parameters, or specific study methods aligned with validated data sources, could be used to study differential serotype associations with ambient air temperatures; since some serotypes manifest differently, there could be serotype-related clinical implications. Future studies with complete serotype data should assess differential serotype incidence associated with local climate change, in regard to the change in incidence and distribution of all *Salmonella* serotypes found to be relatively consistent across a wide geographic range (D’Souza et al. 2004; Zhang et al. 2010).
CONCLUSION

The analyses used in this study were selected to inform preliminary approaches to understanding spatiotemporal salmonellosis risk and ambient air temperatures to guide subsequent research and to target opportunities for intervention in NYS, which defined specifications for (and limited extents of) this focused study. The results describe the strength of the relationship through statistical testing to generate insight into the genesis, development, and spread of *Salmonella* in the context of climate change. The study epidemiologically profiles *Salmonella* cases occurring in NYS between 2002 and 2012, which could be used for targeting interventions and focusing scope of further study. Findings suggest that risk of *Salmonella* occurrence is significantly associated with localized ambient air temperatures, and that an increase in temperatures could result in additional risks for exposed populations. This can be expected to be more pronounced among populations vulnerable to *Salmonella*, as well as on a greater scale as a result of climate change, which is likely occurring in NYS. This information supports confirmation of causal processes and contributes to the understanding of complex causal relationships, guides future research on forecasting the dynamics of disease, and can be used to develop evidence-based policy and recommendations.

CHAPTER 3 REFERENCES


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Chapter 4. Using the Scope, Measure, Analyze, and Calibrate Framework for Communicable Disease Response to Climate Change

INTRODUCTION

Climate change threatens human health through multi-level environmental effects via a myriad of exposure pathways and outcomes, and there is interplay between (and among) these multi-level effects (Butler et al. 2010; Welch et al. 2018). Human morbidity and mortality can be impacted as a result of changing transmission pathways and vulnerabilities. Ecology and biology of pathogens, vectors, and hosts (or any intermediary organisms) can result in changing distributions of communicable diseases. Changes to human health are difficult to predict because of the complex, multifaceted, and dynamic influences of host-agent-environment interactions and relationships (Bradley et al., 2005; National Academy of Sciences 2015). Changes in the ecosystem may shift or expand the range of infectious agents and associated organisms, potentially exposing human or reservoir populations. Climate change may cause environmental contaminants and pollution to proliferate and persist, overwhelm immune systems of vulnerable groups, and lead to increased disease occurrence (Kendrovski et al. 2011; Tirado et al, 2010; Jiang et al. 2015). Climate change combines geographic and temporal elements, and therefore related issues are challenging to combat due to limited information or theoretical models predicting wide ranges of outcomes. As local climatic conditions affect the biology of an organism, predicted communicable disease patterns from mapped seasonal fluctuations and expected variances increasingly become less reliable.
A robust understanding of the effects of climate change on human health can lead to improved public health planning and preparedness. Research methodologies must take into account past trends of climate and epidemiology, as well as present effects of climate change on the incidence of the disease, using existing data and theory to confirm and extrapolate disease patterns based on various climate change scenarios (National Academy of Sciences 2015). Applicable to such scenarios, critical needs among the scientific and public health communities include location-specific policy, systems, and strategies, approaches, and intervention, with a balance of cost and benefit (Webber et al. 2016). Given the multi-level environmental effects and the sensitivity of the epidemiological triad to climate change, there has been an increased interest in the development of data collection, analysis, and reporting mechanisms for efficient and cost-effective exploratory study. Such mechanisms require the increased granularity of data at finer temporal and spatial resolutions. Demand for accurate data on smaller geographical areas with frequent measurement has increased; without this, significant disparities across smaller areas may be less evident, and ecological fallacies may result in insufficient action. Public health agencies need ways to provide localized data that is accessible, inexpensive, feasible to update, and sufficiently generalizable with consideration to time and space.

As the technologies and methodologies improve, there is an increased reliance on geographic-specific indicator projects that disaggregate data at increasingly smaller levels (Webber et al. 2016). Datasets from disparate sources, which are often readily available electronically, enable customized indicators for a given problem. Reporting with graphing, sorting, and mapping of these indicators can provide a way to identify disparate areas where an interplay of social, environmental, and/or health conditions drive outcomes, and can be incorporated into strategies for evidence- and community-based intervention, resource allocation,
and delivery and expansion of health services. This data can be used for benchmarking, establishing goals, and evaluating progress, and can be customized to better understand spatiotemporal trends. In addition to identifying new areas for intervention, projects which customize specific indicators can inform strategies of agencies and organizations already working in specific areas and promote collaboration across domains and industries.

In collaboration with the New York State (NYS) Department of Health (DOH) Office of Public Health Practice (OPHP), our activities and deliverables formed a framework which could be universally applied as a roadmap for communicable disease control and climate change. The Scope, Measure, Analyze, and Calibrate (SMAC) Framework we formed has four steps, each with set purposes and activities. Aspects of our approach were aligned with the Six Sigma improvement model, Define, Measure, Analyze, Improve, and Control (DMAIC), which sequentially maps steps to bolster understanding and improvement, and has established applicability to biomedical and research settings (Schweikhart & Dembe 2009). Although the DMAIC framework is frequently used in comparable research settings, it did not perfectly address aspects of the public health problem we were focusing on; therefore, we proposed the entirely new SMAC Framework. We successfully tested the SMAC Framework on our study of climate change and Salmonella in NYS, and found the SMAC Framework better encompassed the needed processes and procedures than the DMAIC Framework.

We initially formed our refined approach on the basis that there were interactions between climate change and communicable disease outcomes within NYS, with implications for disease control and prevention. For the initial step, the approach was applied to one communicable disease, Salmonella, with substantial and recent analysis related to climate change (Welch et al. 2018; 2019). Potential outcome(s) and focus areas were informed by relevant
literature to further refine where problem areas or opportunities for improvement may exist, and ascertain plausible influence on communicable disease. Our formative processes resulted in a specialized purpose, which was to produce a valid and reliable means for monitoring, evaluating, and reporting change in terms of specific disease outcomes affected by climatic change. Finding the framework to be effective and the deliverables to be valuable, our intent was to make our methods and findings accessible to all.

METHODS

Over a formative period of 14 months, between July 2015 and August 2016, we developed our methods through reviewing literature on operational approaches to addressing the background issues, and studying the contributions to change driven by climatic exposures on communicable disease outcomes in a manner that would inform subsequent pathways and topical areas to explore. In the production of our key deliverables, we formalized the framework into four integral steps: scope, measure, analyze, and calibrate. Additionally, we documented the approach as a viewer-friendly infographic roadmap, which was designed specifically to enable a public health professional, as a potential user of the framework, to quickly ascertain compatibility for the desired context (refer to Appendix Figure 5).

STEP 1: SCOPE

Preliminary literature reviews should be the starting point to systematically identify, appraise, select, and synthesize all high quality, relevant evidence and arguments to focus the scope. The key element differentiating the systematic review from the preliminary literature
The systematic review findings should then set the parameters for developing measurement specifications to quantify relationships between and among environmental exposures and health outcomes. The relationship between the defined outcome (dependent variable) and exposures (independent variables) should be statistically estimated through
measurement. Measuring this relationship can be done by quantifying the change in the value of the dependent variable when any one of the independent variables is changed while holding the other independent variables constant. Studies can integrate environmental monitoring data into the analysis of health outcomes. As appropriate to the specific context, enhanced measurement should encompass both spatial and temporal dimensionality to understand patterns in disease distribution and frequency in consideration to the climate change exposure parameters (Welch et al. 2018). Methods for measuring environmental associations with food- and water-borne disease are well established. Disease outcome variables include laboratory-confirmed case reports with associated demographic information such as age, gender, location, and time of disease onset, weekly counts of disease-related hospital visits, laboratory testing of environmental samples from sites with high human and/or livestock population densities, inferences from weekly government health bulletins, aggregate outbreak reports and household surveys. Climate is often used as the exposure variable in exploring disease outcomes as they relate to changes in the environment. Common climatic variables used in past studies include ambient air temperature, precipitation, and relative humidity. Additional climate data include wind speed, daily hours of sunshine, atmospheric pressure, sea surface temperature, and solar radiation levels. Mandatory notifiable disease reporting provides a relatively complete database enabling access to demographic and disease-specific information for laboratory-confirmed cases. Many studies have extracted geographic information from governmental health authority surveillance systems for mapping purposes. The optimal spatial-level location indicator, or a combination of indicators, are selected based on the objectives of the study and are then geo-matched to corresponding latitude and longitude coordinates, and overlaid with information from census data (Weisent et al. 2011).
Census data can be used for population size determination at given spatial levels, corresponding incidence rates, and linear interpolation of counts between census years. Census data can also be used for determining homogeneous geographic entities and their boundaries.

STEP 3: ANALYZE

Hypotheses should be strategically developed, which integrate both the scope and measurement capacity and use statistical testing. This can validate the defining relationships for a robust understanding of the results. The results of the analysis should be interpreted and discussed with the appropriate context and limitations. Statistical models can be developed to assess the association between the environment and disease through correlation and regression analyses (Elliott & Wartenberg 2004). Exposure metrics can be developed related to selected independent variables of concern and then linked to disease outcome at a selected spatial-level and/or assessed over time. Differences in case frequencies between areas and periods can be ascertained with confidence. Associations can be ascertained through correlation and regressions tests. Seasonality can potentially obscure short-term associations between climate and disease, though this can be controlled for. Models can be adjusted for multiple-lag effects of various variables for evaluating the associations between categorized climate indicators and disease, with further trend tests to examine linear associations.

A time-stratified case-crossover approach is one of the most common analytical methods used to assess the relationship between climatic variables and food- and water-borne diseases (Maclure 1991, Hughes et al. 2013; Welch et al. 2019 When evaluating transient exposures such as ambient air temperature, a case can be self-matched as its own control by looking at the time spent without disease (control window) before and/or after the time spent as a case (case
window). Exposure can be compared between the control window and the case window using regression. Information bias can be mitigated by careful selection of the case/control window period length and timing; through self-matching and administrative data (e.g. case reports, as no control groups are reported through a surveillance system) it is efficient, and seasonal and geographic differences can be inherently controlled for (and adjustments to address unknown spatially or temporally dependent covariates). Mapping approaches can be used to summarize and display information about spatial epidemiology to identify geographic variations in disease distribution in the context of demographic, environmental, behavioral, socioeconomic, genetic, and infection risk factors (Rajabi 2015; Elliott & Wartenberg 2004). Disease mapping produces a visual representation of measurements in analysis, using intricate geographic data. In-depth analytics include geographic correlations, clustering, and surveillance.

**STEP 4: CALIBRATE**

Using the components in the scope, measurement, and analysis, context-specific patterns identified in time and space can be used to adjust the public health response. With new information and greater accuracy, the SMAC Framework can be repeated with a narrower focus. Integrated information can inform policy and guide decision-making. Using health disparities models, further assessment in terms of a model’s criterion results in patterns of vulnerability identified and opportunities for improvement and control (Cutter et al. 2003; Harsig 2013; Webber et al. 2016). One such model is the Social Vulnerability Index, in which factors are additively summarized and can be mapped based on standard deviations from the population mean. Calibration should integrate demographic factors for further investigation and incorporation of specific subpopulations. For calibration purposes, health policy decisions should
be made in the context of unique combinations of factors influencing population and sub-group vulnerability. Identifying vulnerabilities can be adapted to encompass indicators relevant to the research topic. Identifying vulnerable populations can direct research and policy through tailoring recommendations, targeting monitoring and evaluation efforts, and planning activities and resource allocation for intervention. Statistical methods approaches can be used to determine socio-spatial indicators attributed to disease from the analysis. Disease maps are a useful tool to survey high-risk areas to inform policy and direct resource allocation within mapped areas (Rajabi 2015; Elliott & Wartenberg 2004). Methods for mapping and analysis of spatial and temporal distribution of disease are well established for communicable disease epidemiology.

IMPLEMENTATION

We implemented the SMAC framework for the communicable disease response to climate change in NYS, which focused the response on Salmonella outcomes as a result of temperature change. For producing key deliverables for the response, our activities for scoping, measuring, analyzing, and calibrating validated the approach at every step of the SMAC Framework implementation, with the context and descriptions of these activities included for each step (refer to Appendix Table 8).

DISCUSSION

There is a need to understand the interplay, and by extension the processes, of localized climate change and communicable disease with validated, generalizable results in order to formulate a comprehensive plan of action in response to climate change (Welch et al. 2018;
2019). Our intent was to produce peer-reviewed published research for greater knowledge sharing with public health departments, partner agencies, interested domestic and international organizations, and to inform data use and public health projects, provide support for responses in the form of further research and interventions, and shape and monitor projects, programs, and policies. The findings are in the process of being disseminated via NYSDOH as a resource and a guide for bureaus within the NYSDOH to ascertain and evaluate determinants of health that are subject to climate change and ancillary environmental impacts. The output of our implementation, as well as the refined dataset we used, was also provided to BCDC for streamlining further SMAC implementation.

Using the SMAC framework, we were able to focus our study based on strong evidence (e.g. through use of hierarchy of evidence in our systematic literature review), enabling us to formulate validated methodology to strategically mitigate bias, and subsequently to quantify risk of Salmonella associated with of climate change in NYS between 2002 and 2012 (Welch et al. 2018; 2019). Our case-crossover approach was the first to specifically assess the excess risk of increased temperatures during the week of and lagged weeks of sporadic Salmonella cases in this setting. Although our findings had general alignment with other studies looking at similar temperature exposures and Salmonella outcomes, we are confident that our methods were more robust and the results more specific and appropriate to our setting. Due to the different methodology, the size of the excess risks from our study could not be directly compared to other studies published to date, but the findings provide more useful insight for public health response in this specific setting.

Our SMAC framework validates outputs at each step, to allay concerns of bias as a result of indirect linkages inherent to the exposure and outcome. Our measurements were subject to the
dimensionality and interplay of contributing factors, completeness and availability of data, and misclassification, which we strategically worked around through calibrating processes at each step. For limitations we identified, we were then able to address using our framework by supporting improvement processes and developing recommendations for subsequent analyses using the SMAC framework with an even more narrow scope. This included the recommendation for improving the quality of serotype data to support study of differential serotype associations with ambient air temperatures. Some serotypes manifest differently and there could be serotype-related clinical implications (D’Souza et al. 2004; Zhang et al. 2010). Furthermore, in-depth lagged effects, based on the hypotheses we tested with our case-crossover design, would be of interest for subsequent study.

Technical and analytical resources were found to be an integral to this implementation. The overall duration and resource-intensiveness of activities is important to gauge, in consideration of the age of data used in the quantitative components as well as how the implementation timeframe can impact human resources (in our case, the key scientific and professional contributors). We quantified and strategically allocated our limited resources to ensure timely implementation and the production of meaningful results. Interim assessments demonstrated the extent of resources put into the high-caliber work involved in the analytical and technical processes. We recommend an approach which standardizes the robustness of these processes, and which functions to make adjustments to SMAC, between and among steps, to strengthen linkages with the formative strategy. To mitigate interruption of implementation as a result of resource reduction, we calibrated processes during implementation by conducting a cost-benefit analysis to ensure appropriate scale of the methodology for an actionable public health response. We recommend maintaining a level of analytic depth, which can at minimum be
used as a validation step to demonstrate efficacy and value of the framework, and to be used as the evidence basis for continued research or public health practice. For example, aligned with the roadmap, information pertaining to the SMAC framework implementation can be quickly disseminated applying specific steps for the health risk under study to an infographic model (Appendix Figure 5).

Additionally, implementation of this framework enabled improved responsiveness to trends and potential confounding, which may not be immediately notable or are paradoxical. For example, a need for rapid detection of suspected cases may result in increased use of novel clinical testing methods, which may impact study outcomes in terms of case occurrences, if this testing method (itself in response to increasing case occurrence) changes reporting avenues within the study timeframe. Another example is in regard to vulnerable populations: those who are most vulnerable may be less likely to pursue clinical intervention (and be detected via the confirmed case reporting avenue); vulnerable groups may be impoverished and seeking treatment may be cost prohibitive, and this would also limit detection and introduce bias. Hence, there is the need to foster discussion and data sharing both within and between health agencies. Within agencies, continuation of focused study is needed to ensure effective response; therefore, an appropriate mechanism for providing findings and refined data for further study must be in place. For the Salmonella study, the data ownership has been transferred back to BCDC, where the data originated; enhanced data, as a result of implementation, facilitates quick follow-up study based on recommendations also produced. Between agencies would facilitate multi-level interventions and targeted approaches; e.g., if the NYSDOH informed county health departments of localized excess risk findings and specific recommendations.
Integral methods identifying patterns in distribution and frequency while differentiating between systemic and random fluctuations involve matching spatiotemporal data to the exposure and outcome; subsequent study could forecast outcomes to provide early warnings. Aggregate disease data, as our framework had used with *Salmonella*, can be done cost-effectively through use of administrative data to enable the SMAC framework to be cyclically applied, using continuously calibrated outputs for highly specific and purposeful allocation of resources and context-specific best practices.

**CONCLUSION**

Our implementation of the SMAC framework presents feasible solutions for improved resource allocation and greater utility of public health research and practice to mitigate adverse communicable disease outcomes related to climate change. Researchers should be particularly inclined to implement a cost-effective framework, enabling resources to be allocated to priority areas. This framework encourages calibrated implementation in real time, to strategically incorporate resource limitations as a barrier to resolving the overarching public health problem, and this feedback loop optimizes outputs for enhanced public health response. This is an adaptation for realistic implementation of the framework in this context; an inherent instability is introduced when inputs are multi-disciplinary in nature, and barriers are unpredictability and may be attributed changing politics. Evidence-based models applying climate and epidemiological data confirm and extrapolate disease patterns based on various climate change scenarios. A robust understanding of the effects of climate change on human health can lead to improved public health planning and preparedness, and enable adaptation in a changing environment.
CHAPTER 4 REFERENCES


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Appendix

Table 1. Study site location in articles relevant to factors contributing to *Salmonella* vulnerability in humans

<table>
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Table 2. Study site location in articles relevant to aspects of climate change and *Salmonella* necessitating further research

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Table 3. Abstract details of article-level information identified by the systematic review

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<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>LOE</th>
<th>Location</th>
<th>Significance and conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams, M. &amp; Pandis, S. (2013)</td>
<td>Biodiversity changes vulnerable to climate change in the Catskill High Peaks Subregion (Ulster, Delaware, Sullivan, and Greene Counties, New York State)</td>
<td>V</td>
<td>USA</td>
<td>The proposed monitoring protocols vary among the various sites but all are quantitative and are designed to document patterns of change.</td>
</tr>
<tr>
<td>Alena, J., Mather, A. &amp; Sacho, W. (2014)</td>
<td>Antimicrobial resistance profiles and diversity in salmonella from humans and cattle, 2004–2011.</td>
<td>III</td>
<td>USA</td>
<td>Greater profile complexity and depth in human Salmonella may be due to greater diversity of sources entering the human population compared to cattle or due to continuous evolution in the human environment. Genetic diversity was greater in clinical compared to non-clinical cattle Salmonella and this could be due to antimicrobial selection pressure in diseased cattle that received treatment. Expected and observed number of profiles indicate of Salmonella and associated resistance from humans and cattle may not be wholly derived from a common population.</td>
</tr>
<tr>
<td>Akil, L., Ahmad, M. &amp; Reddy, R. (2016)</td>
<td>Effects of climate change on Salmonella infections.</td>
<td>IV</td>
<td>USA</td>
<td>Gastrointestinal infection with bacterial pathogens is positively correlated with ambient temperature, as warmer temperatures enable more rapid replication. Warming trends in the United States and specifically in the southern states may increase rates of Salmonella infections.</td>
</tr>
<tr>
<td>Andino, A. &amp; Henning, I. (2015)</td>
<td>Salmonella enterica survival, colonization, and virulence differences among serovars.</td>
<td>V</td>
<td>USA</td>
<td>Survival in poultry feed may be an independent factor unrelated to virulence of specific serovars of Salmonella. Additionally, Enterobacteriaceae appear to have different host specificity and the ability to cause disease in these hosts is also serovar dependent. These differences among the serovars may be related to gene presence or absence and expression levels of these genes. With a better understanding of serovar specificity, mitigation methods can be implemented to control Salmonella at preharvest and postharvest levels.</td>
</tr>
<tr>
<td>Andrews, J. &amp; Ryan, E. (2015)</td>
<td>Diagnostics for invasive Salmonella infections: Current challenges and future directions</td>
<td>I</td>
<td>Global</td>
<td>Approaches that align incentives with societal goals of limiting inappropriate antimicrobial use, such as substituting diagnostics, may be essential for stimulating development and use of such assays in resource-limited settings. New diagnostics for invasive Salmonella should be developed and deployed alongside diagnostics for alternative etiologies of acute febrile illnesses to improve targeted use of antibiotics.</td>
</tr>
<tr>
<td>Armaneau, K. (2014)</td>
<td>Acidification and climate warming: Understanding the impact of multiple anthropogenic stressors on Adirondack (NY, USA) lakes</td>
<td>IV</td>
<td>USA</td>
<td>Long-term species changes in acidified reference lakes suggest that the recovering lakes will not return to their pre-disturbance state but will instead move to states characterized by an increased abundance of colonial taxa at warmer-water species. Overall, this thesis demonstrates the utility of pairing paleontological techniques with a regional reference site dataset for tracking shifting baselines and defining recovery targets; a method that could be applied to examine other stressors in other regions, thereby addressing a critical management need.</td>
</tr>
<tr>
<td>Banett, J., Rose, J., Deonarine, S., Cameron, A., Prakash, J. &amp; Parker, M. (2011)</td>
<td>Sentinel monitoring for climate change in the Long Island Sound estuarine and coastal ecosystems of New York and Connecticut</td>
<td>VI</td>
<td>USA</td>
<td>Identified priorities for monitoring beyond a pilot monitoring program and future research priorities and data; sentinel monitoring is a dynamic process and sentinel and their priority status may change as new and additional research efforts are undertaken. Recommended next steps are developed based on these findings.</td>
</tr>
<tr>
<td>Bassal, R., Resfield, A., Nesan, I., Agmon, V., Taran, D. &amp; Schubert, B. (2014)</td>
<td>Risk factors for sporadic infection with Salmonella in a matched case-control study</td>
<td>IV</td>
<td>Israel</td>
<td>Consumers should avoid eating undercooked eggs and food handlers should be educated regarding proper handling and cooking of eggs. Meat consumption should be strongly encouraged by public health authorities. The public must be educated on stringent hygiene practices, especially proper cooking of eggs to reduce infection rates.</td>
</tr>
<tr>
<td>Bassal, R., Resfield, A., Andorn, N. &amp; Yanai, R. (2011)</td>
<td>Recent trends in the epidemiology of non-typhoidal Salmonella in Israel, 1996–2009</td>
<td>V</td>
<td>Israel</td>
<td>Tight surveillance and education of food handlers and consumers should be enhanced to reduce the foodborne transmission of Salmonella in Israel.</td>
</tr>
<tr>
<td>Author(s) (Year)</td>
<td>Title</td>
<td>Location</td>
<td>P2</td>
<td>Synthesis and conclusions</td>
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<tr>
<td>Belasco-Bischof, J., González-Cane, J., Ollero-Arandia, J., Marce, C., Trigo-Ruiz, M., &amp; Arnedo-Pena, A. (2007)</td>
<td>Risk factors for the occurrence of Campylobacter, Salmonella and rotavirus diarrhea in preschool children</td>
<td>IV Spain</td>
<td>3</td>
<td>The problems posed by epidemiological study of this issue are discussed. The main findings in each group of cases are interpreted and proposals are made for their application in the control and prevention of these diseases.</td>
</tr>
<tr>
<td>Britton, C., Hales, B., Venugopal, K., &amp; Baker, M. (2010)</td>
<td>Positive association between ambient temperature and salmonellosis notifications in New Zealand, 1985-2005.</td>
<td>IV New Zealand</td>
<td>3</td>
<td>Identified association between temperature and salmonellosis which should be considered when developing public health plans and climate change adaptation policies. Strategies, existing food safety programs to prevent salmonellosis could be intensified during warmer periods. As the association was strongest within the same month, focusing on improving food handling and storage during this time period may assist in climate change adaptation in New Zealand.</td>
</tr>
<tr>
<td>Burns, D., Klaus, J., &amp; Mohal, M. (2007)</td>
<td>Recent climate trends and implications for water resources in the Catskill Mountain region, New York, USA</td>
<td>V USA</td>
<td>1</td>
<td>The future balance between change in air temperature and changes in the timing and amount of precipitation in the region will have important implications for the available water supply in the region.</td>
</tr>
<tr>
<td>Chen, C., Wu, F., &amp; Hwang, C. (2010)</td>
<td>Risk factors for Salmonella gastroenteritis in children less than five years of age in Taiwan</td>
<td>IV China (Taiwan)</td>
<td>3</td>
<td>The principal transmission routes of Salmonella infection in Taiwanese children are person-to-person, waterborne, and environmental contacts. The possibility of powdered milk and groundwater contamination of Salmonella cannot be excluded and requires further investigation.</td>
</tr>
<tr>
<td>Chen, Y., Glass, K., Liu, B., Ho, K., &amp; Kirk, M. (2012)</td>
<td>Salmonella infection in middle-aged and older adults: incidence and risk factors from the AG and up study</td>
<td>III Australia</td>
<td>3</td>
<td>Chicken consumption remains a significant risk factor for Salmonella infection, highlighting the importance of reducing contamination of poultry and improving food safety advice for older people.</td>
</tr>
<tr>
<td>Chen, Y., Glass, K., Liu, B., &amp; Kirk, M. (2016)</td>
<td>Salmonella infection in older adults: a prospective study of incidence and risk factors</td>
<td>III Australia</td>
<td>3</td>
<td>Elderly males had the highest risk of infection-related hospitalization. Chicken consumption remains a significant risk factor for Salmonella infection, highlighting the importance of reducing contamination of poultry and improving food safety advice for older people.</td>
</tr>
<tr>
<td>Chengsheng, J., Shi, C., Upperman, C.R., Blythe, D., Mitchell, C., &amp; Mortugudde, R. (2015)</td>
<td>Climate change, extreme events and increased risk of salmonellosis in Maryland, USA: Evidence for coastal vulnerability</td>
<td>IV USA</td>
<td>3</td>
<td>Adaptation strategies need to account for this differential burden, particularly in light of ever increasing coastal populations.</td>
</tr>
<tr>
<td>Chui, K., Weisb, P., Russell, R., &amp; Naumova, E. (2009)</td>
<td>Geographic variations and temporal trends of Salmonella-associated hospitalization in the US elderly, 1992-2004: A time series analysis of the impact of HACCP regulation</td>
<td>IV USA</td>
<td>4</td>
<td>The impact of HACCP was geographically different. South Atlantic, East South Central, and West South Central divisions should be targeted in further Salmonella preventive programs. Further research is needed to identify the best program type and timing of implementation.</td>
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<tr>
<td>Cookburn, J., &amp; Gavers, J. (2015)</td>
<td>Abrupt change in runoff on the north slope of the Catskill Mountains, NY, USA: Above average discharge in the last two decades</td>
<td>V USA</td>
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<td>Changes to peak daily flow imply more flow in the lower Schoharie more frequently. Seasonal differences drive above average winter runoff, followed by peak runoff in spring and in several cases below average summer and late summer flow. This flow pattern is not just a matter of more water at the time, but more water during the high-flow period and less water during the low-flow period, intensifying annual extremes.</td>
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<td>Conner, J., White, E., &amp; Schiebling, N. (2015)</td>
<td>Adult activity and temperature preference drives regional distributional change: A warming climate</td>
<td>IV USA</td>
<td>1</td>
<td>Intrinsic traits shape a species' response to changing climates and the mechanisms behind such range shifts are fitness-based meta-population processes that adjust phenology to the prevailing habitat and climate regime through a photoperiod filter.</td>
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<td>Author(s)</td>
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<td>Donia, A., Lucarelli, C., Bendetti, I.</td>
<td>2011</td>
<td>Molecular characterisation of multidrug-resistant Salmonella enterica serotype infantis from humans, animals and the environment in Italy</td>
<td>II</td>
<td>Italy</td>
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<td>Dorduy, Y., van Pelt, W., Steen, C., Van Der Horst, F., Van Duyssen, Y., Hoebe, B., &amp; Janssens, R.</td>
<td>2008</td>
<td>Novel insight in the association between salmonellosis or campylobacteriosis and chronic illness, and the role of host genetics in susceptibility to these diseases</td>
<td>V</td>
<td>Netherlands</td>
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<td>Eshel, O.</td>
<td>2015</td>
<td>Recent Southern New York climate change observations, mechanisms, and spatial context</td>
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<td>Feldler, J., Campbell, D., Grass, J., Brown, A., Dickerson, A. &amp; Taler, B.</td>
<td>2015</td>
<td>Identification and characterization of multidrug-resistant Salmonella enterica serotype Alerte isolates in the United States</td>
<td>V</td>
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<td>Frei, A. &amp; Gruber, S.</td>
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<td>Potential impacts of climate change on sustainable water use in the Hudson River Valley</td>
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<td>Graziani, C., Basarin, L., Donia, A.M., Capproli, A., Mazzoni, P., &amp; Hedenström, I.</td>
<td>2011</td>
<td>Virutyping of Salmonella enterica serovar Napoli strains isolated in Italy from human and nonhuman sources</td>
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<td>Guerriero, G., Reed, R., Ammann, C., Barabuci, J., Erik, K., &amp; Benejam, V.</td>
<td>2016</td>
<td>Evaluating the appropriateness of downscaled climate information for projecting risks of Salmonella.</td>
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<td>Hartnett, J., Collins, J., Rudd, M. &amp; Chambers, D.</td>
<td>2014</td>
<td>Spatiotemporal snowfall trends in Central New York</td>
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<td>Hallberg, R. &amp; Chu, J.</td>
<td>2016</td>
<td>Effects of climate change on the persistence and dispersal of foodborne pathogens in modelled ways, especially for environmentally ubiquitous and/or zoonotic microorganisms.</td>
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<td>Hendriksen, R., Bangsund, A., Fulsom, C., Porruangwong, S., Nappornphong, G.</td>
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<td>Risk factors and epidemiology of the most common Salmonella serovars from febrile patients in Thailand: 2002-2007</td>
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<td>serovars in patients from Thailand</td>
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<td>Modeling climate change impacts on the thermal dynamics of polymictic</td>
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<td>Climate trends in indices for temperature and precipitation across</td>
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<td>New York State, 1948-2009</td>
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<td>Jokinen, C.</td>
<td>The distribution of Salmonella antarctica serovars and subtypes in</td>
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<td>surface water from five agricultural regions across Canada</td>
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<td>Jones, L.</td>
<td>Plant-pathogenic corynebacteria, <em>Escherichia coli</em>, and Salmonella</td>
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<td>spp. Frequently found in surface water used for irrigation of fruit and</td>
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<td>vegetable crops in New York State</td>
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<td>affecting New York State</td>
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<td>Kjeilesstrom T.</td>
<td>Climate change and health: impacts, vulnerability, adaptation and</td>
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<td>Modern trends to investigate Salmonella in Foods</td>
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<td>A. &amp; Singh S.</td>
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<td>Lai A., Baker M.</td>
<td>The epidemiology of human salmonellosis in New Zealand, 1997–2003.</td>
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<td>French N., Dufour M. &amp; Hayes S.</td>
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<td>Laid N., Sobash R.</td>
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<td>associated with the New York State Finger Lakes</td>
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<td>Laid N., Desbois</td>
<td>Climatology of lake-effect precipitation events over Lake</td>
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<td>J. Desbois</td>
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</table>
Author (Year) | Title | Location | Significance and Discussion
---|---|---|---
Lake, L., Hooper, L., Abdelhamid, A., Banting, G., Boxall, A., & Draper, A. (2012) | Climate change and food security: health impacts in developed countries | Global | Climate change will have notable impacts on nutrition and food safety in developed countries, but further research is necessary to accurately quantify these impacts. Uncertainty about future impacts, coupled with evidence that climate change may lead to more variable food quality, emphasizes the need to maintain and strengthen existing systems and policies to regulate food production, monitor food quality and safety, and respond to nutritional and safety issues that arise.
Lai, A., Hales, S., French, N., & Baxter, M. (2012) | Seasonality in human zoonicotic enteric diseases: a systematic review. | USA | Proximal environmental influences and host population dynamics, together with cestid, longer-term climatic variability could have important direct and indirect consequences for future enteric disease risk. Additional understanding of the proximal influence of these factors on disease patterns may improve assessment and prediction of enteric disease burden in temperate, developed countries.
Lin, S., Hou, W., Van Zutphen, A., Saha, S., Luber, G., & Khang, S. (2012) | Excessive heat and respiratory hospitalizations in New York State: estimating current and future public health burden related to climate change. | USA | Estimated impacts vary by geographic region and population demographics. When combined with other heat-associated diseases and mortality, the potential public health burden associated with global warming could be substantial, including respiratory hospitalizations.
Lin, S., Sun, M., Fitzgerald, E., & Huang, S. (2010) | Did summer weather factors affect gastrointestinal infection hospitalizations in New York State? | USA | High maximum and minimum temperature, UAT, precipitation, and extreme heat in summer significantly increased the risk of GHI in NYS. The findings also suggest that bacteria might be a significant cause for GIII in the summer, and minority, female and those with bacterial infection may be more vulnerable to heat's effects on GHI.
Lovett, G., Arthur, M., Woodhead, K., & Griffin, J. (2013) | Effects of introduced insects and diseases on forest ecosystems in the Catskill Mountains of New York | USA | The smutcause effects of multiple invasive insects and pathogens, and their interactions with changing climate and air pollution regimes, make it very difficult to predict the future composition of forest ecosystems.
Marcus, R., Vamo, J., Medus, C., &Booth, E. (2007) | Re-assessment of risk factors for sporadic Salmonella serotype enterica infections: a case-control study in five FoodNet Sites, 2002-2003 | USA | Current health expenditures were inadequate when considering climate change impacts. The analysis served as a critical investigation of the methodology used and aim to identify research weaknesses and gaps. There is a broad consensus that climate change will increase the costs arising from diseases such as malaria and diarrhea and, furthermore, that the largest increases will be in developing countries.
Markanda, Y. & Chibue, A. (2003) | Vauling climate change impacts on human health: empirical evidence from the literature | Global | The most recent decade has the highest frequency of extreme warm season events in the last 100 years across the study region. No such trend is observed between November and May, in fact the frequency of 4-day extreme precipitation events during the cold period has declined during the last two decades.
Malone, A. & Fiel, A. (2015) | A seasonal shift in the frequency of extreme hydrologic events in southern New York State | USA | The variability and vigor of this pathogen’s adaptive strategy to cope with bile is emphasized. The adoption of multiple lifestyles by Salmonella in both the intestine and the gallbladder explains the prolific presence of the pathogen.
Michan, C., Ramos, J., & Daniels, C. (2012) | Exploratory probes and biomarkers, chronic Salmonella infections and future vaccines | Global | This study supports the findings of previous case-control studies and identifies risk factors associated with specific phage types and molecular subtypes.
<table>
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<tr>
<th>Author(s) (Year)</th>
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<th>LOE</th>
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<th>Significance and conclusions</th>
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<tbody>
<tr>
<td>Ran, L. et al. (2011)</td>
<td>Laboratory-based surveillance of typhoidal Salmonella infections in China</td>
<td>V</td>
<td>China</td>
<td>3</td>
<td>In the first multiprovince surveillance report of laboratory-confirmed Salmonella infections in China, Enterobacterales and Typhimurium were found to be the most common serotypes and that efforts to reduce antimicrobial resistance among Salmonella in China are needed. Outbreaks were not detected using this system; the findings were used to improve capacity to detect outbreaks.</td>
</tr>
<tr>
<td>Reza Zali, M. et al. (2011)</td>
<td>Emergence of resistant Salmonella spp.; new challenges, new trends</td>
<td>I</td>
<td>Iran</td>
<td>4</td>
<td>Environmental factors from their animal sources seem to be the best inhibitory manner for emergence of resistant strains among these bacteria. Vaccination of animals with a live attenuated Salmonella vaccine or its related DNA vaccine is a suitable method to prevent bacterial colonization in these bacteria. Use of preservative food additives will reduce microbial infections. However, the elimination of any possible source of infection for Salmonella spp. instead of antibiotic therapy seems to be a well-advised solution for controlling the emergence of more resistant Salmonella serotypes.</td>
</tr>
<tr>
<td>Robinson, S. et al. (2010)</td>
<td>A 23-year assessment of vegetation composition and changes in the Adirondack alpine zone, New York State</td>
<td>IV</td>
<td>USA</td>
<td>1</td>
<td>Changes in the plant communities may also reflect effects of global warming and atmospheric deposition on alpine plant communities.</td>
</tr>
<tr>
<td>Rosenzweig, C. (2011)</td>
<td>Responding to climate change in New York State: the ClimAID integrated assessment for effective climate change adaptation in New York State. Final report</td>
<td>I</td>
<td>USA</td>
<td>1</td>
<td>Within each of the sectors, climate risks, vulnerabilities, and adaptation strategies are identified; integrated themes across all of the sectors are equitability and environmental justice and economics.</td>
</tr>
<tr>
<td>Rozali, D. &amp; Wong, T. (2013)</td>
<td>Effects of climate change on groundwater resources at Shelter Island, NYS, USA</td>
<td>V</td>
<td>USA</td>
<td>1</td>
<td>The unexpected groundwater volume increase under unfavorable climate change conditions in New York State was explained by a clay layer under the island that restricts the maximum depth of the aquifer and allows for an increase in freshwater lens volume when the water table rises.</td>
</tr>
<tr>
<td>Sehie, S. et al. (2011)</td>
<td>Vulnerability of at-risk species to climate change in NY</td>
<td>VI</td>
<td>USA</td>
<td>1</td>
<td>Species at the southern edge of their range in NYS might become extinct from the state. Additional species in need of assessment include plants, crayfish, cave obligates, and functional or habitat groups of species. Aquatic and terrestrial habitat connectivity must be maintained and restored. For some species, stressor other than climate change are more limiting to their viability and climate change will likely result in their extinction no matter what management actions are taken. Long-term monitoring is vital to detecting changes in NYS wildlife populations. Results agreed broadly with those from Pennsylvania and West Virginia.</td>
</tr>
<tr>
<td>Schuster, W. et al. (2000)</td>
<td>Changes in composition, structure and aboveground biomass over seventy years (1930–2000) in the black oak forest, Hudson Highlands, southeastern NYS</td>
<td>IV</td>
<td>USA</td>
<td>1</td>
<td>Over 75 years, red oak canopy trees stored carbon at about twice the rate of similar-sized canopy trees of other species. However, there has been a significant loss of live tree biomass as a result of canopy tree mortality since 1999.</td>
</tr>
<tr>
<td>Semenza, J. et al. (2012)</td>
<td>Knowledge mapping for climate change and food and waterborne diseases</td>
<td>I</td>
<td>Global</td>
<td>4</td>
<td>Frequency profiles revealed an abundance of data on weather and food-specific determinants, but also exposed extensive data deficiencies, particularly with regard to the potential effects of climate change on the pathogens evaluated. A reprioritization of public health research is warranted to ensure that funding is dedicated to explicitly studying the effects of changes in climate variables on food- and waterborne diseases.</td>
</tr>
<tr>
<td>Shaw, S. &amp; Riha, S. (2011)</td>
<td>Assessing possible changes in flood frequency due to climate change in mid-sized watersheds in New York State, USA</td>
<td>IV</td>
<td>USA</td>
<td>1</td>
<td>Annual maximum discharges could be offset by a reduction in the discharge resulting from maximum snowmelt events. While only intended as a heuristic tool to explore the interaction among different flood-causing mechanisms, use of a compound flood frequency distribution suggests a case can be made that not all water bodies in humid, cold regions will see extensive changes in flooding due to increased rainfall intensities.</td>
</tr>
<tr>
<td>Straw, L. et al. (2014)</td>
<td>Distributions of Salmonella subtypes different in two U.S. produce-growing regions</td>
<td>II</td>
<td>USA</td>
<td>2</td>
<td>Distributions of Salmonella subtypes different in two U.S. produce-growing regions. These findings suggest the potential for PFGE-based source tracking of Salmonella in production environments.</td>
</tr>
<tr>
<td>Author(s) and Year</td>
<td>Title</td>
<td>LOE</td>
<td>Location</td>
<td>RG</td>
<td>Significance and conclusions</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------------------------------------------------------</td>
<td>-----</td>
<td>----------</td>
<td>----</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Walsh, M. (2012)</td>
<td>The role of hydrography and climate in the landscape epidemiology of West Nile virus in New York State from 2000 to 2010.</td>
<td>USA</td>
<td>USA</td>
<td>1</td>
<td>While the results are only suggestive due to the county-level aggregated data, these findings do identify a potentially important surveillance signal in the landscape epidemiology of West Nile virus infection.</td>
</tr>
<tr>
<td>Wardekker, J., de Jong, A. van Bree, A., Turkenburg, W. &amp; van der Sluijs, J. (2012)</td>
<td>Health risks of climate change: An assessment of uncertainties and its implications for adaptation policies</td>
<td>Netherlands</td>
<td>Netherlands</td>
<td>4</td>
<td>For possible climate-related health impacts characterized by ignorance, adaptation policies that focus on enhancing the health system's and society's capability of dealing with possible future changes, uncertainties and surprises are most appropriate. For climate-related health effects for which rough risk estimates are available, robust decision-making is recommended. For health effects with limited social and policy relevance, recommendations are to focus on no-regret measures. For highly relevant health effects, precautionary measures can be considered.</td>
</tr>
<tr>
<td>Watt, P., Horrocks, L., Pye, R., Saat, A. &amp; Hunt, A. (2005)</td>
<td>Impacts of climate change in human health in Europe. PESERA, Human health study</td>
<td>Global (Europe)</td>
<td>Global (Europe)</td>
<td>4</td>
<td>Found significant effects on heat and cold related mortality. With a warmer climate, it is expected that there will be more heat related deaths in Europe, but also fewer cold related deaths. There is a need to consider adaptation responses such as air conditioning that can help populations cope with future temperature extremes. There are likely to be many other health effects from climate change in Europe, in addition to those assessed here. Research priorities included effects within Europe, cross-sectoral effects, and the implications to Europe from global health effects.</td>
</tr>
<tr>
<td>Weller, D., Wedmann, M. &amp; Strawn, L. (2015)</td>
<td>Irrigation is significantly associated with an increased prevalence of Listeria monocytogenes in produce production environments in New York State.</td>
<td>USA</td>
<td>USA</td>
<td>2</td>
<td>Interventions at the irrigation level may reduce the risk of produce contamination.</td>
</tr>
<tr>
<td>Yang, X., Kuang, D., Meng, J., Pan, M., Shen, J. &amp; Zheng, J. (2015)</td>
<td>Antimicrobial resistance and molecular typing of Salmonella Stanley isolated from humans, foods, and environment.</td>
<td>China</td>
<td>China</td>
<td>3</td>
<td>An epidemiologic profile of this particular serovar was developed, including route of exposure and extent of antimicrobial resistance. PFGE typing also indicated that aquatic products might serve as a transmission reservoir for Salmonella Stanley infections in humans.</td>
</tr>
<tr>
<td>Zhang, Y., Bi, P. &amp; Hiller, J. (2010)</td>
<td>Projected burden of disease for Salmonella infection due to increased temperature in Australian temperate and subtropical regions</td>
<td>Australia</td>
<td>Australia</td>
<td>3</td>
<td>Temperature-related health burden of Salmonella infection in Australia may increase in the future due to change in climate and demographic in the absence of effective public health interventions. Relevant public health strategies should be developed at an early stage to prevent and reduce the health burden of climate change.</td>
</tr>
<tr>
<td>Zhang, Y., Bi, P. &amp; Hiller, J. (2010)</td>
<td>Climate variations and Salmonella infection in Australian subtropical and tropical regions.</td>
<td>Australia</td>
<td>Australia</td>
<td>3</td>
<td>A potential 1 degree C rise in maximum or minimum temperature may cause a very similar increase in the number of cases in the two regions. The association between climate variations and Salmonella infection could be very similar in subtropical and tropical regions in Australia. Temperature and rainfall may be useful as key meteorological predictors for the number of cases in both regions.</td>
</tr>
<tr>
<td>Zion, M., Pradhanang, S., Pierson, D., Anandhi, A., Lounsberry, D., Metzner, A. &amp; Schnaderman, E. (2011)</td>
<td>Investigation and modeling of winter streamflow timing and magnitude under changing climate conditions for the Catskill Mountain region, New York, USA</td>
<td>USA</td>
<td>USA</td>
<td>1</td>
<td>The shift in timing of snowmelt-influenced streamflow events is measured by the winter-early spring center of volume (WSCV), defined as the Julian Day on which half the total streamflow volume from January to May occurs. Studies of streamflow, precipitation, and temperature trends in the last 50 years have shown that the WSCV is already earlier by about 5-10 days.</td>
</tr>
</tbody>
</table>

Table 4. Age group and sex of laboratory-confirmed *Salmonella* cases in NYS versus NYS population, 2002-2012.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Population(^a)</th>
<th>n</th>
<th>Cases (% of study sample)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5 Years</td>
<td>5.65%</td>
<td>1728</td>
<td>15.07%</td>
</tr>
<tr>
<td>5-17 Years</td>
<td>17.05%</td>
<td>2431</td>
<td>21.20%</td>
</tr>
<tr>
<td>18-64 Years (adults)</td>
<td>62.68%</td>
<td>5775</td>
<td>50.35%</td>
</tr>
<tr>
<td>65+ Years (elderly)</td>
<td>14.62%</td>
<td>1500</td>
<td>13.08%</td>
</tr>
<tr>
<td>Not reported</td>
<td>&lt; 1%</td>
<td>34</td>
<td>0.30%</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>50.94%</td>
<td>6179</td>
<td>53.88%</td>
</tr>
<tr>
<td>Male</td>
<td>49.06%</td>
<td>5288</td>
<td>46.11%</td>
</tr>
<tr>
<td>Not reported</td>
<td>-</td>
<td>1</td>
<td>0.01%</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td>100%</td>
<td>11469</td>
<td>100%</td>
</tr>
</tbody>
</table>

\(^a\)Calculated using 2012 ACS Census data; NYS population (excluding NYC) as the denominator totaling 11,198,904.
Table 5. Annual laboratory-confirmed *Salmonella* cases and overall incidence in NYS, 2002-2012.

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence&lt;sup&gt;a&lt;/sup&gt;</th>
<th>n</th>
<th>Cases (% of study sample)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>11</td>
<td>1235</td>
<td>10.76%</td>
</tr>
<tr>
<td>2003</td>
<td>9</td>
<td>1060</td>
<td>9.24%</td>
</tr>
<tr>
<td>2004</td>
<td>8</td>
<td>940</td>
<td>8.20%</td>
</tr>
<tr>
<td>2005</td>
<td>9</td>
<td>1037</td>
<td>9.04%</td>
</tr>
<tr>
<td>2006</td>
<td>9</td>
<td>1033</td>
<td>9.01%</td>
</tr>
<tr>
<td>2007</td>
<td>10</td>
<td>1102</td>
<td>9.61%</td>
</tr>
<tr>
<td>2008</td>
<td>10</td>
<td>1075</td>
<td>9.37%</td>
</tr>
<tr>
<td>2009</td>
<td>9</td>
<td>1015</td>
<td>8.85%</td>
</tr>
<tr>
<td>2010</td>
<td>9</td>
<td>1046</td>
<td>9.12%</td>
</tr>
<tr>
<td>2011</td>
<td>8</td>
<td>947</td>
<td>8.26%</td>
</tr>
<tr>
<td>2012</td>
<td>9</td>
<td>979</td>
<td>8.54%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Per 100,000 population; calculated using 2012 ACS Census data; NYS population (excluding NYC) as the denominator totaling 11,198,904.
Table 6. Independent contribution of *Salmonella* risk from ambient air temperature in NYS, 2002-2012

| Timeframe     | Pr > $\chi^2$ | Parameter estimate | Hazard ratio (95% CI) | Excess risk per 10°F$^a$
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H$_1$: temperature at the timeframe in regard to culture collection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks 1</td>
<td>0.6379</td>
<td>0.00125</td>
<td>1.001 (0.996 to 1.006)</td>
<td>0.1</td>
</tr>
<tr>
<td>Weeks 2</td>
<td>0.0295</td>
<td>0.00441</td>
<td>1.004 (1.000 to 1.008)</td>
<td>0.4</td>
</tr>
<tr>
<td>Weeks 3</td>
<td>&lt; 0.0001</td>
<td>0.00752</td>
<td>1.008 (1.004 to 1.011)</td>
<td>0.8</td>
</tr>
<tr>
<td>Weeks 4</td>
<td>&lt; 0.0001</td>
<td>0.00877</td>
<td>1.009 (1.006 to 1.011)</td>
<td>0.9</td>
</tr>
<tr>
<td>Weeks 8</td>
<td>&lt; 0.0001</td>
<td>0.01186</td>
<td>1.012 (1.010 to 1.040)</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>H$_2$: temperature of precedent week to account for one-week lag</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks 1</td>
<td>0.4804</td>
<td>0.00233</td>
<td>1.002 (0.996 to 1.009)</td>
<td>0.2</td>
</tr>
<tr>
<td>Weeks 2</td>
<td>&lt; 0.0001</td>
<td>0.00882</td>
<td>1.009 (1.005 to 1.013)</td>
<td>0.9</td>
</tr>
<tr>
<td>Weeks 3</td>
<td>&lt; 0.0001</td>
<td>0.01022</td>
<td>1.010 (1.007 to 1.014)</td>
<td>1.0</td>
</tr>
<tr>
<td>Weeks 4</td>
<td>&lt; 0.0001</td>
<td>0.01035</td>
<td>1.010 (1.008 to 1.013)</td>
<td>1.0</td>
</tr>
<tr>
<td>Weeks 8</td>
<td>&lt; 0.0001</td>
<td>0.01264</td>
<td>1.013 (1.011 to 1.014)</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>H$_3$: temperature of precedent month to account for cumulative temperature effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks 1</td>
<td>0.3813</td>
<td>0.00212</td>
<td>1.002 (0.997 to 1.007)</td>
<td>0.2</td>
</tr>
<tr>
<td>Weeks 2</td>
<td>0.0201</td>
<td>0.00477</td>
<td>1.005 (1.001 to 1.009)</td>
<td>0.5</td>
</tr>
<tr>
<td>Weeks 3</td>
<td>0.0005</td>
<td>0.00612</td>
<td>1.006 (1.003 to 1.010)</td>
<td>0.6</td>
</tr>
<tr>
<td>Weeks 4</td>
<td>&lt; 0.0001</td>
<td>0.00747</td>
<td>1.007 (1.004 to 1.011)</td>
<td>0.7</td>
</tr>
<tr>
<td>Weeks 8</td>
<td>&lt; 0.0001</td>
<td>0.01148</td>
<td>1.011 (1.010 to 1.013)</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Note: Timeframe relates the temporality of the two retrospective and prospective control windows to the case index window.

$^a$Calculated as $(HR - 1) \times 100\%$
Table 7. Combined contribution of *Salmonella* risk from cumulative ambient air temperature in NYS, 2002-2012

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Cumulative Hazard ratio (95% CI)</th>
<th>Cumulative Excess risk per 10°F</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;: temperature of precedent month to factor cumulative temperature</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within one week</td>
<td>1.002 (0.997 to 1.007)</td>
<td>0.2</td>
</tr>
<tr>
<td>Within two weeks</td>
<td>1.007 (0.998 to 1.016)</td>
<td>0.7</td>
</tr>
<tr>
<td>Within three weeks</td>
<td>1.013 (1.004 to 1.020)</td>
<td>1.3</td>
</tr>
<tr>
<td>Within four weeks</td>
<td>1.021 (1.007 to 1.021)</td>
<td>2.1</td>
</tr>
</tbody>
</table>

<sup>1</sup>Calculated as the exponentiation of the hazard coefficients for the denoted independent contributions of the weeks.

<sup>2</sup>Calculated as \((HR - 1) \times 100\%\).

<sup>3</sup>Cumulative contribution is not statistically significant (95% confidence interval of the HR contains the null value).
Table 8. Implementation of SMAC Framework for *Salmonella* and climate change in NYS.

<table>
<thead>
<tr>
<th>Step</th>
<th>Activities</th>
</tr>
</thead>
</table>
| **Scope** | - Identified indirect factors, such as the geography and topography of NYS which influences local ecosystems, and in turn organisms or mechanisms that affect public health.  
- Reviewed the evidence for current and future climate impacts, accounting for the indirect factors, for multiple communicable diseases to ascertain which is of greatest concern.  
- Assessed *Salmonella* as the communicable disease of greatest concern; other communicable diseases had potentially significant knowledge gaps in regard to climate change implications (which prompted our intent to publish this framework for broader use).  
- Developed concise research questions to facilitate definition of the ideal study parameters, and staged these questions to be answered using a formal systematic review methodology.  
- Identified, appraised, selected, and synthesized information met criteria for quality and relevance; the improved understanding of the dynamic epidemiological profile.  
- Mapped causal processes of *Salmonella* and climate change in NYS.  
- Developed the rationale and methods for exploration of validated elements aligned with ideal study parameters. |
| **Measure** | - Identified study-specific priority areas, risk factors, and preliminary barriers and limitations to measuring and analyzing.  
- Improve capacity to measure specific key outcome and quantify relationships of interest  
- Selected data elements based on access and availability of data sources and ability to match by date and location, which were key study parameters enabling us to establish a sampling frame for the timeframe and geographic area of measurement for targeted study.  
- Assessed study integrity for variables of interest during the measurement period and within the measurement area to confirm eligibility of indicators based on inclusion and exclusion criteria.  
- Identified and addressed inconsistencies between and among data sources.  
- Refined outcome data: culture confirmed human salmonellosis cases were provided by NYS DOH Bureau of Communicable Disease Control (BCDC), which were originally collected through routine NYS DOH reportable disease surveillance; multiple administrative data sources were pooled, using case reports to identify cases and provide data for our specified variables of interest, including residence, age, gender, dates for symptom onset, culture collection date, laboratory-confirmed diagnosis, serotypes, and information related to outbreak and travel history.  
- Specified study cases (i.e. identified when and where a case occurred within study parameters using culture collection date and address entries from case reports, as *Salmonella* is a communicable disease with mandatory laboratory reporting requirements)  
- Refined exposure data: climate data was provided by the NYS DOH Center for Environmental Health (CEH); historical meteorological data (with spatiotemporal dimensionality) was collected by satellite and obtained from NASA’s North America Land Data Assimilation System, and we used the climate data to compute weekly mean ambient air temperatures.  
- Specified study exposures: highly specific locations within NYS for every week from 2002 through 2012 were determined based on relationship to case populations, high-resolution daily heat metrics which were spatially-interpolated into a statewide grid at hourly intervals were abstracted from a data warehouse maintained by CEH.  
- Assessed technical approaches to matching refined datasets, and comparative approaches to integrate population-level demographics using data from the US Census Bureau. |
| **Analyze** | - Using geographic information software (ArcGIS) to link climatic and epidemiological data by assigning the geocoded locations of cases and temperatures, occurring at the same time, to the corresponding grid cell, spatiotemporally linked 11,405 eligible *Salmonella* cases to the high-resolution heat metrics.  
- Used statistical analysis software (SAS) to develop custom indicators though manipulating the data to conduct multiple tests in our analysis based on known characteristics of *Salmonella*, to determine risk of *Salmonella* occurrence relative to proximal spatiotemporal temperature exposures.  
- Implemented a time-stratified case-crossover design to determine the likelihood of case outcomes compared to controls, which quantify excess risk of *Salmonella* following exposure to ambient air temperatures (an effective approach to mitigate misclassification bias with cost-effective and strategic selection of retrospective and prospective scanning windows for controls, temporally ordered in relation to the matched case; the bi-directionality of measured effects contrasts for seasonality by design.  
- Conducted descriptive analysis for additional context using data applicable for the measurement period. |
| **Calibrate** | - Documented considerations and evidence basis of drivers linked to the local environment of NYS for implementation and control methods, which encompassed rationale for evidence-based public health solutions through synthesis of our robust analysis with existing research.  
- Identified the need for resources and capacity building to explore on a more granular level where practical public health actions can target specific locations or groups.  
- Concluded that serotype data needed further refinement, but could then be useful for projections; changing serotypes prevalence should take into consideration antibiotic resistance and increase virulence as potential barriers to efficacious intervention; further exploration of serotype trends is particularly important in the context of antimicrobial resistance, as climate change may differentially effect serotypes with higher levels of resistance and virulence.  
- Framed use of study findings to repeat implementing the framework with increasingly narrowed scope for forthcoming research studies and for public health intervention.  
- Reported evidence-based conclusions and recommendations which use trend data for climate and epidemiological data, as well as present effects of climate change on the presence of *Salmonella*; existing data applied to evidence-based models can confirm and extrapolate disease patterns based on various climate change scenarios; robust understanding of the effects of climate change on human health can lead to improved public health planning and preparedness, and enable adaptation in a changing environment. |
Figure 1. Steps and phases of the systematic literature review process
Figure 2. Flowchart of articles identified and excluded at screening levels in the systematic review

- 3923 articles identified from search of Electronic Databases
- 3576 articles excluded by title screen
- 347 articles selected based on title
- 148 articles excluded by abstract screen
- 199 articles selected based on abstract
- 108 articles excluded by full text screen
- 91 articles selected for abstraction for one or more of the 4 research questions (30 articles for RQ1; 5 articles for RQ2; 33 articles for RQ3; and 28 articles for RQ4)
Figure 3. Causal process diagram of factors linked to *Salmonella*
Figure 4. Month of *Salmonella* cases in NYS, 2002-2012

Note: Data label above each bar is the percentage of the total study sample (n = 11,469) that were confirmed as a case during the given month in the study period.
Figure 5. SMAC framework infographic