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Climate change and human infectious diseases: A synthesis of research findings from global and spatio-temporal perspectives

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ABSTRACT

The life cycles and transmission of most infectious agents are inextricably linked with climate. In spite of a growing level of interest and progress in determining climate change effects on infectious disease, the debate on the potential health outcomes remains polarizing, which is partly attributable to the varying effects of climate change, different types of pathogen-host systems, and spatio-temporal scales. We summarize the published evidence and show that over the past few decades, the reported negative or uncertain responses of infectious diseases to climate change has been growing. A feature of the research tendency is the focus on temperature and insect-borne diseases at the local and decadal scale. Geographically, regions experiencing higher temperature anomalies have been given more research attention; unfortunately, the Earth's most vulnerable regions to climate variability and extreme events have been less studied. From local to global scales, agreements on the response of infectious diseases to climate change tend to converge. So far, an abundance of findings have been based on statistical methods, with the number of mechanistic studies slowly growing. Research gaps and trends identified in this study should be addressed in the future.

1. Introduction

Although the evidence of climate change has grown significantly during recent years, the level of confidence varies among different climatic variables owing to availability of homogeneous long-term data records (IPCC, 2013). The Intergovernmental Panel on Climate Change's 2014 report has stated that warming of the climate system is unequivocal, with each of the past three decades being successively warmer than any preceding decade since 1850. Confidence in global average precipitation change over land areas since 1901 is low prior to 1951 and medium afterwards, but is estimated high for increased number of heavy precipitation events in more regions than it has decreased. It is very likely that global near surface and tropospheric air specific humidity has increased since the 1970s. However, the conclusions on changes of extreme events, such as drought, tropical cyclone activity, storminess, hail, and thunderstorms, remain less clear at a global scale (Hartmann et al., 2013).

The nonlinear and chaotic nature of the climate system imposes more residual uncertainties about the rate and magnitude of future climate change (Kirtman et al., 2013). However, there is little doubt that a fundamental global climate change presents a threat to human health in a variety of ways (McMichael et al., 2006; Costello et al., 2009; Watts et al., 2015). Globally, 23% of all deaths in 2012 were attributable to the environment and an additional 250,000 potential deaths annually from 2030 to 2050 for well understood impacts of climate change (Hales et al., 2014). The causal pathways between climate change and health outcomes are operated in both direct and indirect mechanisms. Human infectious diseases are affected by both mechanisms and thus their interactions and the estimates of exposure to climate health risks is particularly complex.

Heat wave, storms, drought, and flood present direct risk to human infectious disease (Watts et al., 2015). Temperature affects the survival rates of pathogens. Some population and certain regions are more vulnerable to infectious disease due to their lack of the ability to effectively respond to the stresses imposed by elevated temperature (Wei et al., 2012). Excessive bursts of precipitation could cause sanitary sewer overflow and promote the emergence and spread of infectious disease ranging in severity from mild gastroenteritis to life-threatening ailments such as cholera, dysentery, infections hepatitis (EPA, 1996).

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Glossary of terms

Climate change a general term used here to indicate major changes in climate properties, such as temperature, precipitation, extreme events, or wind patterns, among others, that persist for an extended period of time, typically decades or longer.

Climate variability variations in the mean state and other statistics of the climate on all temporal and spatial scales, beyond individual weather events (World Meteorological Organization). Climate variability is mostly due to natural oscillations in the Earth systems.

Drought a period of abnormally dry weather long enough to cause a serious hydrological imbalance.

Positive climate change-infectious disease relationship a positive relationship signifies a higher probability of disease outbreak with the increased magnitude of climatic variables.

Temperature anomaly a departure from long-term temperature averages.

Temperature variability the change in standard deviation in detrended annual temperature, comparing against the periods before and after a certain year.

Indirect risks are mediated through changes in the biosphere (e.g., the life cycles and shifting distribution of vectors) and other through social processes (e.g., human-vector contacts). For diseases transmitted by vectors, such as Lyme disease and West Nile virus, greater pathogen transmission is tried closely with biodiversity loss—a well-established consequence of climate change. High pathogenic avian influenza virus that caused serious outbreaks in Europe and North American poultry farms came from migrant wild fowls—the avian flu virus's natural reservoir whose migration timing is heavily controlled by temperature (Lycett et al., 2016). Long-term warming and temperature anomalies can mediate the bacterial communities of *Vibrio* infections, as seen in costal Chile, Israel, and the U.S. Pacific Northwest (Baker-Austin et al., 2013; Vezzulli et al., 2016).

Nonetheless, although human infectious diseases have gained considerable attention in discussions about climate change, many details remain controversial (Altizer et al., 2013). This uncertainty can be exemplified by the controversial responses of malaria to rising temperatures reported in different studies (e.g., Akinbobola and Omotosho, 2013; Alonso et al., 2011; Omumbo et al., 2011). A critical necessity to maintain and enhance human health in the face of increasingly changing climate trends is to identify knowledge gaps and trends in this field. In spite of many existing climate change and infectious disease (CC-ID) review efforts, the question of how the scientific consensus towards their relations has shifted over time, location and variables has been overlooked. Such questions are of critical importance to public and environmental health because they address the design of site-specific and disease-dependent proactive mitigation and reliable projections of vulnerability. Given their importance, nonetheless, some obstacles hinder the investigation of the complex CC-ID relations that involve many interacting socio-environmental components over space and time.

First, the feedback mechanism of CC-ID is subject to different climate variables, disease types, and environmental settings. The richness in the types of exploratory and response variables confine the comparability of studies that probed on distinct diseases or risk factors. Second, inconsistencies in the spatial scale and time range can result in discrepancies between correlation and causation. Depending on the study objectives and data availability, individual studies range from hospital level to global assessments and span from days to hundreds of years. Although local cases can afford in-situ measurements with fine details, large-scale studies tend to use aggregated and coarse resolution data to link with disease incidence cases. Spatial aggregation errors can significantly alter the coefficient values and inferences drawn from models. Meanwhile, considering the time lag effects in many phenomena or processes, differences in the length of study duration could also impair the comparability of results. Third, knowledge generalization is further complicated by the disciplinary diversity inherent in CC-ID research, as reflected by the wide spectrum of the background of researchers and methods ranging from questionnaire-based interviews to laboratory experiments, statistical analyses, and process-based modeling. The discrepancies in the degree of causality and quality of evidence of these methodologies impose challenges in information synthesis.

To achieve a general understanding towards the CC-ID feedback mechanism, identify research gaps to date, and offer prospects for future research, a synthesis of knowledge on the current research progress over various spatio-temporal scales and a diversity of analytic approaches is presented. Specifically, this review is driven by the following four questions:

1) How do scientific opinions change towards the CC-ID relations over space and time?
2) To what level do current CC-ID research hotspots correspond to regions undergoing large climate change?
3) Do we have a better understanding on the mechanisms of the interaction between climate change and infectious diseases?
4) Will the direction and certainty of research findings shift as the spatial and temporal scales of CC-ID studies change?

An overview of current CC-ID research was provided in a data-intensive meta-discovery manner. The literature database construction and the classification scheme for climatic variables and disease types are described in Sections 2 and 3. A meta-data analysis was then conducted to address the above questions, and the main findings are presented in Section 4. Finally, we summarize the key messages synthesized in this research and include case study discussions.

2. Search strategy and selection criteria

A comprehensive search was conducted in several mainstream bibliographic databases including the ISI Web of Science, Scopus, ScienceDirect, and PubMed. Our approach first involved performing searches of article abstract/title/keywords using strings of [('climate change' or 'climate') and 'infectious disease']. After a first round of search, papers focusing on human-related infectious disease were retained and the information on climatic and disease type was extracted to have a crude knowledge about their themes. To add missing articles that were not identified by the initial search, another round of search was conducted. We applied all keyword combinations from one climatic variable and one disease type to bind the population of cases under consideration. Specifically, search string for climatic variables include ['climate change' or 'temperature' or 'climate variability' or 'extreme events' or 'humidity' or 'precipitation'] and disease groups include ['infectious disease' or 'communicable disease' or 'Fecal oral' or 'food borne' or 'water contact' or 'airborne' or 'insect borne' or 'vector' or 'zoonoses'].

The search was applied to publications before 2015 and articles published before 2000 were combined because relatively few references were published on the topic prior to this year. The initial literature database was further manually screened with the following rules: 1) duplicated and non-English papers were removed; 2) non-peer reviewed articles were not considered to be of a trustworthy scholarly validity; 3) articles that did not report a health outcome related to climate change were not considered, such as review, editorial, or commentary articles; and 4) non-human infectious disease-related articles were

excluded. We carefully selected the papers to guarantee the literature quality, which is a tradeoff for quantity. Those strict literature search and screening processes yielded 245 articles (Supplement File S1).

Essential article information was extracted from each paper: 1) direct information including the title, journal, publishing year, authors; 2) place name and spatial scale of the study area; 3) study period; 4) research methods used; 5) types of infectious disease studied; 6) types of climatic variable studied; 7) the conclusions made about the impacts of climate change on human infectious disease. Those themes capture an overview of the information required for the present analysis (Fig. 1).

3. Hierarchical classification system for diseases and climatic variables

A wide range of disease and climatic terms is not beneficial to synthesis efforts considering the potential statistical bias caused by insufficient cases for a certain disease or climate type, and the difficulties in result interpretation. The broad categories in the database should thus be merged into several concise classes based on their similar functional characteristics.

However, there is no perfect way to build either an infectious disease or climate classification system. Climate change affects infectious diseases via the pathogen, host and transmission environment, among which, transmission is likely the most sensitive component to variations of the external environment because the contact patterns of human-pathogen, human-vector, or human-host can be influenced (Wu et al., 2016). To best categorize the different responses of disease to climate change, we adopted Webber's infectious disease classification system, which is built upon means of transmission (Webber, 2005). Five broad classes were included (Table S1): *fecal-oral* (transmitted by person-to-person contact through water, food or directly to the mouth); *airborne* (transmitted by airborne routes); *insect-borne* (diseases transmitted by flying vectors); *ectoparasite zoonoses* (diseases with both humans and animals involved and transmitted by non-flying vectors, such as fleas and lice); and *domestic & synanthropic zoonoses* (infections caused by the close association of humans with domestic or other animals). Several skin infections and diseases transmitted via body fluids were also found in the database but were excluded from analysis because of the small number of cases ($n < 5$). The climatic variables were categorized into seven groups including air temperature, precipitation, humidity, extreme events, climate variability, ocean, and others (Table S2).

4. Results

4.1. How do scientific opinions about the CC-ID relations change over space and time?

The potential for the severity and distribution of infectious diseases affected by climate change had been recognized decades ago. After a notable detection of the influence of climate variation on marine and terrestrial pathogens (Harvell et al., 2002), the number of CC-ID related research papers has increased steadily (Fig. 2).

To reflect how scientific opinions change over time, the articles were examined according to different directions of CC-ID relations. A positive relation signifies a higher probability of disease outbreak with the increased magnitude of climate variables and vice versa. Articles rated as uncertain do not permit any constant causal inference, and the outcome can be non-linear or unrelated. The results highlight the growing portion of articles reporting negative or uncertain associations (Fig. 3).

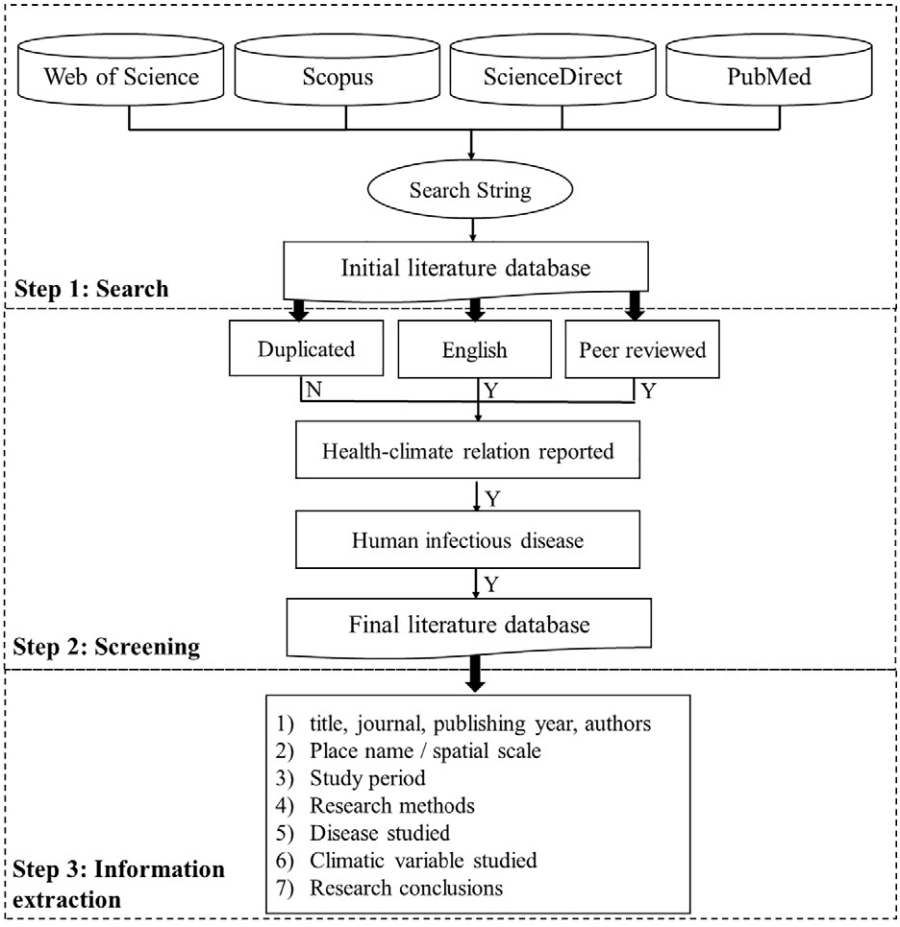

Fig. 1. Literature search and screening flow.

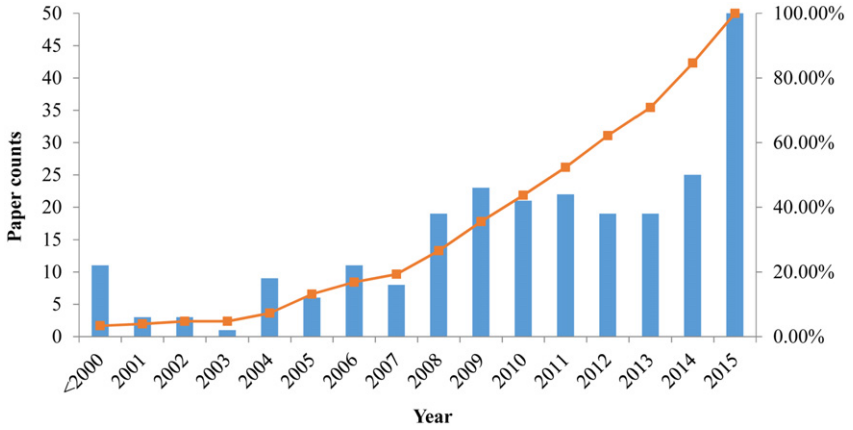

Fig. 2. Rising interest in climate change and human health interactions. The blue bars indicate the number of papers published annually following our literature search criteria. The orange line shows the cumulative amount of papers.

We further partitioned the articles by time. Insect-borne diseases predominated research attention at the early stage, but more diverse disease types have been investigated in recent years (Fig. 3). The research trends exhibit different patterns in each relation category: a gradual shift from insect-borne diseases to a mixture of disease groups occurred in the positive category; an abrupt transition from airborne to insect-borne diseases was apparent in the negative category; and the change of research foci in the uncertain category was less clear, in which insect-borne, airborne, and fecal-oral diseases were all identified with high weights in some years (Fig. 3).

Finally, we summarized the scientific opinions on CC-ID relation according to disease group by examining the counts of records for each disease-response pair over the past two decades (Table 1; Fig. S1). The number of positive responses to climate change displayed a decrease for the airborne diseases; instead, we observed an increase in negative responses. Few negative or uncertain relations have been discussed with regard to domestic zoonoses, and the opinions reflecting positive effects have become weaker over time. Ectoparasite zoonoses and fecal-oral diseases have displayed an increasing trend in both positive and uncertain responses to climate change, with a few exceptions of negative relationships. For the insect-borne diseases, the number of papers reporting positive responses, negative responses and uncertain effects has all increased, but positive responses have increased the fastest.

4.2. Do CC-ID research hotspots correspond to the regions undergoing large climate change?

Geographically, the CC-ID study locations are highly uneven. The top 10 most studied countries account for half of the publications, and a preponderance of research has been conducted in the United States and China (Fig. 4a). North America, Middle Asia, Europe, Australia, and South Africa are the most intensively studied continents. Different parts of the world face various climate change issues. We chose temperature variability, temperature anomaly, and extreme weather events as three key representative variables in the contemporary climate scenario and compared those variables with a map of CC-ID research hotspots.

Presumably, populations in climate vulnerable regions experiencing more climatic fluctuations or having a large deviation from historical reference values are likely to suffer higher adverse climate-related disease risks, and consequently, more research attention should be paid to these areas (Altizer et al., 2013). Nevertheless, research has not yet focused on regions experiencing increasing temperature variability, such as the northern part of South America, Southeast Asia, and Middle

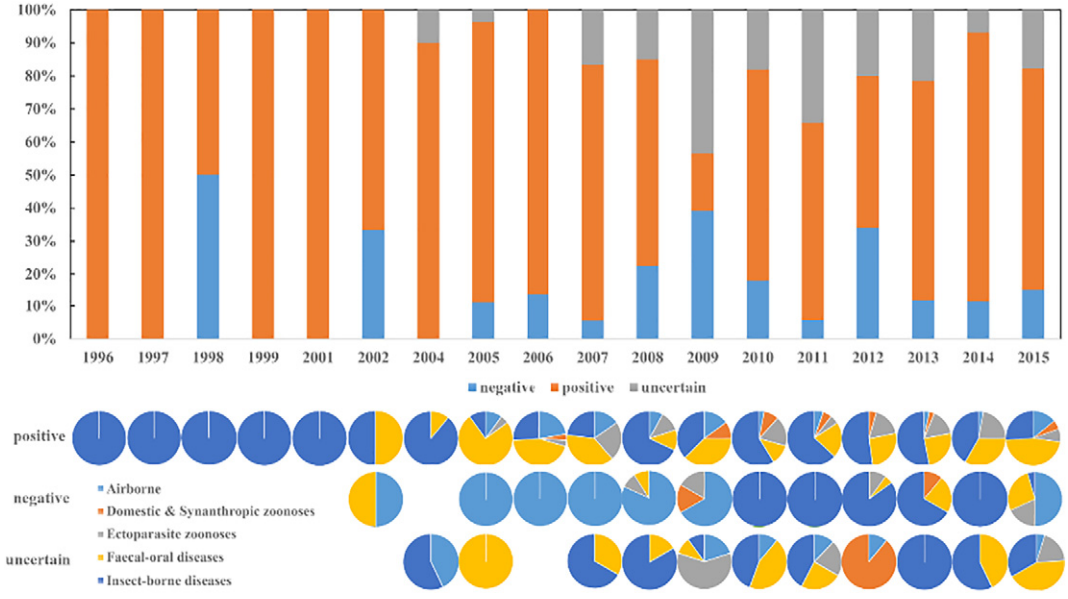

Fig. 3. CC-ID research trend. The bar figure shows the annual total number of related peer-reviewed literature, and the colors indicate the three relation types. The percentage of positive, negative and uncertain responses to climate change is scaled by the total number of cases. The pie charts show the proportion of ID types in each response relation over time.

Table 1
Trend of disease responses to climate change over the past 20 years.

	Positive	Negative	Uncertain
Airborne	↓	↑	↑
Domestic & synanthropic zoonoses	↓	↔	↔
Ectoparasite zoonoses	↑	↔	↑
Fecal-oral diseases	↑	↔	↑
Insect-borne	↑	↑	↑

and South Africa (Fig. 4b). A large body of research has been conducted in regions with mild or no increasing climate variability, in which the percentage change in climate variability is negatively related to the article counts (Fig. 4b). Despite the overlook of climate variability effects on infectious diseases, researchers tend to favor places undergoing a large positive temperature departure from the long-term average, which can be reflected from the positive association between the country-averaged temperature anomaly with the corresponding article counts (Fig. 4c).

Climate change is projected to alter the frequency, timing, intensity, and duration of extreme weather (Karl et al., 1995). Globally, the flood frequency is estimated to increase by 42% of the land grid cells (Hirabayashi et al., 2013). Although recent and historical experiences indicate that infectious disease outbreaks often follow extreme weather events (McMichael, 2015), the geographic pattern of research concerning the effects of floods on infectious diseases has a large discrepancy with areas at high flooding risks (Fig. 4d). By 2100, the frequency of flood occurrence will increase across large areas of South Asia, Southeast Asia, Peninsular India, Northeast Eurasia, eastern and low-altitude Africa, and the northern half of the Andes, whereas it will decrease in northern and eastern Europe, Anatolia, Central Asia, central North America and southern South America (Hirabayashi et al., 2013). Unfortunately, among the thirteen papers discussing the topic of flooding and infectious disease, only half of the study sites are located in projected high-risk regions, such as China and Bangladesh. The remaining sites are located in the US and Europe.

4.3. Have the mechanisms of CC-ID relations been better understood?

The "climate-disease-method-scale" semantic network is a web-like illustration of connections among various thematic terms, including disease types, climate variables, methodology, and spatial-temporal scales (Fig. 5). The multivariate nature and the complex interactions of CC-ID relation with a heterogeneous level of connectivity among thematic terms are revealed. Global, intra-annual, extreme events, domestic, and synanthropic zoonoses are relatively isolated compared to other terms. Statistical analyses and regressions are two of the most commonly applied tools in CC-ID studies with heavy connections with thematic terms from other categories. Most research activities are conducted at local and national levels with time spans from inter-annual to decadal; these studies rarely occur beyond trans-boundary scales.

Mechanism-based models most frequently occur at intra-annual and decadal scales, but are rare at or above the continental scale (Table S4). By contrast, statistical models are widely used at decadal and inter-annual scales. Both statistical analysis and mechanistic model based CC-ID studies have increased in number and favor insect-borne and fecal-oral diseases, but the former is rising at a much faster pace (Fig. 6).

4.4. Does the CC-ID relationship change in different spatial-temporal scales?

Both climate change and infectious disease outbreaks can occur at multiple spatial and temporal scales. However, whether their associations are constant over space and time remains unknown. Our generalized schematic representation of the CC-ID relation tendency implies that as the spatial extent increases, the reliability of positive relation becomes higher for most climatic variables, except for climate variability (Fig. 7). Conversely, the negative relationships are more robust at smaller spatial scales and become less evident above the national scale. More uncertain relations are shown at large spatial scales.

Timewise, approximately 56% of the studies are supported by a decadal-long dataset and 33% by inter-annual records, whereas only 11%

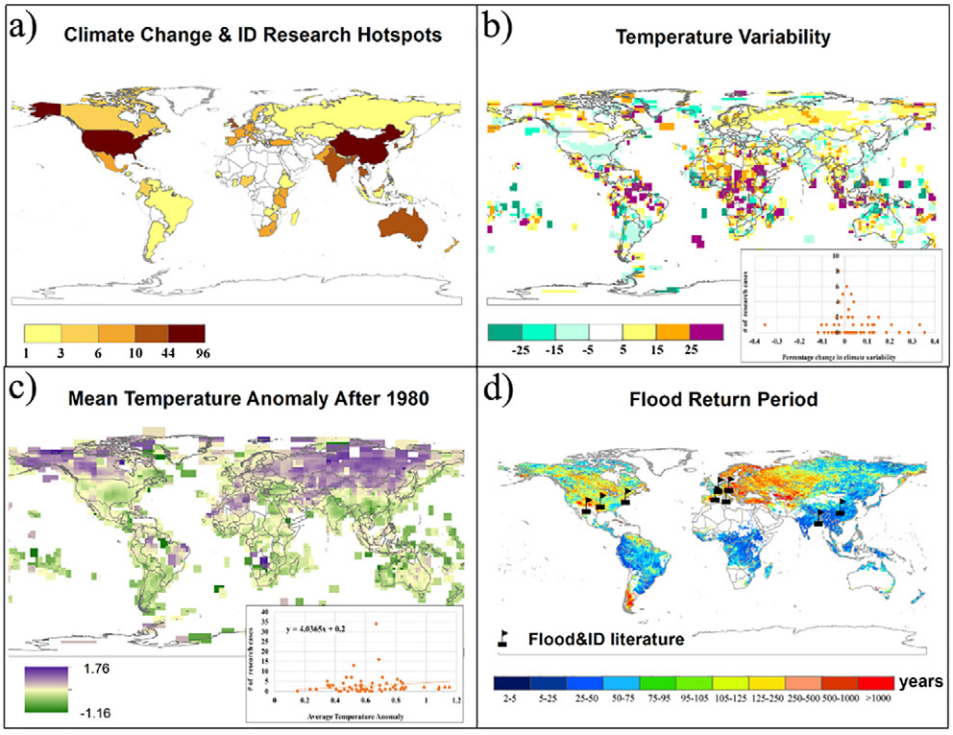

Fig. 4. This panel displays the spatial patterns of CC-ID research hotspots and climate vulnerable regions. a) Total counts of CC-ID related literature by country; b) gridded global temperature variability; c) gridded global mean temperature anomaly; d) projected flood return interval and the overlaid study locations of flood-ID literature.

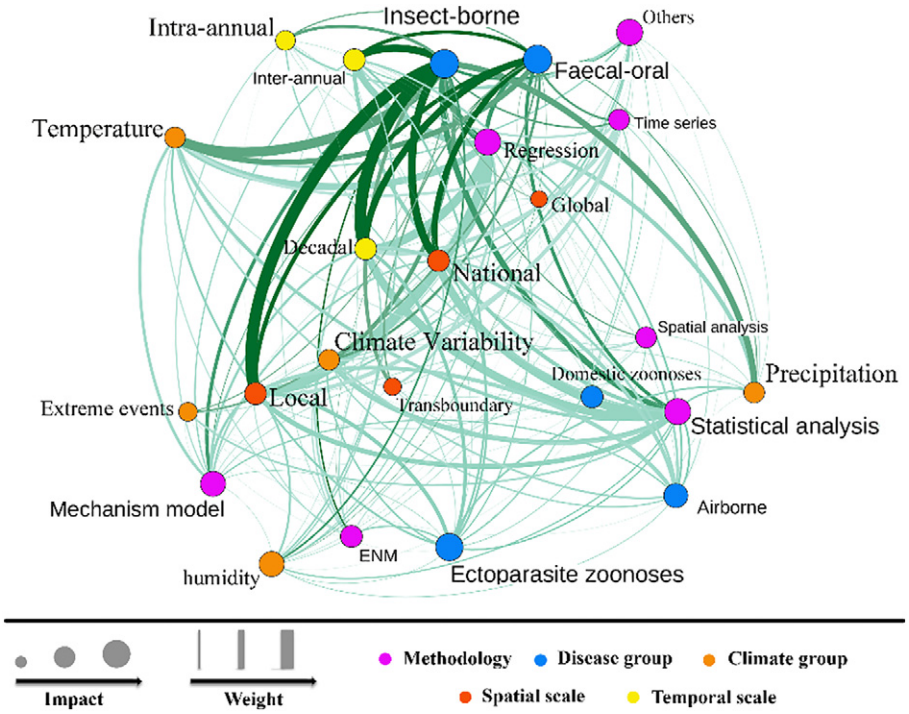

Fig. 5. Climate-disease-method-scale thematic network. Each node indicates one thematic term, and its size tells the level of connectivity. The thickness of the curved edges is a proxy for the occurrence frequency of this relation. Note: ENM - ecological niche modeling.

are intra-annual studies. From the intra-annual to decadal scale, the percentage of positive relations increases for most climatic types except for precipitation, whereas the proportion of uncertain responses decreases other than humidity (Fig. 7). Within the category of negative relations, the tendency differs across climatic types, with an increasing trend in humidity, a decreasing trend in extreme events, and the remaining variables are relatively constant.

5. Discussion

5.1. Observed increase in research efforts yields more diverse infectious disease responses to climate change

Despite the rising anxiety about human infectious disease allied with the growing concern about climate change, predicting the consequences of climate change for infectious diseases has been surrounded by controversy. The articles published between 1995 and 2014 were analyzed to demonstrate that there was an increasing number of articles reporting negative or uncertain responses, indicating a shift of academic opinions towards the CC-ID relationships from unanimously positive to more conflicting views.

This reflects the fact that with more diverse data available at finer scales, more indirect factors can be considered in inferring the climate-disease causal links, such as socio-economic status (e.g., Feldstein et al., 2015; Olago et al., 2007), topographic factors (e.g., Amek et al., 2012), land cover and land use changes (e.g., Ermert et al., 2012), and host mobility (e.g., Wesolowski et al., 2015). In our bibliographic database, approximately 40% of the papers after 2006 reporting uncertain responses have incorporated a number of indirect factors into their analyses. Without adjusting for those indirect factors, the effects of climate change could be overshadowed and be less detectable. An intriguing example is schistosomiasis in China. From the mid-1950s to the 1980s, the estimated number of infected patients in China decreased from 10.5 million to 1.52 million (Chen and Zheng, 1999). If a crude

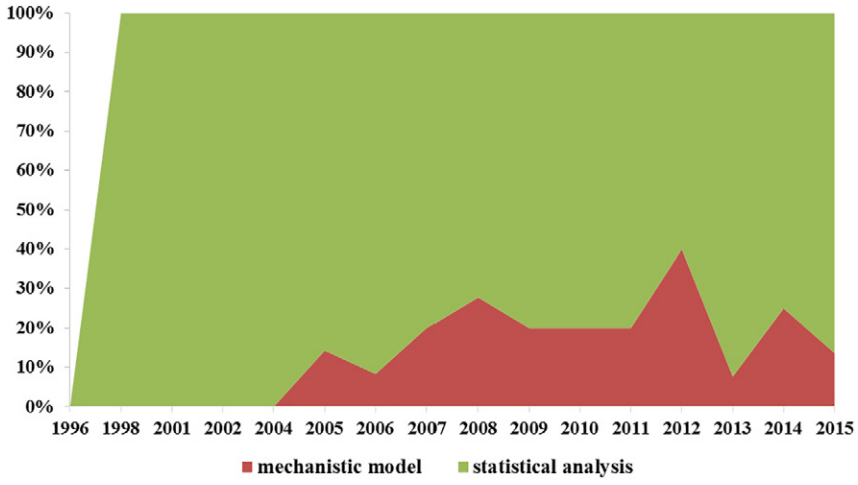

Fig. 6. The overall trend of statistical analysis and mechanistic model based research.

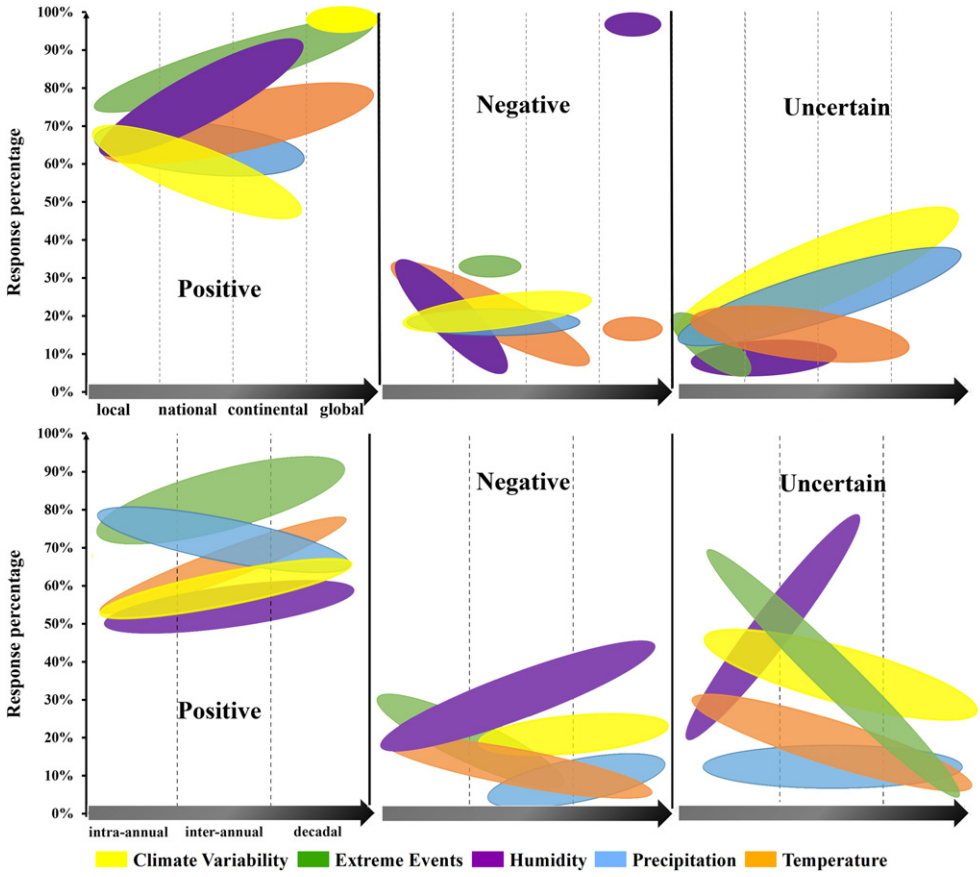

Fig. 7. Schematic representation of the trend of uncertain, positive, and negative disease responses to climate variables across four spatial scales and three time scales. The scales on the y-axis are the rough percentage values for each response type, and the actual values for each spatial-climate-response set can be found in Table S3. The width of the ellipse's minor axis identifies the uncertainties in proximity to the actual percentage values. The slimmer the ellipse is, the closer it is to the actual percentages.

association between the rising temperature and the decreasing patient numbers was examined, a spurious negative relationship will be revealed. In fact, many laboratory experiments and biology-driven models still suggest the increasing risk of parasite development with temperature (e.g., Zhou et al., 2008; McCreesh et al., 2015). The underestimation of climate change contribution results from the failure to account for the human-induced snail elimination and chemotherapy effects. The similar effects have also been observed in schistosomiasis in Africa (Stensgaard et al., 2013).

Moreover, from a statistical point of view, the inclusion of co-factors can change the response magnitude or sign of an outcome to its independent variable. With higher quality measurements and more plentiful confounding variables available at small spatial scales, more diverse and controversial findings of CC-ID relationships could emerge. Since there are many unmeasured or undetected variables, it will not be surprising to discover that some studies fail the significant test between disease and climatic variables whereas the others find a spurious relationship.

5.2. CC-ID research hotspots do not geographically coincide with regions of large climate change

Although climate change is a well-established worldwide phenomenon, its effects vary geographically. Tackling a global challenge such as climate-induced diseases requires more research efforts in regions suffering severer climate change. We represented temperature variability, mean temperature anomaly, and projected flooding frequency in grids and compared their geographic patterns with the CC-ID research hotspots. The mismatch suggests that *high priority climate change regions do not have sufficient research coverage in the CC-ID research domain*. Research so far has mostly been concentrated in countries with good economic conditions, such as European countries and the United States, or those with growing research investments, such as China.

Moreover, *regions with rising temperatures have received more research attention, but few research efforts have been devoted to regions with higher temperature variability*. We must realize that although infectious diseases are most frequently studied as a consequence of a warming climate, the greatest climatic impact will not necessarily be the result of secular changes in temperature over decades, but rather the result of short-term variability and extremes (IPCC, 2012). Short-term temperature variability controls the emerging, spread, persistence, and re-emergence of disease outbreaks, and directly affects the survival rate of pathogens outside the host and their dissemination (Morand et al., 2013). El Niño and Southern Oscillation driven climate variation has been linked to increases in the transmission cycle of vector-borne diseases (e.g., dengue: Hales et al., 1999; Halide and Ridd, 2008; malaria: Wandiga et al., 2010), fecal-oral disease (e.g., cholera: Cash et al., 2014), airborne disease (e.g., influenza: Zaraket et al., 2008) and ecto-parasite zoonoses (e.g., hemorrhagic fever with renal syndrome: Xiao et al., 2013). Climate variability may also have an indirect effect on the likelihood of disease transmission by changing the social behavior of host or vector populations (Gomez et al., 2006; Remais et al., 2007).

The Earth's most vulnerable regions to floods have not been adequately or frequently studied. As a major climate-related disaster, there is now higher confidence in the projected increases in extreme weather events and their adverse effects (IPCC, 2012). Several recorded historical infectious disease outbreaks have followed extreme weather events, particularly flooding (McMichael, 2015). For example, the 2010 nationwide floods in Pakistan resulted in millions of medical consultations for

gastroenteritis, respiratory infections, and malaria in two months (Warraich et al., 2011; Whitmee et al., 2015). West Nile Fever has resurged in Europe and US subsequent to flooding (Soverow et al., 2009). Heavy precipitation was associated with endemic gastrointestinal symptoms in US (Wade et al., 2004) and with bacillary dysentery and enterovirus infections in Taiwan (Chen et al., 2012). At the national scale in the US, outbreaks due to surface water contamination were strongly associated with extreme precipitation (Curriero et al., 2001). Flooding-induced disease risks include the contamination of drinking-water facilities, expansion in the number and range of vector habitats, and changes in human behavior (De Man et al., 2014). However, the hotspots of current flood-ID related research activities do not coincide with the projected high flood frequency regions, which considerably constrains the investigation of flooding effects on infectious disease. This limitation will become even more evident considering the uncertainties in predicting the spatial and temporal scopes of the impact of an extreme weather event.

5.3. Do we have a better understanding of the CC-ID relationship?

The "climate-disease-method-scale" semantic network highlights that the most commonly studied topics are those in relation to temperature and insect-borne diseases at the local and decadal scale. *A large portion of CC-ID findings so far are drawn based on statistical methods, with a slowly increasing tendency to use mechanism-based approaches*. Statistical methods are advantageous in their relative simplicity, but they have been criticized for their failure in modeling the process of infectious disease, i.e., the interaction between the pathogenic microorganism, the climatic environment, and the host. By contrast, mechanism-based models are of high causality because of their capacity in capturing the dynamic nature and spread of the disease by describing disease development and transmission processes as realistically as possible (Cheng et al., 2016). However, their inherent complexity determines the disease-specific characteristics and is not flexible for universal application. The sheer number of both climatic parameters and behavioral response variables also pose challenges to the construction and understanding of mechanistic models (Ostfeld and Brunner, 2015). Although various types of mechanism-based infectious disease models have been developed, such as the sub-population model (Kausrud et al., 2007), probabilistic spatial model (Reiner et al., 2012), spatial phylogenetic analysis (Liang et al., 2010; Liang et al., 2014) and vectorial capacity model (Jetten and Focks, 1997; Liu-Helmersson et al., 2014), the application in the CC-ID field remains scarce, particularly at the continental and global scale. The scarcity in the number of large-scale studies involving mechanistic models is attributable to the lack of sufficient calibration data, and only diseases whose epidemiology has been studied for a long time, such as insect-borne and fecal-oral diseases, can receive sufficient modeling attention.

The usage of different methods can sometimes lead to inconsistent or even contradictory results. For example, in a study that investigated the climatic effects on the dengue outbreaks for the city of Singapore, temperature explains a great portion of the variance in a multivariate Poisson regression model (Pinto et al., 2011). However, using the same data source but based on an autoregressive integrated moving average time-series model, another study did not report any significant temperature and dengue associations (Wilder-Smith et al., 2010). We must realize that a better understanding of the mechanisms of CC-ID interactions requires integration of methods with detailed monitoring. However, this has been rare in existing literature. For example, the basic reproductive number R_0 in infectious disease transmission models that describe the number of cases of a disease that arise from one case of the disease introduced into a population of susceptible hosts is heavily determined by the extremely temperature sensitive extrinsic incubation period (Rogers and Randolph, 2006). The conventional way to retrieve the incubation period is through the usage of the average monthly temperature in an empirical equation, without a thorough consideration about whether the structure and parameters of the equation reflect the realities of that site and scale. A contradictory case is found in a malaria study in Africa, where temperature fluctuation was found to substantially alter the incubation period of the parasite (Paaijmans et al., 2009). Thus, a successful simulation of the climate-driven disease transmission process requires adequate site-specific knowledge of linkage strength between climate variables and disease risks, which can be inferred from the association drawn from statistical analyses. A marriage of different types of methods is useful to bridge the current research gaps and nurture effective study designs for mapping out the disease transmission mechanisms.

5.4. Will the direction and certainty of the CC-ID relation shift with scale changes in time and space?

Our review suggests that the directions of reported CC-ID associations are not constant over different spatial-temporal scales. *As the spatial and temporal scales increase, agreements on the infectious disease responses to climate change tend to converge, whereas the types of responses increase at finer scales*. Climatic conditions differ greatly across longitudinal and latitudinal gradients. It is thus not surprising to observe a mixture of climate effects on disease at small spatial scales because climate change is expected to manifest quite differently in distinct geographic zones. In a broad-scale calculation using a climate-driven mosquito population model, the West Nile virus vector's responses to climate change were found to be heterogeneous across the southern United States and varied with local temperature and precipitation conditions (Morin and Comrie, 2013). In China, the responses of human plague to precipitation were found to be opposite in the southern and northern parts, where the dry and wet conditions are highly distinct (Xu et al., 2011). In addition to the variation in the magnitude of climate change, the discrepancies in the degree of adaptability and resilience of the host and pathogen to climate change across different spatial-temporal scales can also lead to different results. A recent assessment of the climate change effects on the behavior of the primary dengue vector *Aedes aegypti* suggests that the influences of diurnal temperature are geographically distinct. With a rising diurnal temperature range, the dengue epidemic potential increases in cold temperatures or extremely hot climates, whereas it decreases in tropical areas (Liu-Helmersson et al., 2014).

Meanwhile, higher research data availability at the local scale and a shorter time span can also result in discrepant results. Findings based on datasets from varying sources with considerable and unavoidable inconsistences are prone to be different, whereas using a uniform dataset is more likely to reach unambiguous statements. This trend is intensified by the fact that data production channels of global and local climatic datasets are restricted and similar, such as land stations, satellite observations or climate model simulations, whereas more options exist for local scale datasets.

6. Conclusions

Failure to invest in the adaptation of human health or the mitigation of climate change may leave communities and nations poorly prepared, thus increasing the probability of severe adverse consequences (World Health Organization, 2009). To address the rising anxiety about human infectious diseases allied with the growing concern about climate change, this review led an effort in examining the existing evidence on CC-ID associations and identified the knowledge gaps from a spatial-temporal perspective. Although the search can hardly be exhaustive, the selected literatures should have a good representation of the research trends. Knowledge generalization on CC-ID studies has been difficult because cases are inherently independent in terms of variable selection, geographic coverage, and temporal extent. The meta-data analysis used here allows the review to go beyond single cases to generate a number of pertinent observations.

Not considering the potential bias introduced from the intentional overlook of non-English publications, we found that increasing research efforts has been devoted to studying climate change effects on infectious disease. Insect-borne diseases have been the foci for CC-ID research. A higher degree of diversification on the reported disease responses of climate change has been observed in recent years, and the trend is transiting from a positive response-dominated pattern to more non-linear relationships. However, contradictory to the ongoing research efforts, the significant mismatches between the hotspot areas of CC-ID research and areas of great concern in rising climate variability and extreme events remain challenging. The imbalanced and disproportionate research geographical coverage will impair effective disease monitoring and surveillance. With the current better data availability and accessibility, it is imperative that the scientific community pay more attention to those high priority climate change areas that do not currently have sufficient coverage and to close the knowledge gaps from a geographic perspective. Moreover, the agreements on the directions of CC-ID associations change with spatial and temporal scales. As the scale goes up, the scientific opinions tend to converge. Finally, we found that despite a growing trend regarding the use of mechanism-based techniques to analyze CC-ID interactions, the mainstream methods are still confined to statistical analysis, such as ecological niche modeling, regression, time series analysis and other statistical analyses. Although no model is universally applicable to study the complex pathogen-host-climate system, harmonizing and integrating various techniques can be a feasible solution to identify the severity of climate variable changes over various spatial-temporal scales and the health risk shifts due to climate change.

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Appendix A

A.1. CC-ID research and climate change hotspot analysis

We summarized CC-ID publications by country and plotted the numbers on world maps to identify where the studies were most intensively conducted and whether those research hotspots geographically correspond to the climate hotspots that were facing critical climate change issues.

We used the NASA Goddard Institute for Space Studies gridded seasonal and annual temperature anomalies dataset (GISS) spanning from 1880 to the present on a regular $2^\circ * 2^\circ$grid to calculate the temperature variability (Hansen et al., 2010). We preferred to use temperature anomaly over absolute temperature because it describes climate variability over larger areas better, and it allows more meaningful comparisons between locations. The method from Huntingford et al. (2013) was adopted, which calculates the percentage change in standard deviation of monthly temperature anomaly after and before 1980 for each geographical grid:

$$\text{temperature variability} = \frac{\text{std}(\text{TA}_{>\text{year 1980}}) - \text{std}(\text{TA}_{<\text{year 1980}})}{\text{std}(\text{TA}_{<\text{year 1980}})} \quad (A.1)$$

where TA stands for monthly temperature anomaly.

The trend of temperature changes is depicted by the mean temperature anomaly, which was calculated by averaging the GISS monthly surface temperature anomaly data after 1980. Similar to temperature variability, this is a grid-based representation of temperature increases or decreases compared to the 1951–1980 reference period.

A.2. Direction of the ID-related disease responses of climate changes across various scales

To generalize the direction of possible health effects of climate change over spatio-temporal scales, we first stratified the spatial scale into the local, national, continental and global levels, and we classified the time span into intra-annual, inter-annual (<10 years) and decadal levels. For each climatic variable, we then summarized the proportion of case studies reporting positive, negative and uncertain effects on infectious diseases at different spatial-temporal scales (Table S3) and generalized the direction of CC-ID findings based on the percentage value in Fig. 7. For example, the proportion of positive responses in the temperature-ID relationship stably increased from 60% to 80% from the local to global scale, which can be reflected as a positively ascending buffered line in Fig. 7. By contrast, the percentage of positive climate variability-ID relationships decreased from approximately 70% to 40% when the spatial scale went up, and a decreasing line was used to depict this relation.

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