

***Salmonella* and the changing environment: systematic review using New York State as a model**

Kevin Welch, Asante Shipp-Hilts, Millicent Eidson, Shubhayu Saha and Shelley Zansky

ABSTRACT

Salmonella is a public health concern, for which a complex interplay between host, agent, and environment exists. An improved understanding of causal processes can be used to better gauge the causes and trajectory of *Salmonella* in a changing environment. This would be useful in determining the impact of climate change on the New York State (NYS) environment, the effect of climate change on *Salmonella* in NYS, factors contributing to *Salmonella* vulnerability in humans, and aspects of climate change and *Salmonella* which necessitate further research. A systematic review was conducted to study associations between *Salmonella* and the environment. Using the search criteria, a total of 91 relevant articles were identified from four electronic databases. Key information was abstracted, organized, and synthesized to identify causal processes and linkages between climate change, the environment of NYS, and *Salmonella*-related outcomes, as well as risk factors to characterize *Salmonella* vulnerabilities. Three inter-related domains were identified for consideration and application to epidemiological research to confirm and extrapolate disease patterns using climate change scenarios: improved quantification of causal relationships, inclusion of factors linked to sectors not immediately associated with the exposure and outcome, and increased capacity to validate models in diverse settings.

Key words | causal processes, climate change, environment, *Salmonella*, systematic review, temperature

Kevin Welch (corresponding author)

Asante Shipp-Hilts

Millicent Eidson

Department of Epidemiology and Biostatistics,
University at Albany School of Public Health,
1 University Place, Rensselaer, New York, 12144,
USA

and

Office of Public Health Practice,
New York State Department of Health,
1092 Corning Tower, Albany, New York, 12237,
USA

E-mail: kwelch@albany.edu

Shubhayu Saha

Department of Environmental Health,

Rollins School of Public Health,

Emory University,

1518 Clifton Road, Atlanta, Georgia, 30322,
USA

Shelley Zansky

Bureau of Communicable Disease Control,

New York State Department of Health,

651 Corning Tower, Albany, New York, 12237,
USA

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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

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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):

1. PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>)
2. Web of Science (<http://ipsience.thomsonreuters.com/product/web-of-science/>)
3. ScienceDirect (<http://www.sciencedirect.com>)
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 the level of evidence hierarchy (Figure 1), which was 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



Figure 1 | Level of evidence hierarchy.

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 A (available with the online version of this paper) 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 (Figure 2), 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

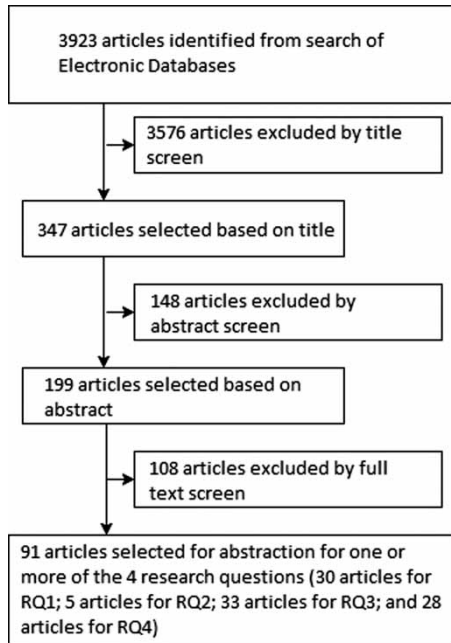


Figure 2 | Flowchart of record counts by screening level.

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 A 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 A 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.

Climate trends were linked to changes in local species of flora and fauna (Robinson *et al.* 2010; Treyger & Nowak 2011, Sun *et al.* 2012, Schuster *et al.* 2008, Lovett *et al.* 2013; Taner *et al.* 2011; Adams & Parisio 2013; Corser *et al.* 2015; Schlesinger *et al.* 2011; Barrett *et al.* 2011), geology and/or hydrology (Burns *et al.* 2007; Frei & Gruber 2010;

Rozell & Wong 2010; Shaw & Riha 2011; Zion *et al.* 2011; Walsh 2012; Matonse & Frei 2013; Arseneau 2014; Cockburn & Garver 2015; Eshel 2015; Hetherington *et al.* 2015), disease and negative health outcomes in humans (Rosenzweig 2011; Lin *et al.* 2012; Walsh 2012), and weather-related outcomes and extreme events (Vermette 2007; Laird *et al.* 2008, 2009; Shaw & Riha 2011; Insaf *et al.* 2012; Hartnett *et al.* 2014; Kim *et al.* 2015).

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; Figure 1), 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 A 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 A 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 (Table 1). Additional countries

Table 1 | Location of articles relevant to factors contributing to *Salmonella* vulnerability in humans

Location	Articles	%
Country	31	94
United States	7	21
China	4	12
Australia	4	12
Italy	3	9
Canada	3	9
Thailand	2	6
New Zealand	2	6
Spain	1	3
Kenya	1	3
Vietnam	1	3
Israel	1	3
The Netherlands	1	3
Ethiopia	1	3
Global	2	6
Total	33	100

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 temperature (Zhang *et al.* 2010; Britton *et al.* 2010; Ran *et al.* 2011; Lal *et al.* 2012; Varga *et al.* 2013a, 2013b; Akil *et al.* 2014; Jiang *et al.* 2015; Liang *et al.* 2015) as well as through modeling projections (Zhang *et al.* 2010; Akil *et al.* 2014; Hellberg & Chu 2016).

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). Understanding sources transmission dynamics of drug resistance were also the objective 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, 335 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 A for details of individual articles selected for abstraction to answer this RQ. The United States represented the largest proportion of articles on locale

Table 2 | Location of articles relevant to aspects of climate change and *Salmonella* necessitating further research

Location	Articles	%
Country	18	64
United States	5	18
Australia	4	14
The Netherlands	4	14
Belgium	1	4
China	1	4
Iran	1	4
Israel	1	4
South Korea	1	4
Global	10	36
Not continent specific	8	29
Europe	2	7
Total	28	100

(5/28; 18%), followed by Australia and the Netherlands (each with 4/28; 14%) with additional countries contributing one article each (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 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 with *Salmonella* (Bi *et al.* 2009; Akil *et al.*

2014; Liang *et al.* 2015) as well as other key indicators and proxies (Chui *et al.* 2009; Watkiss *et al.* 2009; Bassal *et al.* 2011; Newell *et al.* 2011; Lake *et al.* 2012; Lal *et al.* 2012; Michan *et al.* 2012; Semenza *et al.* 2012; Wardekker *et al.* 2012; Milazzo *et al.* 2016; Guentchev *et al.* 2016; Hellberg & Chu 2016; Park *et al.* 2018) to understand trends and health-related outcomes.

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 (Figure 3). As an analytical tool to mitigate potential bias

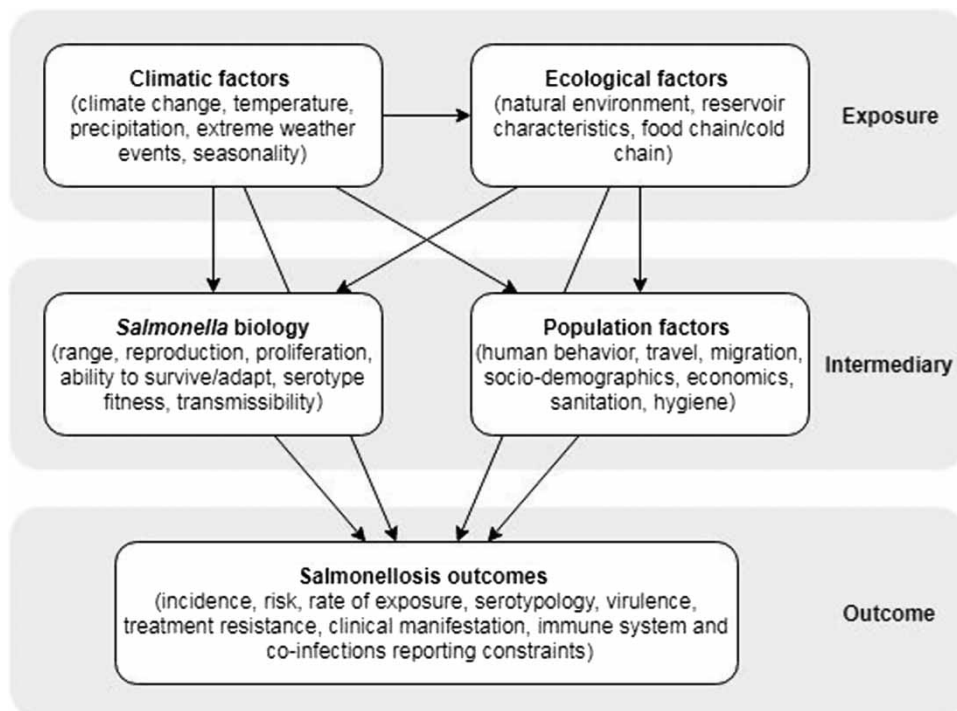


Figure 3 | Causal process diagram of factors linked to salmonellosis.

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 sub-population 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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