Department of Public Health Sciences

Degree Project for the Master's Programme in Global Health

The impact of climate change on zoonotic infectious diseases

Identifying possible climate sensitive infections

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May 2017

I hereby certify that I formulated the research question, performed the literature review used in this report, developed and implemented the study design, analysed the data, and interpreted the results. I also confirm that the project presented reflects my own work, that the report was written using my own ideas and words, and that I am the only person held responsible for its contents. All sources of information, printed or electronic, reported by others or myself are indicated in the list of references in accordance with international guidelines.

ABSTRACT

Background: The health aspects of climate change are of importance and is a phenomenon that affects all countries and people around the globe. The linkage between environment and health are gaining ever more recognition. Emerging infectious diseases are believed to increase worldwide due to climate change and become an even larger health burden in the future. Only Malaria and Dengue have yet been recognized as being sensitive to climate by the WHO. Since a clear definition is lacking, we define a climate sensitive infection (CSI) as an infectious disease that is geographically confined by climatic factors, and hence have a potential of migrating with climate change. This study is part of a larger ongoing project (CLINF), aiming at filling knowledge gaps regarding how climate change effects on the emergence of zoonosis in the northern hemisphere. The zoonosis in focus are Borreliosis, Tick-borne encephalitis, Tularaemia, Nephropathia epidemica (Nephropathia), Cryptosporidiosis, Leptosporosis, Q-fever, Brucellosis and Anthrax.

Aim: This study aims at finding out if there exist any significant correlations between climate variables and nine selected zoonosis, and hence to infer whether the selected diseases may be considered as being ‘climate sensitive’.

Method: A surveillance based longitudinal data analysis looking at the associations between geographical prevalence of nine zoonotic infectious diseases in Sweden. Based on empirical data, the county-wise prevalence of nine zoonotic infectious diseases were statistically correlated with a number of standard climate-proxy variables. Hence, the zoonosis Borreliosis, Tick-borne encephalitis, Tularaemia, Nephropathia, Cryptosporidiosis, Brucellosis, Q-fever, Leptospirosis and Anthrax were correlated with the climate proxy-variables “accumulated temperature sum”, “humidity”, “duration of snow cover” and “agricultural growth zones”. Data regarding climate and diseases prevalence were merged in ArcGIS software (ArcGIS v. 10.4) in order to produce county-wise climate-proxy values that were matched with the corresponding diseases data. After having exported the resulting matched data-set to statistical software (STATISTICA ver. 13), pair-wise Pearson’s r correlations were estimated across diseases- and climate-proxy variables. In the next step, a multivariate best-subset regression was deployed, where Mallow’s Cp was used to identify the combination of climate-proxy variables that best explain the observed variation of county-wise diseases prevalence.

Results: It was found that the prevalence of Borreliosis, TBE, Tularaemia and Nephropathia has increased. Borreliosis and Tularaemia also seem to have spread to newer geographical areas whereas TBE and Nephropathia keep to the same regions. These diseases showed strong and significant correlations to the climate variables humidity, temperature, growth zones and durations of snow cover. It was also demonstrated that the variation of distribution among different counties in Sweden could be explained to a high degree (49-92%), by certain climate variables, depending on disease at the county scale.

Conclusions: By showing the strong correlations between prevalence and geographic distribution of these diseases and climate variables that relate to the proposed definition of climate sensitive infections, Borreliosis, TBE, Tularaemia and Nephropathia could then be considered being ‘climate sensitive’.

Key words: Climate sensitive infections, zoonosis, distribution, vector-borne diseases, climate variables, climate change.

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ABBREVIATIONS

CLINF	Climate-change Effects on the Epidemiology of Infectious Diseases and the Impacts on Northern Societies
SLU	Swedish University of Agricultural Science
CSI	Climate sensitive infections
Nephropathia	Nephropathia epidemica
TBE	Tick-borne encephalitis
WHO	World Health Organization
IPCC	International Panel on Climate Change
UNEP	United Nations Environmental Program
HELI	Health and Environment Linkage Initiative
EID	Emerging infectious diseases
SMHI	the Swedish Meteorological and Hydrological Institute
SBL	National Bacteriological Laboratory
NCE	Nordic Centre of Excellence
GIS	Geographic Information System
SVA	National Veterinary Institute
EU	European Union
EEA	European Economic Area

INTRODUCTION

The impact of climate change on global health and development

Climate change is a phenomenon that affects all countries and people around the globe. It has an impact on the resilience of this planet, on sustainable development as well as public health. The topic is broad as well as multidisciplinary in its nature. The linkages between development and health are widely known and climate change affects socioeconomic development as well as health directly and indirectly. In 2015, it was agreed upon that Climate Action would be one of the UN sustainable development goals (1).

Climate change is mainly referred to as changes in temperature globally, that is a warming climate. The main reason for this is believed to be the increased emission of greenhouse gases (mostly CO_2). Although, there has always been natural fluctuations throughout time of CO_2 levels in the atmosphere and of temperature, the consensus being that the speed in the increase of these two variables is unprecedented and to a large part due to human activities. Geologists have renamed the era we live in from Holocene to Anthropocene, i.e. man-made changes (2). The consequences are as well a changing and unpredictable weather.

Through the International Panel on Climate Change (IPCC), United Nations has worked with involving experts from all over the world to gather information about the situation. It started in 1990 and the last report, IPCC 2013-14, also for the first time included a chapter on Human health, while previous reports have had a focus on natural science (3). Nations have started to realize that there will be an impact on human societies and public health as a consequence of the changes in ecosystems (3, 4). There is an urgent need to study how climate change affects humans, as a species among others.

It is estimated that 4.2 billion people have been increasingly affected by weather-related disasters during the past 20 years, including a significant loss of lives (5). 'Environmental hazards are responsible for an estimated 25% of the total burden of disease worldwide, and nearly 35% in regions such as sub-Saharan Africa' (6). Weather changes like heat waves, heavy precipitation events, flooding, droughts, more intense storms, sea level rise, and air pollution cause health problems directly but as well indirectly by disturbing food-producing ecosystems, and biodiversity, that impact food-supply and risking clean water supply (6).

Climate change is expected to cause approximately 250 000 additional deaths per year, from malnutrition, malaria, diarrhoea and heat stress (7). The direct damage costs to health (i.e. excluding costs in health-determining sectors such as agriculture and water and sanitation), is estimated to be between US$ 2-4 billion/year by 2030 (7). Due to large development gaps, it is the most vulnerable people that are being affected the most, largely caused by inequalities. The areas most affected are as well those where a larger concentration of poor and marginalized people live, which comprise arid, semi-arid and dry sub-humid aridity zones, covering about 40 per cent of the earth's land. About 29 per cent of the world's population (almost 3 billion people) live in those areas and are facing additional challenges owing to climate change (5).

The effects of climate change on the burden of infectious diseases

One consequence of a changing climate and its effect on ecosystems, is believed to be an increased burden of infectious diseases, with an impact on both health and development. It is believed that there will be a change in the geographical distribution, as well as emergence of infectious diseases due to climate change. This is especially the case for vector-borne and zoonotic infections, i.e. transmitted between animals and humans, which comprise more than 70% of all current human infections (8). So far, malaria and dengue have been recognized as being sensitive to climate and therefore labelled 'climate-sensitive' by the WHO (9). This pose a great challenge for already resource poor settings in Africa. Developing countries with weak health systems will have difficulties to adapt and respond (7). However, all parts of the world are believed to be at risk of an increased burden of infectious diseases, even the Arctic. What different parts of the world have in common, is that it is the indigenous people and the people living close to nature, as well as the poorest populations, that are most vulnerable to climate change. Many indigenous people and populations that previously have not been exposed to certain types of diseases have a low level of immunity and are more susceptible to illness. This fact points to another challenge when diseases move to other geographical areas.

The WHO has a department for Health Security and Environment, with a strong focus on the linkage between climate change, ecosystems, biodiversity and environmental pollution which influences each other and the significant importance it has for public health and development of human societies (7). On the global level, WHO and UNEP are collaborating on a 'Health and Environment Linkage Initiative' (HELI), to support developing country policymakers in addressing the linkage of human health and economic development to valuation of ecosystems that provide air, food, water and energy as well as healthy living environments (6). Collaboration between different fields of expertise in necessary to tackle these complex issues.

The link between climate change, ecosystems and infectious diseases distribution

It is believed that a warming and unstable climate is playing a role in driving the global emergence (expansion of host ranges and geographical areas), resurgence and redistribution of infectious diseases (10). This is especially the case for vector-borne diseases, zoonosis, as well as water-borne pathogens, i.e. cholera (11). The link is that a changing climate affects the environment and ecosystems in which vectors and pathogen hosts thrive. It can be that original habitats shrink, with a consequence that animal hosts and vectors will relocate to other areas. With perturbation of ecosystems, and with species on the move, microorganisms will be in transitions as well, and move into new geographical zones (11, 12). A theory suggests that host-shifts from microorganisms in large part results in emerging infectious diseases, (EID) (13). EIDs arise when microbes begin infecting and causing disease in host species with which they have no previous history of association (13, 14). As human behavior will also change due to a changing climate, these movements will result in new possible exposures for humans for previously unknown infections in that particular area.

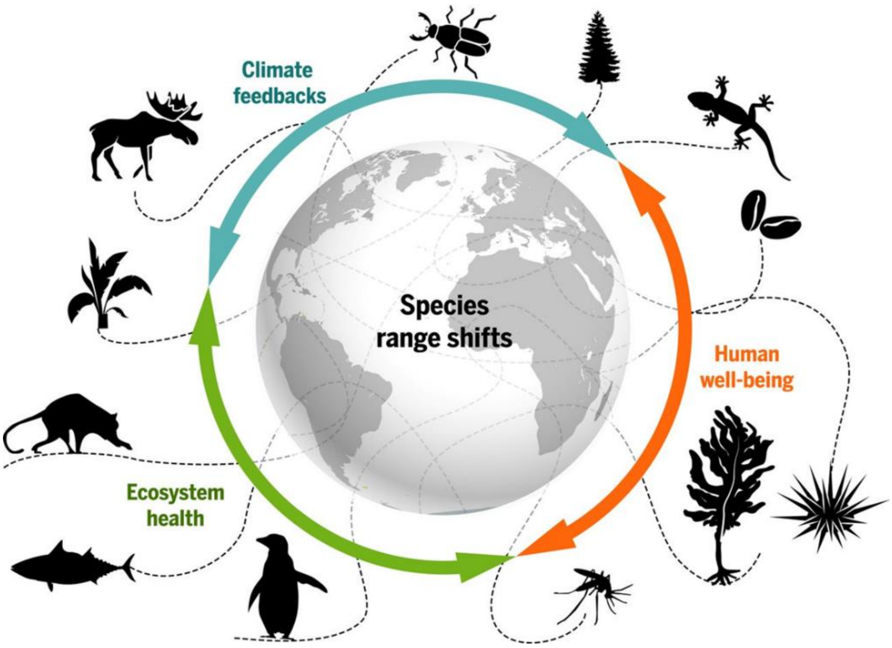

Fig.1. Link between climate change, ecosystems and human well-being.
Source: Gretta T. Pecl et al. Science 2017;355:eaai 9214.

Vectors, pathogens and hosts each thrive within a range of optimal climatic conditions: temperature and precipitation are the most important, while sea level elevation, wind, and daylight duration are also important (15). Extreme weather events may also help create the opportunities for more clustered disease outbreaks or outbreaks at non-traditional places and time (16). Overall, climate conditions constrain the geographic and seasonal distributions of infectious diseases, and weather affects the timing and intensity of disease outbreaks (17, 18).

Recent studies have found that some vector-borne human infectious diseases, including Malaria, African trypanosomiasis, Lyme disease, TBE, Yellow fever, Plague, and Dengue have distributed to a wider range (19). Most of these diseases have extended into areas of higher latitude, following the habitat expansion of mosquitoes, ticks, and midge vectors (20). Hantavirus and plague are also diseases evidently affected by climate (21-23), but salmonellosis (9), cholera and giardiasis, may also show increased outbreaks due to elevated temperature and flooding.

Dengue fever is associated with climate variables like temperature, precipitation and humidity at both the global and local levels (with high confidence), whilst malaria has positive associations to temperature at the local level (with high confidence) (24, 25). Research in the highlands of Western Kenya found high associations between warming temperature and increased incidence of malaria even after considering other potential drivers for disease such as drug resistance in their modelled projections. The results showed that a warmer temperature has a significant effect of on exacerbation of malaria in this area, and could explain a significant portion of this increase (26, 27) (annexes fig. 16).

TBE has been associated with increase in temperature and Borreliosis (Lyme disease) with increase in temperature and humidity (28, 29). A warm temperature is important as it governs the duration of different stages of the life cycle of ticks. The ability for the tick to lay eggs and hatch depend on a stable average temperature the sum as well as of effective temperature (30). In north European countries, like the Czech Republic, TBE-infected ticks were found at a higher altitude than before and TBE cases occurred in those areas (28, 31). Researchers found that the northward expansion of tick habitat and tick-bite incidence rate were strongly linked with the rise in TBE incidence rate (28, 32).

In the last fifty years, there has been changes in the ecosystems in Europe, probably caused by climate change (33). This has led to a changes in the vegetation landscape and caused northward expansion of forested area in northern Russia and with it a northward distribution of many species of wild mammals and with it ticks and TBE (28). In Canada, the habitat of the tick I. persulcatus, shifted northward by 200-1,000 km due to a rise by a few degrees in mean air temperature, according to research (34).

Another example of how climate anomalies are affecting infectious disease risk globally is the El Nino phenomenon causing floods and droughts that if persisting could increase the risk of cholera, dengue, malaria, Rift Valley fever, etc. in these regional hotspots as seen earlier (9). The recent outbreak of anthrax in northern Siberia is said to be caused by the thawing of the permafrost, as in Siberia alone there are more than 7000 places where animals dead of the bacillus have been buried (35).

The Arctic region in focus – the North – Sweden.

The Arctic is an important region of the world influencing the climate system regionally and globally. At the same time, climate warming is occurring at a greater speed and magnitude in the Arctic than in the rest of the world. It is stated to be almost three times faster (36), so this is where changes will be first observed and to a greater magnitude. The observations that can be made are of value for the Arctic, but also for the rest of world for what is to come.

The effects of a warming climate on the environment, animals and people are most clearly felt in northern communities which depend on natural resource use for survival (37). The most vulnerable people are the ones living close to nature, often indigenous people. In northern Scandinavia, there are the Sami people, and in northern Russia there are about 35 different peoples speaking at least 12 different languages. It is of importance for reasons as human rights to monitor changes that have potentials to intervene in the livelihood of these groups (8, 13, 38-41).

In many Arctic communities, the physical infrastructure was built on permafrost. Weakening of this permafrost foundation will likely damage water intake systems and pipes, and result in contamination of community water supplies. Moreover, the failure of the foundation of access roads, boardwalks, water storage tanks, and wastewater treatment facilities can turn water distribution and wastewater treatment systems inoperable (42). Food- and water-security are difficult to maintain. Climate change in these communities is therefore threatening socio-economic development.

Many northern societies depend on animal husbandry, such as sheep and reindeer herding, hunting, fishing and tourism for their livelihoods. These societies are dealing with the challenges climate change pose, concerning not only their health but the health of their animals and the environment as well, since those are so closely intertwined with each other. In the North, animals also play a central role in culture, art and world views. Therefore, an altered panorama of existing and emerging zoonotic infectious diseases both in humans and in animals pose an important threat to public health in the North.

Importance of the study

Over the past decade our knowledge about many aspects of climate change effects and adaptation strategies has increased significantly (37), but a large knowledge gap still exists regarding how climate change effects on climate sensitive infections (CSIs) will affect humans and animals (43, 44). Therefore, there is a need to acquire more information about the spread of possibly CSIs in the northern hemisphere, and to clarify the impacts of climate change on humans and animals among animal husbandry households, which are particularly exposed and sensitive to such changes, through the changed geographical distribution and epidemiology of CSIs.

A recently started research project led by CLINF in collaboration with the Nordic Centre of Excellence aims at filling this knowledge gap and this understanding would then be of importance for risk management and preparedness and turn into practical tools for decision-makers responsible for the development of northern societies. An important goal is contributing to the development of an early warning system for increased risk of spread of CSI at the local level, a so called, alarm system intervention. This thesis will contribute to the work of identifying climate sensitive infections as well as helping in defining the meaning of an infection being climate sensitive.

Description and epidemiology of the selected zoonotic infectious diseases

There are some zoonotic infectious diseases that are believed to have a greater impact on human health in the Northern societies, including Sweden, due to climate change. Several factors were considered when these nine potentially climate sensitive infections were chosen by experts in the field. Transmission-mode, clinical relevance, temporal and spatial relevance, type of arthropod vectors, type of reservoir/ intermediate host animal, drivers of epidemiology being the most important. The selected diseases are: Anthrax, Borreliosis, Brucellosis, Cryptosporidiosis, Leptospirosis, Nephropathia epidemica, Q-fever, TBE, and Tularaemia.

Tick-borne encephalitis, (TBE)

TBE is a human viral infectious disease, spread by the tick Ixodes ricinus in Sweden and Europe. The virus is rapidly infecting the human after the bite and is involving the central nervous system, which can result in long-term neurological symptoms, even death. The virus belongs to the Flavivirus genus, which includes three subtypes: European subtype (central, eastern and northern Europe), transmitted by the tick Ixodes ricinus, far eastern subtype (far-eastern Russia, China and Japan), transmitted by the tick I. persulcatus as is the Siberian subtype (Urals region, Siberia and far-eastern Russia/ Europe). All subtypes are endemic in rural and forested areas.

The European subtype is associated with milder diseases, with 20-30% of patients experiencing the second phase, mortality rates of 0.5-2.0% and severe neurological sequelae in up to 10% of patients. The far eastern subtype is associated with more severe disease: monophasic illness, with no asymptomatic interval preceding the onset of neurological disease, mortality rates of up to 35%, and higher rates of severe neurological sequelae. The Siberian subtype is associated with a less severe disease (fatality rate of 1-3%) with a tendency for patients to develop chronic or extremely prolonged infections. A TBE vaccine is available in some endemic areas.

In Sweden, the disease is geographically distributed to the regions in and around Stockholm, Västra Götaland, Skåne, Blekinge and Gotland. In 2016, there was a total number of 238 reported cases to the Public Health Agency of Sweden, and the majority of cases are men (65.5%) (45).

Borreliosis (Lyme disease)

Borreliosis is caused by the bacterium Borrelia burgdorferi and spread by the tick Ixodes ricinus. The spread to man occurs 24 hours after the bite of infected ticks. The infection often causes symptoms of a distinct skin rash (erythema migrans) but can spread to the nervous system (neuroborreliosis) resulting in more severe disease manifestations of chronic nature. The disease is treated with antibiotics.

The disease can be found mainly in Europe, North America and temperate Asia. The overall mean prevalence of B. burgdorferi genospecies in ticks in Europe has been estimated at about 12% and Central Europe is the region with the highest tick infection rates (nymphs >10%; adult ticks >20%) (46). The B. burgdorferi complex comprises at least 15 genospecies worldwide; still, only five are significantly pathogenic to humans; Borrelia afzelii and B. garinii are the two most pathogenic genospecies found in Europe, B. burgdorferi sensu stricto found in North America and some parts of Europe, B. bavariensis and B. spielmanii in Europe (46).

There is no national summary over Borrelia cases in Sweden since the disease is not notifiable but studies show that Borreliosis, is highly endemic in the southeastern part of Sweden, with highest incidence rates in the counties Blekinge and Stockholm-region. There are also indications of incidences of LB increasing in these areas of Sweden (29).

Ticks- transmission style

Ticks are small (0,5-15 mm) ectoparasites (external parasites) and dependent on a host to reproduce. Ticks become infected when they feed on birds or mammals that carry the pathogen in their blood. Tick live for three years, with larvae and nymphs as the host-seeking stages. In Eurasian endemic areas, Borrelia burgdorferi genospecies circulate between hard ticks of the Ixodes ricinus complex and vertebrate hosts, including many species of small mammals and ground-feeding birds, which are the principal feeding hosts for larva and nymphs. Adult ticks usually feed on larger animals such as deer, which are not reservoir-competent for borrelia, but help to maintain the ticks' reproductive stage.

Competent reservoir hosts of TBE virus are mainly small rodents (voles, mice), but also insectivores (birds) and carnivores. Indicator hosts supporting virus circulation indirectly by enabling tick multiplication include different species of wild and domestic mammals (i.e. foxes, bats, hares, deer, wild boar, sheep, cattle, goats, dogs). Humans are incidental and dead-end hosts. When infected, ticks can transmit the TBE virus throughout their life (mainly nymphs and adults).

Climate factors

Tick activity and life cycle and hence the abundance of ticks, depend on climatic factors (temperature, soil moisture and relative humidity). The most suitable microhabitats for tick development and survival have greater than 85% relative humidity, then they are most active in seeking a host, below this humidity rate they climb down to lower vegetation to rehydrate (29). Wet summers and mild winters tend to increase tick population density. In central Europe, two peaks of activity of I. ricinus have been observed in April/May and in September/October. Questing ticks are found mainly on low-lying vegetation. Sporadic cases during the cold season are however reported. Optimal habitats are represented by deciduous or mixed woodlands, but I. ricinus ticks can also be found in heathland, open grassy meadows and in suburban and urban environments, including urban parklands.

Mild winters, and warm, humid summers tend to increase the incidence of Borreliosis in southern Sweden (29). A study found that incidence rates of erythema migrans correlated to mean summer temperatures, mean summer precipitation and number of summer days with humidity above 86% as well as number of winter days with temperatures below 0 degrees Celsius which negatively affect tick abundance by reducing the survival of ticks (29). The risk of infections seems therefore to be influenced by climatic factors correlating to the abundance of ticks but as well as on the prevalence of infected ticks.

Tularaemia

Tularemia is caused by the bacterium *Francisella tularensis.* Symptoms vary depending on the route of infection. The bacterium can enter the human body through the skin, eyes, mouth, or lungs. The incubation time is 2-10 days. Host animals for Tularemia are rabbits, hares, and rodents. Humans can become infected in several ways, including bites from ticks, mosquitoes and deer flies. Skin contact with infected animals, for instance when handling infected animal tissue, skinning rabbits after hunt etc. Ingestion of contaminated water, inhalation of contaminated aerosols or agricultural dusts and laboratory exposure. In addition, humans could be exposed as a result of bioterrorism (47). Although tularemia can be life-threatening, most infections can be treated successfully with antibiotics.

Francisella tularensis comprises 4 subspecies but nearly all cases of tularemia are caused by subspecies *tularensis* (type A), the most virulent type, which is found in North America, or subspecies *holarctica* (type B), which is the most widespread species in Europe.

Tularemia is endemic in large areas of the Northern hemisphere and causes seasonal outbreaks. Sweden, Finland, and Turkey have reported the highest incidences of tularemia worldwide (48). According to a previous study, the incidence of tularemia was higher in the boreal and alpine ecologic regions as well as around lakes and rivers (48).

Cases of Tularemia has been reported in Sweden since 1931. For a long time, the disease only occurred within a geographically confined area in the county Norrland, but a trend in southward movement have been observed during the last fifteen years. It is occurring mostly in the counties of Norrland, Västra Götaland and Svealand (49).

The number of cases vary greatly from year to year, from zero cases to several hundred with a record of 2700 cases in 1967. During the last decade, there has been a slightly changing trend with years of higher prevalence occurring more often than before. Disease incidence has increased 10-fold, over the past thirty years in Sweden, according to studies (45, 48).
The majority of cases in Sweden are transmitted through mosquitoes. Most cases are reported during August and September (82%) (49).

Nephropathia epidemica

During the 1970'ies it was determined that Nephropatia was caused by a virus through analysis of serum from acutely ill patients containing antobodies to Hantaan virus, belonging to the family of Bunyaviridae comprising many different types of viruses. In 1984 the virus was isolated from lung tissue of voles and was called Puumula-virus after the village in Finland where it was detected.

The virus is found in voles and is transmitted through contact with excrements (urine) or aerosol containing dried urine. Depending of virus there is a difference in preferred type pf rodent reservoir, geographical distribution and potency in causing illness. In most cases, there is a mild illness. The incubation time is 1-8 weeks. Fever and pain in the abdomen and lower back are common symptoms, as well as headaches, nausea, vomiting and the patient feels very sick. In a lesser extent, hemorrhagic fever with severe bleedings, renal syndrome, and a few deadly cases have occurred. The mortality is <0,5%. Treatment of Nephropathia is symptomatic and focusing on monitoring electrolyte- and fluid-balance in the acute phase of illness.

The disease occurs in Scandinavia, western Europe and in Russia (west of Ural). In Sweden, the disease is most prevalent in the northern counties, from Norrland to Värmland, Bergslagen and northern Uppland. The prevalence varies cyclically with 3-4 years between the peaks. The disease prevalence co-vary with the rodent (vole) population. The incidence is around 30/ 100 000 inhabitants and year during the peaks. Seroepidemiological studies have shown that 5-9% of adults in endemic areas do have antibodies and that only a lesser part of the total number of infected people is diagnosed as the symptoms can be very mild.

Q-fever

The disease is worldwide and caused by the bacteria *Coxiella burnetii*. The disease was first described among butchers in Australia 1935 and got the name “query fever” (query= question mark) because it was not known what caused the disease. Humans are often very susceptible to the disease, and very few organisms may be required to cause infection. Foremost farm animals like cattle, sheep and goats are reservoirs for the bacteria, but it can persist in many types of mammals and birds as well after infection. Transmission can also occur from tick bites. Usually, transmission occurs by inhalation of these organisms from air that contains airborne barnyard dust that is contaminated. Organisms are excreted in milk, urine, and faeces as well as during birth of infected animals since high numbers of the bacteria is found within the amniotic fluids and the placenta. Transmission occurs with contact with these fluids or ingestion of unpasteurized milk or dairy products. Human to human transmission exists but these are rare.

The bacterium can persist for long periods of time in the host after infection. The organism is extremely hardy and resistant to heat, drying, and many common disinfectants which enable the bacteria to survive for long periods in the environment.

Acute symptoms in humans can develop 2-3 weeks after exposure, including; high fevers, severe headache, general malaise, myalgia, chills and/or sweats, non-productive cough, nausea, vomiting, diarrhoea, abdominal pain and chest pain. However, as many as half of humans infected with *C. burnetii* are asymptomatic. Some patients develop a more severe disease, including pneumonia, granulomatous hepatitis, myocarditis and central nervous system complications. Pregnant women who are infected may be at risk for preterm delivery or miscarriage. The estimated case fatality rate is low. *A* post-Q fever fatigue syndrome has been reported to occur in 10-25% of some acute patients. Chronic Q-fever is a severe disease occurring in <5% of acutely infected patients causing endocarditis in 60-70%. Treatment of Q-fever with the correct antibiotic may shorten the course of illness for acute Q-fever. Patients with endocarditis require early diagnosis and long-term antibiotic treatment (at least 18 months) for a successful outcome.

Q-fever occurs worldwide. In Europe, 822 cases were reported in 2014 from twenty-seven EU/EEA countries. Most of the cases occurred in Germany (262) and France (209). Overall, there was an overrepresentation of males (63.5%). There seems to be an increase in cases during the summer months (April-July). Observations over a four-year period (2010-2014), revealed an increase in incidence in 2010, but after 2011 the trend has been stable (50).

The disease usually occurs in outbreaks which happened in the French alps in 2002 with 79 cases. Transmission was believed to be airborne and come from farms close by. There have also been larger outbreaks in the Netherlands before 2010 and the source being infected goats. Denmark has had a few cases where humans have been in close contact with infected animals (mostly farmers and veterinarians). In Sweden, there are only very few cases yearly and usually the infection was caught abroad. Very low frequency of antibodies has been found among cattle (51).

Leptospirosis

Leptospirosis is caused by spirochetes of the genus Leptospira. The disease is distributed worldwide, with majority of cases in the tropics. The organism infects mammals, especially rodents. Reservoir animals shed the organism in their urine and contaminate the environment. Humans can be infected after exposure to urine and contaminated soil.

Leptospirosis presents with abrupt onset of fever, myalgia and headache. Most cases are mild to moderate but can be complicated by renal failure, haemorrhage, pulmonary symptoms and myocarditis. Incidence increases during e.g. flooding. Leptospirosis can be treated with antibiotics.

Cryptosporidiosis

Cryptosporidiosis is a disease caused by microscopic parasites called *Cryptosporidium*. It lives in the intestine of infected humans or animals. Cryptosporidiosis may be found in soil, food, water, or surfaces that have been contaminated with the feces from infected humans or animals. Several community-wide outbreaks of cryptosporidiosis have been linked to contaminated drinking municipal water or recreational water.

The patient mainly suffers from symptoms of gastroenteritis, like watery diarrhea, stomach cramps and pain, dehydration, nausea, vomiting, fever and weight loss. Some people with Crypto will have no symptoms at all. For people with weakened immune systems, symptoms can be severe and could lead to severe or life-threatening illness. Most people who have healthy immune systems will recover without treatment. Diarrhea can be managed by drinking plenty of fluids to prevent dehydration.

Many species of *Cryptosporidium* exist that infect humans and a wide range of animals. Although *Cryptosporidium parvum* and *Cryptosporidium hominis* (formerly known as *C. parvum* anthroponotic genotype or genotype 1) are the most prevalent species causing disease in humans, infections by *C. felis*, *C. meleagridis, C. canis,* and *C. muris* have also been reported. The disease is usually spread to humans through contaminated drinking waters. There has been two bigger outbreaks in Sweden during recent years.

Brucellosis

The disease is caused by the coccobacilli Brucella spp. Transmission occurs through contact with fluids from infected animals (sheep, cattle e.g.) or derived from food products such as unpasteurized milk and cheese. Laboratory workers handling Brucella cultures are at high risk of acquiring the disease. Brucellosis occurs worldwide but is endemic in the Mediterranean area.

Clinical manifestations include fever, night sweats, malaise, arthralgia and weight loss. The onset of symptoms may be abrupt or developing over weeks. Treatment with antibiotics is efficient. Brucellosis may be prevented via vaccination of animals or by pasteurization of milk.

Anthrax

Anthrax is caused by Bacillus anthracis, a sporulating gram positive rod found in soil and mammals. It can be part of the normal flora but sometimes undergo a burst of local multiplication which increases the risk of infection in herbivores. Humans become accidentally infected through contact with infected animals or their products.

There are three major anthrax syndromes depending on route of infection:

1. Cutaneous anthrax with ulcer is the most common, with case-fatality rate <1 % with antibiotic therapy, untreated up to 20 %.
2. Inhalation anthrax results from the inhalation of B. anthracis spores when working with animal products; or by intentional release, such as bioterrorism. It has the highest case-fatality rate, presenting initially with myalgia and fever, and later leading to respiratory collapse and shock.
3. Gastrointestinal anthrax develops following the consumption of undercooked infected meat from animals with anthrax.

Several diagnostic tests are available, such as standard culture in reference lab and molecular testing. Treatment with antibiotics should be administrated as soon as possible. AVA is a vaccine licensed to prevent anthrax for at-risk adults before exposure to anthrax. Outbreaks occur among cattle and a recent outbreak among reindeers occurred in 2016 in the Yamal peninsula killing more than 2000 animals and at least one child.

HYPOTHESIS AND RESEARCH QUESTIONS

The hypothesis is that a changing and warmer climate has an impact on prevalence and distribution of zoonotic infectious diseases in Sweden and that they therefore might be climate sensitive. The selection of the diseases Anthrax, Borreliosis, Brucellosis, Cryptosporidiosis, Leptospirosis, Nephropathia, Q-fever, TBE, and Tularaemia, was made by experts from several fields of expertise during a workshop, and is supported by a literature review. They represent different types of modes of transmission to humans such as via air, water, insects, food, rodents, thus reflecting the changing eco-systems due to climate change.

We define a climate sensitive infection (CSI) as an infectious disease that is geographically confined by climatic factors, and hence have a potential of migrating with climate change.

Another way of expressing this is that if an infectious disease is climate sensitive, climate-change effects regulate its occurrence in space and time. It is therefore possible to empirically test whether there exists a statistically significant correlation between observations on CSI incidences and geographically distributed variables that reflect local and/or regional climate characteristics (climate proxy variables). By studying the variation of diseases incidence across the vast climate variation of Sweden, it is possible to test whether assumptions regarding the climate sensitivity of any infectious disease is statistically valid. Such tests are crucially important since the present knowledge regarding the climate sensitivity of infectious diseases is largely missing.

Research questions:

- What are the geographical distributions of the prevalence of these nine infections?
- How does the spatial distribution correlate to climate proxy variations?

AIM

The aim is to empirically investigate if any significant correlations may be demonstrated between the geographic distribution of the nine identified infectious diseases in Sweden, and climate. The specific objective is to test whether the chosen infectious diseases may be considered as being climate sensitive by answering the research questions above.

METHODOLOGY

Study design

A surveillance based longitudinal data analysis looking at the associations between prevalence of diseases and climate variables. It allowed to correlate the geographic locations of disease prevalence over time to climate variables.

Data collection

Study area

The geographical area is Sweden, subdivided into 21 counties. The area of Sweden comprises a steep climate gradient along its 2000 km north-south stretch at high latitudes of different climatic zones due to its long shape (from north to south degrees). The nine zoonoses are commonly occurring in Sweden with typical different areas of distribution within Sweden.

Disease data

The actual number of observed disease cases, were provided for each of the counties, within the same time-span, from 1969 to 2012. However, the data available during this time-span vary between the different types of zoonosis. The prevalence range from a few hundred cases for Borreliosis, Tularemia, Nephropathia, TBE and Cryptosporidiosis, but quite few cases (between 0-10) for Leptospirosis, Brucellosis, Q-fever and Anthrax.

Climate data

Four types of standard climate proxy variables covering Sweden were collected from SMHI. These are “accumulated temperature sum”, “humidity” and “duration of snow cover”. Data regarding “agricultural growth zones” that is reflecting climate was collected from SLU.

Data sources

Data has been collected through the website and from paper reports provided from the Public Health Agency of Sweden, the Swedish Institute for Infectious Disease Control, the National Archives of Sweden (providing earlier epidemiological reports from SBL). The data collected provides information regarding the actual number of cases reported for each disease and geographical location subdivided by counties.

Data handling

Data was collected in collaboration with the ongoing CLINF-project and the NCE. Data about climate proxy variables in the form of maps that could be handled in the GIS program was downloaded. The collected diseases data will be registered and stored in Excel format, to become more manageable. Thereafter it will be worked within a Geographic Information System (ArcGIS v. 10.4) and statistical software (STATISTICA v. 13 and/or SAS v. 9.8).

Variables and statistical analysis

Disease prevalence

These zoonotic infections were chosen because of they represent different types of mode of transmission. They are believed to pose an increased risk for humans to be infected due to a changing climate in the northern countries. To adjust for population size, the accumulated number of disease cases were divided by the county population size, to estimate the prevalence. In the analysis, the population size of year 2000 was chosen as a median year within the timespan (1969-2012) when calculating the prevalence. Since there have not been any reported cases of Anthrax in humans during the time-period 1969-2012, it was excluded from the study. By using this long time-span for disease prevalence, it assures where the diseases have been most prevalent during these years, since that can differ between single years.

Climate variables and definitions

The selection of climate proxy variables was based on the standards used by SMHI, where the chosen variables are considered as being robust and well defined.

The variable "temperature sum" provides annual information regarding daily average temperatures (degrees Celsius) cumulated through the vegetation period of a year while excluding days with average temperatures below the threshold temperature of +5 during a day above +5 degrees Celsius. The vegetation period varies from one place to another, and from one year to another. When the arithmetic mean of annual temperature sums were calculated through the climatic reference period of thirty years stretching back from the current year, a climate reference is obtained per definition.

The variable "humidity" reflects the balance of precipitation minus potential evaporation, where the former is observed and the latter modelled. When the average annual humidity is averaged through the thirty-year reference period, the associated climate reference is obtained. The variable "snow cover duration" provides the annual number of days with a snow cover representative of at least 5 mm rain-equivalents of precipitation. When averaged across the thirty-year reference period, the corresponding climate reference is obtained.

The climate-proxy variable "agricultural growth zone" comprises nine ordinal levels of growth conditions, ranging from coastal warm climates to cold alpine. The nine levels are based on empirical knowledge regarding the hardiness of plants, as well as of geographic and meteorological characteristics (52).

Geographic Information System (GIS)

Data collected, regarding disease cases for each county and year were merged in ArcGIS software to show the geographic distribution of disease cases for each of the counties, cumulated through the period of 1969 to 2012. A suitable map of Sweden, correctly subdivided into the 21 counties as the administrative unit was acquired. Here, an administrative standard map of the Swedish Land Survey authorities, Lantmäteriet, called Sverige_1000 was used.

The four standard, climate-proxy variables were also downloaded into ArcGIS, and overlaid the maps of diseases distribution per county. By processing in ArcGIS, county-wise climate proxy values were extracted for each county and matched with the corresponding diseases data. With climate-proxy variables varying widely within counties, counties were represented with an area weighted mean proxy value.

Statistical methods

Data were arranged in a matrix containing column-wise diseases and climate-proxy variables, and case-wise county-specific values with separate rows hence representing separate counties. Applied on this matrix, pair-wise Pearson's r correlation coefficients were calculated across diseases- and climate-proxy variables (eight diseases and four climate-proxy variables).

In the next step, a multivariate best subset regression was deployed, where Mallow's Cp criteria was used to identify the regressor matrix of climate-proxy variables that best combine intra-matrix independence with optimal explanation of the variation observed regarding county-wise diseases prevalence.

Limitations

The data collected and used in this study are reported from laboratories and clinicians around the country. It means that only people that become ill and develop symptoms of disease are reported but we know that humans can be carriers of pathogens without developing symptom and how large this number is remains unknown. This is however not affecting the spread of disease since these diseases are spread from animals to humans and not between humans.

The prevalence of vaccinated people for TBE has not been considered which could influence the prevalence and distribution of the reported TBE cases.

Ethical considerations

The data used in the study was provided from public health reports available to society. In such reports, no data can be linked to any specific patient. Therefore, no ethical approval was needed for this study.

RESULTS

The geographic distribution of disease prevalence

Borreliosis

The cumulated number of disease cases between the years 1984-93, showed that prevalence of the diseases is located to the southern parts of Sweden, with most cases in the Stockholm region (2216 cases), Västra Götaland (342 cases) and Skåne (305 cases) (fig. 1). There were in total 4882 reported cases during this 10-year period. There were on average 542 reported cases per year ranging from minimum 255 cases to 779 cases. There is an overall increase in prevalence during the period (annexes fig. 1).

Tick-borne encephalitis (TBE)

The cumulated number of disease cases between the years 1972-2012 are 3641 cases. However, it is only between the years 1978-93, that the disease cases are specified to a county with a total of 680 cases. The prevalence is located to the south-eastern parts of Sweden, with most cases in the Stockholm region (522 cases), Uppsala (39 cases) and Södermanland (29 cases) (fig. 3). There were on average 42.5 reported cases per year ranging from minimum 17 cases to 75 cases. Over this period the number of reported TBE cases have increased in Sweden. For the first 8 years, there were 229 cases and the second 8 years 451 cases, that is a double increase. Also, when looking at a 4-year division 1978-81 (97 cases), 1982-85 (132 cases), 1986-89 (205 cases) and 1990-93 (246 cases), the increase is steady (annexes fig. 2).

Tularaemia

The cumulated number of disease cases between the years 1969-2012, showed that prevalence of the diseases is located to the northern and middle parts of Sweden, with most cases in the county of Gävleborg (1372 cases), Norrbotten (978 cases), Dalarna (644 cases) and Örebro (565 cases) (fig. 2). There were in total 6366 reported cases during this 44-year period. That is on average 144 cases per year. However, there are fluctuations in prevalence between years, ranging from minimum zero cases to 698 cases with cyclic variations. From the first 22-year period to the next, the number of cases increased from 1693 to 4671. Most of this increase happened during the last 11 years, with 3793 cases only in this period. In the earlier periods the disease prevalence was more confined to a few counties (Norrbotten, Västerbotten, Dalarna, Gävleborg) but since the last 11-year period it seems that the disease has spread to wider geographical areas and more southwards including Stockholm, Södermanland and Västmanland (annexes fig. 3-5).

Nephropathia epidemica

The cumulated number of disease cases between the years 1985-2012, showed that prevalence of the diseases is located to the northern parts of Sweden, with most cases in the county of Västerbotten (2777 cases), Norrbotten (2004 cases) and Västernorrland (1715 cases) (fig. 4). There were in total 8519 reported cases during this 28-year period. The prevalence is quite steady around a few hundred cases per year but fluctuating as well in a three-year cyclic manner. In the year 2007 there were an exceptionally high number of 2195 cases in Sweden. The disease seems to keep within this geographical area but in 2007 there were in addition many cases in the county of Jämtland and Gävleborg. Dividing this period by four there is an increase in prevalence over these periods, 1985-91 (1067 cases), 1992-98 (1488 cases), 1999-2005 (2117 cases) and 2006-2012 (3634 cases) (annexes fig. 6-8).

Q-fever

The cumulated number of disease cases between the years 1969-2012, were 91. Only in the years 1981, 1993 and 2005-2012 the disease cases were specified to a county, in total 44 cases. Most of these cases (38), were reported from the counties of Stockholm, Västra Götaland and Halland (8-10 per county) and almost all of them were reported after 2004. There is increase in prevalence during the period, (annexes fig. 9).

Cryptosporidiosis

The cumulated number of disease cases between the years 1994-2012, were 2312. Only in the years 2005-2012 the disease cases were specified to a county, in total 1599 cases. Most of these cases were reported from the counties of Stockholm (804), Västerbotten (173), Jämtland (161), Jönköping (103), Skåne (78) and Västra Götaland (78). The cases appear in clusters in different areas for instance in Jämtland 2010 and Västerbotten 2011, but there is an overall increase in prevalence, (annexes fig. 10, 11).

Brucellosis

The cumulated number of disease cases between the years 1969-2012, were 166 of which 132 were county-specific. Most of these cases were reported from the counties of Stockholm (53 cases) and Västra Götaland (25 cases). The cases appear sporadically over the years and with 1-2 cases in different areas of Sweden, (annexes fig. 12, 13).

Leptospirosis

The cumulated number of disease cases between the years 1972-2012, were 40. There was no reporting of the disease in the period 1997-2003. Most of these cases were reported from Stockholm (13). The cases appear sporadically over the years and with 1-2 cases in different areas of Sweden, (annexes fig. 14).

Correlations between spatial disease distribution and climate

Strong significant correlations between climate-variables and prevalence of Borreliosis, TBE, Tularaemia and Nephropathia were found. Q-fever, Leptospirosis, Cryptosporidiosis and Brucellosis showed no significant correlations. Results are shown in table 1. With multivariate best subset regression, it was found that the one or a combination of two variables were more favourable than the others. Results shown in table 2. This means that with infectious diseases defined as climate sensitive if their prevalence depends on climate characteristics, four out of eight chosen diseases may be considered as being climate sensitive infections (CSIs').

Borreliosis (Lyme disease)

Strong significant correlations were found between the prevalence and each one of the four climate variables when tested with Pearson's r correlations. Borrelia was positively correlated with temperature ($r = 0.61$, $p < 0.01$) but negatively correlated with humidity ($r = -0.57$, $p <$

0.01), duration of snow cover ($r = -0.54$, $p < 0.05$) and growth zone ($r = -0.66$, $p < 0.01$), adding up to fewer cases in the northern parts of Sweden. With multivariate best subset regression, it was found that the combination of humidity and growth zone were favourable, explaining 49% of the variation concerning Borreliosis observed across Swedish counties ($p < 0.001$). (See fig. 2, 6, 8 and 10).

Tick-borne encephalitis (TBE)

Prevalence was significantly and negatively correlated to humidity ($r = -0.84$, $p < 0.005$) and growth zone ($r = -0.46$, $p < 0.005$), when tested with Pearson's r correlations. TBE was positively but not significantly correlated with temperature ($r = 0.43$, $p < 0.6$), and negatively, not significantly correlated to duration of snow cover ($r = -0.32$, $p < 0.2$), adding up to fewer cases in the northern parts of Sweden. With multivariate best subset regression, it was found that humidity explaining 69% of the variation concerning TBE observed across Swedish counties ($p < 0.001$). (See fig. 4, 6 and 11) (annexes fig. 15.).

Tularaemia

Strong significant correlations were found between the prevalence and three out of four climate variables when tested with Pearson's r correlations. Tularaemia was significantly and negatively correlated with temperature ($r = -0.74$, $p < 0.05$), significantly and positively correlated with duration of snow cover ($r = 0.85$, $p < 0.01$) and growth zone ($r = 0.76$, $p < 0.01$) and not significantly correlated to humidity ($r = 0.14$, $p < 0.06$). With multivariate best subset regression, it was found that the combination of temperature and duration of snow cover were favourable, explaining 85% of the variation concerning Tularaemia observed across Swedish counties ($p < 0.001$). (See fig 3, 7, 9 and 12).

Nephropathia epidemica

Strong significant correlations were found between the prevalence and three out of four climate variables when tested with Pearson's r correlations. Nephropathia was significantly and negatively correlated with temperature ($r = -0.85$, $p < 0.01$), significantly and positively correlated with duration of snow cover ($r = 0.94$, $p < 0.01$) and growth zone ($r = 0.51$, $p < 0.01$), but not significantly correlated to humidity ($r = 0.21$, $p < 0.4$), With multivariate best subset regression, it was found that the combination of temperature and duration of snow cover were favourable, were favourable, explaining 92% of the variation concerning Nephropathia observed across Swedish counties ($p < 0.001$). (See fig. 5, 7 and 9).

Brucellosis

No significant correlations were found between the prevalence and any of the four climate variables when tested with Pearson's r correlations. Brucellosis was negatively correlated with humidity ($r = -0.14$, $p < 0.6$), but positively correlated with temperature ($r = 0.64$, $p < 0.8$), duration of snow cover ($r = 0.003$, $p < 1$) and growth zone ($r = 0.29$, $p < 1$). Because the results were not significant it was not analysed further with multivariate best subset regression.

Q-fever

No significant correlations were found between the prevalence and any of the four climate variables when tested with Pearson's r correlations. Q-fever was positively correlated with temperature ($r = 0.13$, $p < 0.6$), humidity ($r = 0.28$, $p < 0.3$), and negatively correlated with duration of snow cover ($r = -0.14$, $p < 0.6$) and growth zone ($r = -0.077$, $p < 1$). Because the results were not significant it was not analysed further with multivariate best subset regression.

Cryptosporidiosis

No significant correlations were found between the prevalence and any of the four climate variables when tested with Pearson's r correlations. Cryptosporidiosis was negatively correlated with temperature ($r = -0.41$, $p < 0.07$), and positively correlated with humidity ($r = 0.21$, $p < 0.4$), duration of snow cover ($r = 0.39$, $p < 0.09$) and growth zone ($r = 0.36$, $p < 0.2$). Because the results were not significant it was not analysed further with multivariate best subset regression.

Leptospirosis

No significant correlations were found between the prevalence and any of the four climate variables when tested with Pearson's r correlations. Leptospirosis was positively correlated with temperature ($r = 0.15$, $p < 0.6$), and negatively correlated with humidity ($r = -0.23$, $p < 0.4$), duration of snow cover ($r = -0.10$, $p < 0.7$) and growth zone ($r = -0.17$, $p < 0.5$). Because the results were not significant it was not analysed further with multivariate best subset regression.

Table 1. Correlations between spatial disease distribution and climate

	Temperature sum	Humidity	Duration of snow cover	Growth zone
Borreliosis				
Pearson's r:	0.61	-0.57	-0.54	-0.66
Significance	**p= 0.003**	**p=0.007**	**p=0.012**	**p=0.001**
TBE				
Pearson's r:	0.43	-0.84	-0.32	-0.46
Significance	p=0.53	**p= <0.001**	p=0.157	**p= 0.038**
Tularaemia				
Pearson's r:	-0.74	0.14	0.85	0.76
Significance	**p=<0.001**	p=0.54	**p=<0.001**	**p=<0.001**
Nephropathia				
Pearson's r:	-0.85	0.21	0.94	0.81
Significance	**p=<0.001**	p=0.37	**p=<0.001**	**p=<0.001**
Brucellosis				
Pearson's r:	0.64	-0.14	0.003	0.29
Significance	p=0.783	p=0.553	p=0.991	p=0.901
Cryptosporidiosis				
Pearson's r:	-0.41	0.21	0.39	0.34
Significance	p=0.066	p=0.365	p=0.082	p=0.130
Leptospirosis				
Pearson's r:	0.15	-0.23	-0.10	-0.17
Significance	p=0.514	p=0.311	p=0.651	p=0.469
Q-fever				
Pearson's r:	0.13	0.28	-0.14	-0.077
Significance	p=0.571	p=0.217	p=0.544	p=0.740

Table 2. Correlations between spatial disease distribution and climate

Mallow's test	TBE	Borrelia	Tularemia	Nephropathia
R^2 (adj). :	0.69	0.49	0.85	0.92
F/p:	46.5/ < 0.001	20.8/ <0.001	39.7/ <0.001	113.2/ <0.001
Level of significance				
Humidity	***	*	-	-
Temperature sum	-	-	***	***
Duration of snow cover	-	-	***	***
Growth zone	-	**	*	*

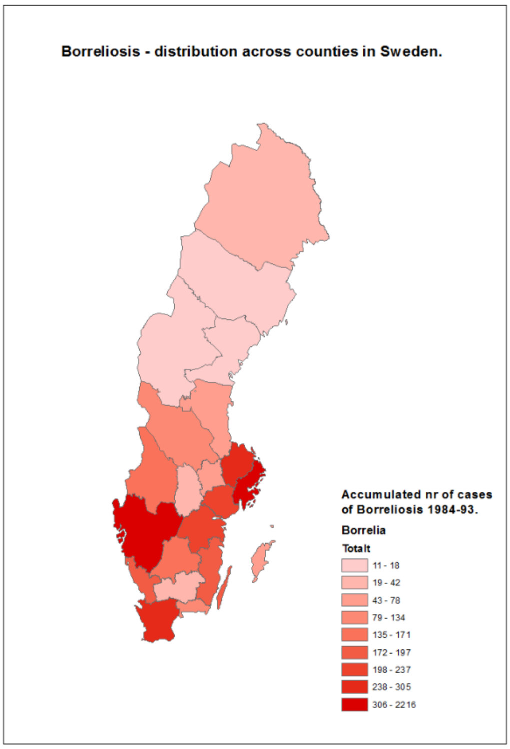

Fig. 2. Distribution per capita of Borreliosis across counties Sweden. Acc. Nr. of cases during the years 1984-1995.

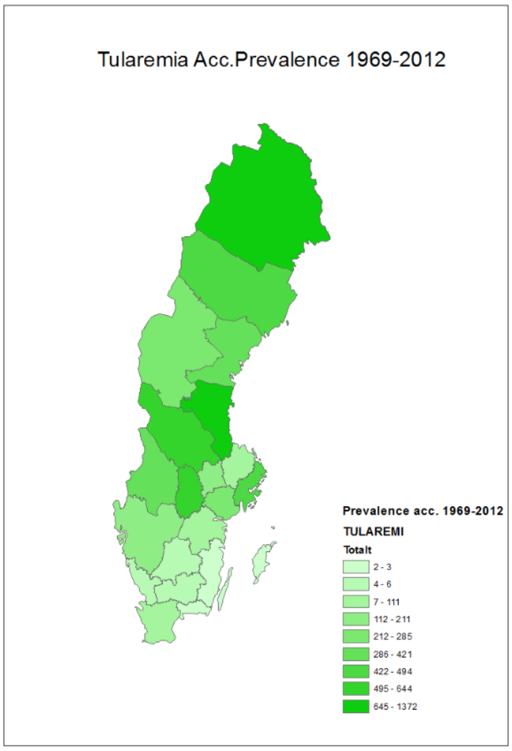

Fig. 3. Distribution per capita of Tularaemia across counties Sweden. Acc. Nr.. of cases during the years 1969-2012.

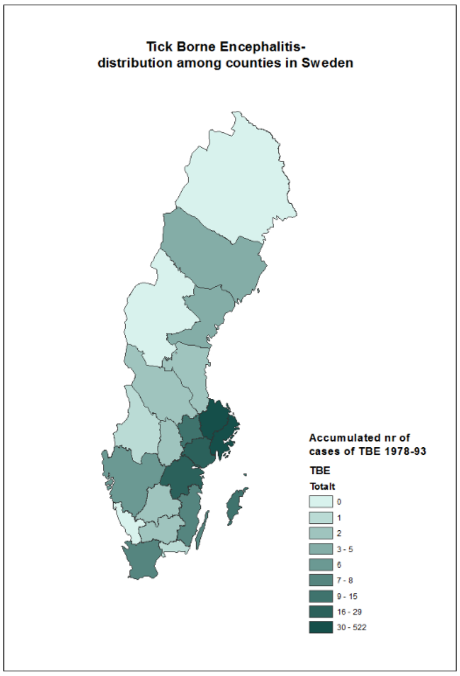

Fig. 4. Distribution per capita of TBE across counties Sweden. Acc. Nr. of cases during the years 1978-1993.

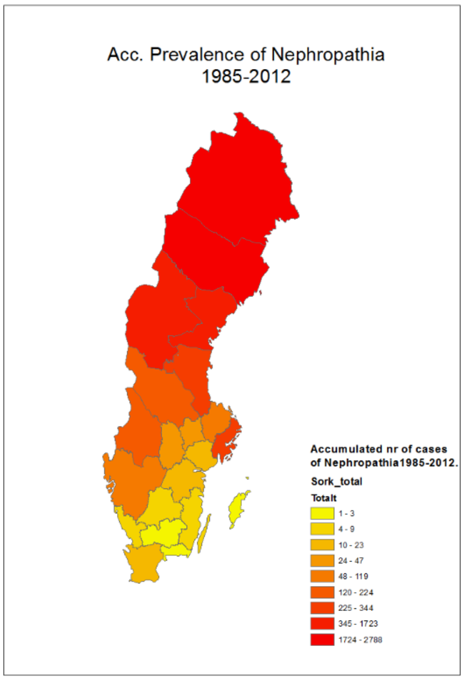

Fig. 5. Distribution per capita of Nephropathia across counties Sweden. Acc. Nr. of cases during the years 1985-2012.

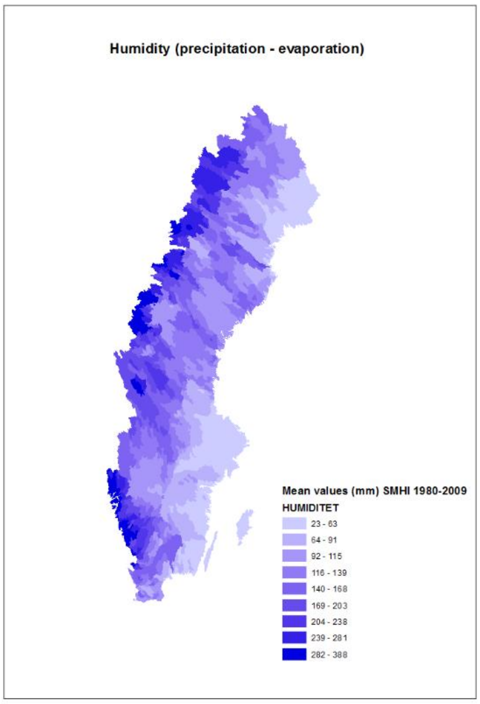

Fig. 6. Average annual daily humidity through the reference period (1984-2009).

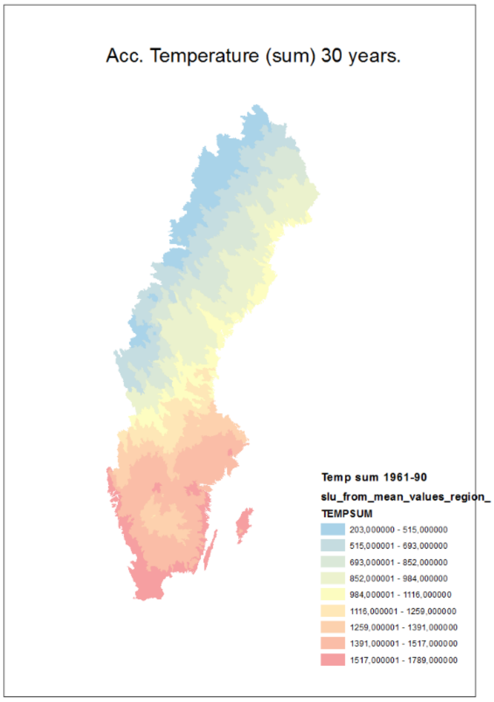

Fig. 7. Average annual daily average temperatures (degrees Celsius) cumulated during the period 1961-1990.

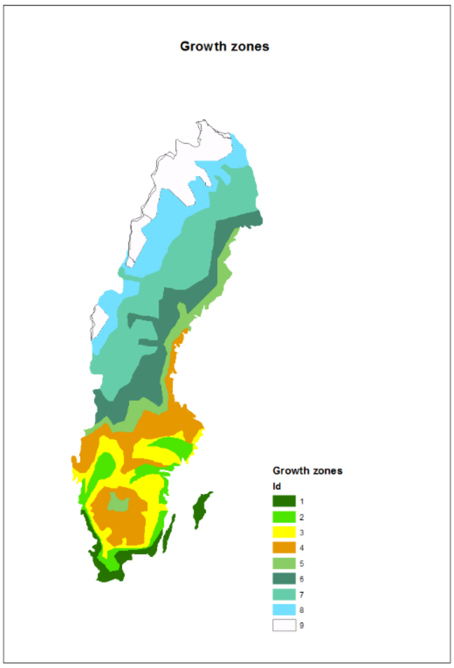

Fig. 8. Growth zones: comprises nine ordinal levels of growth conditions.

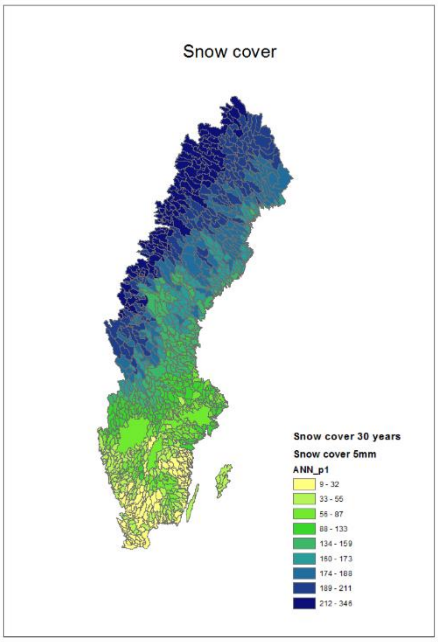

Fig 9. Duration of snow cover: the annual number of days with a snow cover representative of at least 5 mm rain-equivalents of precipitation .Cumulated 1961-90.

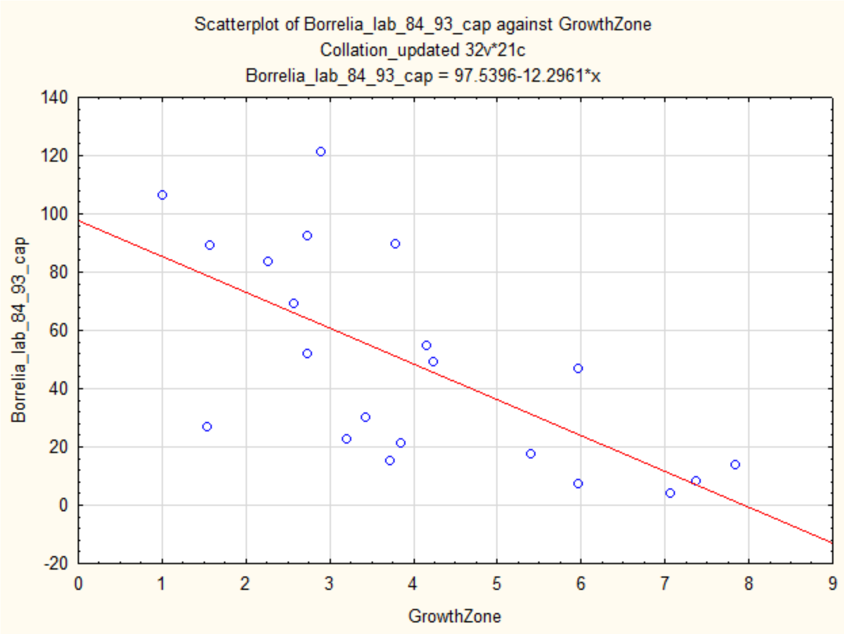

Fig. 10. Correlation between Borreliosis and Growth zones.

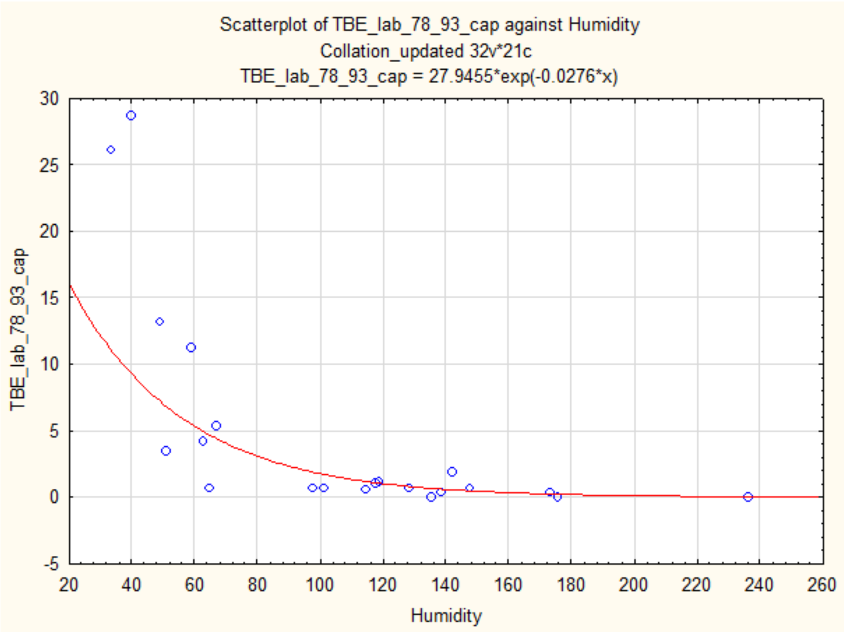

Fig. 11. Correlation between TBE and humidity.

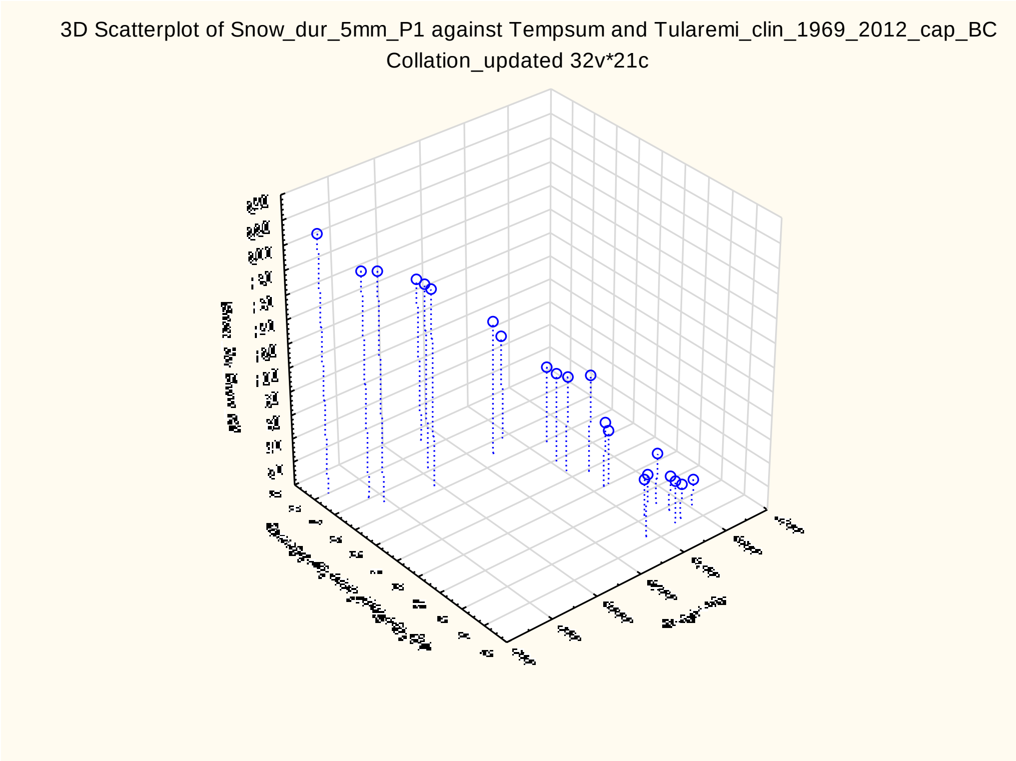

Fig. 12. Correlation between Tularaemia, Temperature sum and snow cover.

DISCUSSION

Borreliosis

The geographical distribution of Borreliosis has been in the southern and coastal areas of Sweden, but after 1990, there was a slight change in geographical distribution towards northern areas. This could indicate that the disease is migrating north. Unfortunately, after 1993 there has been no more county-wise reporting of Borreliosis so it was not possible to follow the trend.

Coherent with previous research and empirical knowledge, Borreliosis was significantly and positively correlated with temperature but contrary to previous knowledge, it was found to significantly negatively correlated to humidity (29, 34). The reason for growth zone and not temperature having a larger influence in the multivariate best subset regression is probably because temperature as well as humidity are reflected in the constitution of growth zone definition. Growth zones as well reflect altitude above sea level which regulates climate and alters in north-west direction across Sweden (52). This also correlates well with Borreliosis being more prevalent in coastal type of climate.

The finding is that Borreliosis significantly correlated to all four climate variables, in such a way that the disease seems favored by a milder climate and has increased in prevalence would suggest that Borreliosis has a potential to increase and migrate north as well in the coming decades.

Borreliosis has as well always been reported on a voluntarily basis and therefore one can assume that the disease is as well largely underreported. It is a clinical diagnosis and the most common symptom is erythema migrans and therefore there is as well a bit of uncertainty involved. Since this disease is common and as well can lead to more severe illness (neuroborreliosis) this could as well imply that there would be more cases of neuroborreliosis in the future.

Tick-borne encephalitis (TBE)

The geographical distribution of the disease prevalence does not seem to have changed over the period but the number of reported cases have increased in Sweden. TBE has as well been reported on a voluntarily basis but became notifiable in 2012. However, since patients get very ill and hospital care is almost always needed, the data is perhaps more reliable. The diagnosis is verified with good certainty through laboratory tests. A weakness, is that the prevalence of TBE-vaccinations has not been accounted for. However, if the trend continues there will be more TBE cases in the future as well in the same geographical locations. This knowledge means that it is in those areas that vaccinations need to be promoted.

Strong significant correlation was found between TBE and humidity which also was the factor having highest degree of explanation for variation in prevalence between counties. This finding is interesting since previous studies confirms that ticks thrive in humid and warm areas and temperature is the climate variable that have been highlighted most so far, when it comes to TBE and sensitivity to climate (28) (53) (fig. 11, appendix fig 15.). More research to understand this result would be needed.

Tularaemia

The prevalence of disease is located to the northern and middle parts of Sweden but it seems that the disease has spread to wider geographical areas and more southwards during the last 15 years. There is an overall increase in prevalence and that the peaks in disease outbreaks are occurring more frequently than before (annexes fig. 3-5), as well described previously (45, 48, 49). The fluctuations in prevalence between years, peaking in cyclic variations, is believed to correlate to the animal reservoir population. The disease prevalence correlates with colder climate and longer lasting snow cover as is coherent with the geographical distribution in the northern counties (49, 54). These finding are as well coherent with other studies for Tularaemia, made on a European scale, that number of disease cases seem to increase with temperature and ecologic zones (54, 55). However, this does not explain why the disease seem to migrate southwards and more studies are needed in collaboration with other fields of expertise for instance in ecology.

Nephropathia epidemica

The prevalence of the diseases is located to the northern parts of Sweden, The disease seems to keep within this geographical area but in 2007 there were in addition many cases in neighbouring more southward counties probably because there as well were exceptionally high number of cases that year. Prevalence is quite steady around a few hundred cases per year but fluctuating as well in a three-year cyclic manner believing to be correlated to vole population. It seems that the prevalence is as well increasing since 1985, the year the disease started being reported as a notifiable disease (annexes fig. 6-9). The disease prevalence correlates with colder climate and longer lasting snow cover as is coherent with the geographical distribution in the northern counties. These finding are as well coherent with other studies for Nephropatia, made on a European scale, that snow over and cold climate during winter seems to increase the disease cases due to better virus ex-vivo survival (56).

Cryptosporidiosis

The majority of cases were reported from the county of Stockholm, followed by Västerbotten, Jämtland, Jönköping, Skåne and Västra Götaland. The cases appear in clusters in different areas for instance in Jämtland 2010 and Västerbotten 2011. These findings correlates to a community-wide outbreak that took place in Östersund in 2010-2011 and in Skellefteå 2011, through contaminated drinking water and is as well believed to increase in the environment due to global warming (57). The opposite finding in this study however were a negative almost significant correlation to temperature. The reason for this finding is difficult to answer but could for instance be a scale problem that outbreaks occur in areas with local changes in temperature.

Leptospirosis

Sporadically occurring with a few cases across Sweden, where most were reported from the county of Stockholm. Even if not significant, the correlations between disease prevalence and temperature was positive and negative to the other climate variables. From earlier studies, it is confirmed that the disease is favoured by warm and humid climate. However, most cases were caught abroad which makes this analysis not totally representative.

Q-fever

There were only 44 cases specified to a county in the reports and of these most cases (38), were reported from the counties of Stockholm, Västra Götaland and Halland (8-10 per county) and almost all of them were reported after 2004, because then the disease became notifiable. The disease was not significantly correlated to any climate variables and the reason for this could be that most of these cases were probably caught abroad (51) so this analysis was not really representative.

Brucellosis

There were only 132 county specific cases in the period 1969-2012 and most of these cases were reported from the counties of Stockholm and Västra Götaland. The cases appear sporadically over the years and with 1-2 cases in different areas of Sweden. However, most cases were caught abroad which makes this analysis not really representative.

Possibly climate sensitive infections

It is well known that Tularemia and Nephropathia, are more common in the northern parts of Sweden, as well as that TBE has a higher prevalence in the region of Stockholm, the southern and south-western parts of Sweden. Borreliosis occurs everywhere, but to a lesser extent in the north. However, the reason for this specific geographical pattern of these diseases is not clear, but from the findings in this study it seems that they strongly correlate to specific climate variables in these areas, since climate is very different in different parts of Sweden due to its long climatic gradient from south to north and as well coastal climate and mountainous climate in the north-west. These findings could therefore suggest that these diseases are in fact climate sensitive and that climate could play an important role in explaining their geographical distributions.

For Cryptosporidiosis, Leptospirosis, Brucellosis and Q-fever no such correlations were found. Nevertheless, these diseases and the information collected is important for further studies, since for instance It is believed that Leptospirosis is one of the emerging infectious diseases due to changes in climate, animal husbandry and people movement because of large outbreaks that have occurred in recent decades around the world (58). Leptospirosis can cause outbreaks in relation to flooding which is not uncommon due to climate change and therefore it is an important disease that needs to be considered. Cryptosporidiosis is as well important since it causes community-wide outbreaks from time to time due to contaminated drinking water and is believed to correlate to global warming. Q-fever is seldom diagnosed in Sweden and is probably underdiagnosed but of interest because of its transmission via mosquitos to humans. Brucellosis is not uncommon among carribous (wild reindeers) in Canada and sometimes occurring in Sweden, and is a risk to people working with reindeer herding or otherwise closely with animals. Even though no cases of Anthrax have been reported in Sweden during this period (1969-2012), outbreaks in close countries like Russia have occurred in Siberia and spread to reindeers and one human case due to thawing of the tundra due to global warming.

Many other factors are as well in play influencing the spread and distribution of the diseases, such as preferred habitats for vectors and reservoir animals. Such information can for instance indicate where ticks would be in abundance but not tell the prevalence of the bacteria B. burgdorferi or the TBE virus within the tick population. Both pathogens are spread by the tick Ixodes ricinus but still Borreliosis are more widespread. Complex ecological factors are as well in play regarding Tularaemia and Nephropathia of many are still unknown. However, climate is believed to play a role on these factors as well. Therefore, it is of interest to link the prevalence of diseases directly to climate variables which was the aim of this study.

Other confounding factors could be socio-economic factors, awareness of health authorities, or more frequent contacts with ticks due to agricultural activities etc. Probably depending on disease and geographical setting the influence of these could vary. There are studies that have considered this regarding TBE in the Komi Republic in northern Russia and not found to have any particular role in increased incidence rates of TBE. It was neither likely that TBE diagnostics suddenly improved in this particular region (28).

If these diseases will migrate with a changing climate is early to know, but it seems that Borreliosis has made its way northward along the eastern coast, where the climate has become increasingly milder.

Strengths of the study

Even though previous studies have confirmed associations between these diseases and climate, this study is quite unique in the way data has been collected from 44 years back and mapping the prevalence for each year and each of the 21 counties in Sweden and using ArcGIS to process data in the form of maps displaying information about climate variables across Sweden together with the prevalence data of diseases at county level. This approach has enabled the study to scientifically and statistically show the strength of the correlations between these diseases and climate variables at county level across Sweden. The analysis also indicates what types of climate variables that can best describe the variance in prevalence between counties for each disease and as well to a high degree of explanation.

The climate proxy variables chosen were standard climate variables that are being used by SMHI, and hence very solid and trustworthy as a source of climate information and proxy selection. In other studies, other variables have been used as well, for instance precipitation and NDVI (Normalized Difference Vegetation Index). NDVI indicates the amount of living vegetation and is an effect of humidity, soil fertility etc., that can be observed from satellites over large areas, however this index shows great local variabilities and is not a good measurement of climate per se and is not actually a climate proxy. Precipitation is also a climate proxy used in these kinds of studies. However, in this case, humidity was chosen instead because humidity incorporates precipitation in its own. Precipitation also show large variability geographically and is not very stable as a climate proxy.

Transferability of the study

Studies like this one could be conducted in the same way in any region or country in the world as long as there is available data on climate variables and disease prevalence that can be located geographically.

Global health relevance

Emerging infectious diseases is believed to be an increasing global health burden due to climate change and so also in the Arctic region. Even though this study focused on Sweden, it is part of a larger ongoing project CLINF, which aims at addressing this issue in the Arctic region including Sweden. These results will be analysed together with data from other countries to map the situation in the Arctic. More knowledge regarding the effects of climate change on the emergence of infectious diseases is needed since only a few diseases are being recognized as sensitive to climate (annexes fig. 16.)

Practical implications

Knowledge regarding the effects of climate on the spread of infectious diseases will most likely become more important due to global warming and weather hazards like flooding. To find out if these diseases are sensitive to changes in climate, is important to try and predict where outbreaks or epidemics can occur in the future. This is of value for preparing health care institutions as well as the public and to know which areas or counties are in need for interventions.

CONCLUSIONS AND RECOMMENDATIONS

In this study, it was found that disease prevalence seems to increase for Borreliosis, TBE, Tularaemia and Nephropathia within the period that data was analyzed, ranging from 10-44 years depending on disease between the years 1969-2012. There might be a trend of Borreliosis migrating northwards. Tularaemia has also spread to wider geographical areas and more southward, whereas TBE and Nephropathia seem to keep within their geographical areas.

Strong and significant correlations between disease prevalence of Borrelia, TBE, Tularaemia and Nephropathia, and climate, were found based on the data used ($p < 0.004$). It was also demonstrated that the variation of distribution among different counties in Sweden could be explained to a high degree (49-92%), by certain climate variables, depending on disease at this scale.

It seems that climate could play an important role in explaining an increase in prevalence and likely changes in distribution for Borreliosis since it seems to correlate with a milder climate over time and the geographical distribution correlate significantly to those types of climate variables. This would suggest that Borreliosis has a potential to increase and migrate north as well in the coming decades. The prevalence of distribution of Tularaemia and Nephropathia across counties correlated to a colder climate suggests that distribution of these diseases is more sensitive to these climate variables. However, the finding that Tularaemia is spreading more southward does not match with colder climate, but still it is most prevalent in the northern counties. TBE seems as well to keep to its specific geographical areas over this time.

To what extent the climate is driving the prevalence of these diseases is unclear but it is believed to have an important impact, even though many other factors are influencing as well. By showing the strong correlations between disease prevalence and geographical distribution of these diseases and relating to the proposed definition of climate sensitive infections that was used, these diseases could be considered being ‘climate sensitive’.

All of the diseases, can lead to severe illness with long-term complications, hospitalizations, loss of life quality, as well individual and societal costs. The bacterial infections are treated with antibiotics which is important to consider when antibiotic resistance is becoming an increasing threat. All of these reasons advocate for the importance of good surveillance system and collaboration between the Northern countries would be preferred since these disease cross borders. It is recommended to conduct further studies and as well in collaboration with other fields of discipline for the greater understanding of what is driving these diseases, to build more knowledge for risk management and preparedness for decision makers.

ACKNOWLEDGEMENTS

I want to thank my supervisor Professor of infectious diseases Birgitta Evengård for her expertise and advise in the field and for initiating me to this interesting and important topic together with prof. assoc. Tomas Thierfelder, who guided me in the methodological and statistical work that made this analysis possible. I also want to thank my co-supervisor dr. Helena Nordenstedt for her professional support and positive spirit, as well as dr. Anna Omazic from SVA together with the other members of the CLINF-team.

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ANNEXES

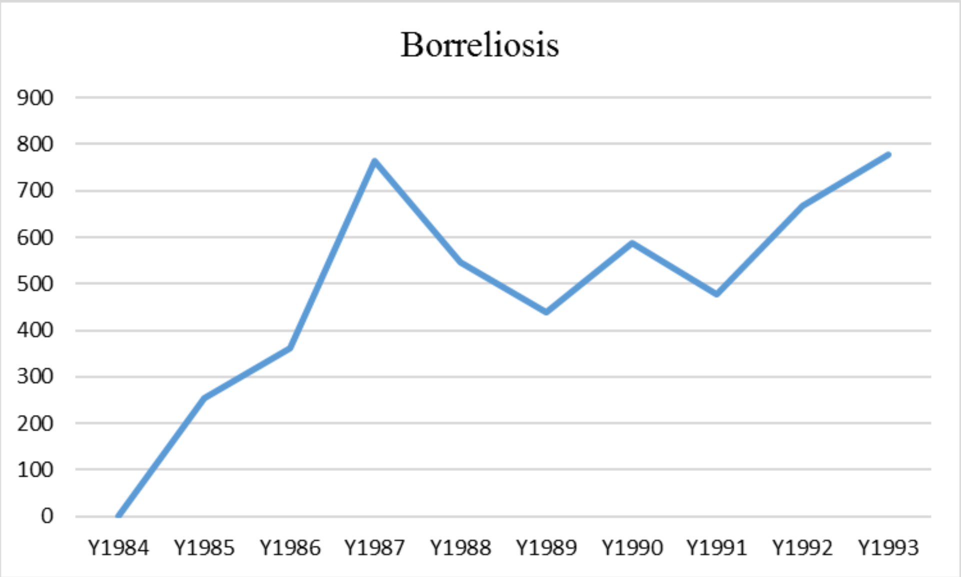

Fig. 1. Prevalence of Borreliosis per year in Sweden 1984-1993.

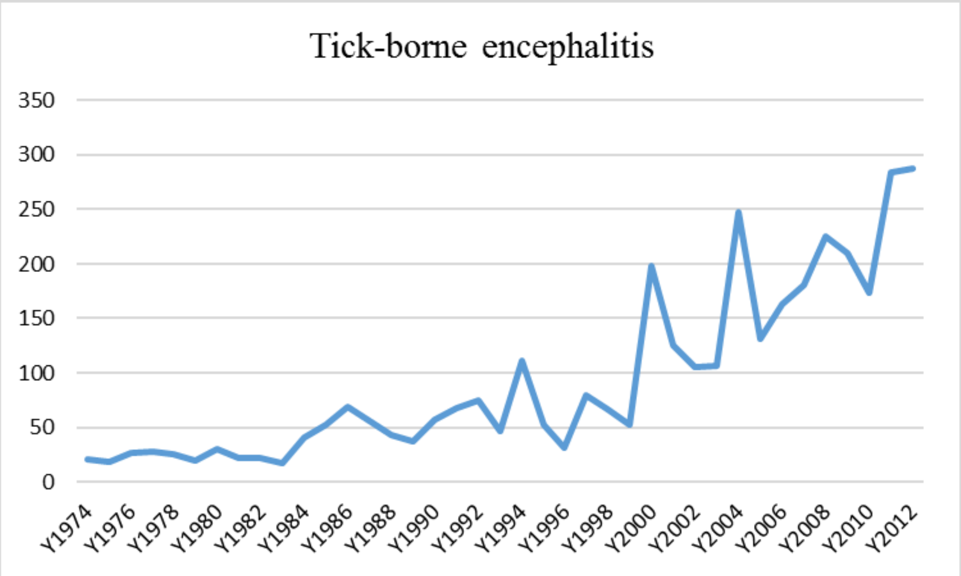

Fig. 2. Prevalence of TBE per year in Sweden 1974-2012.

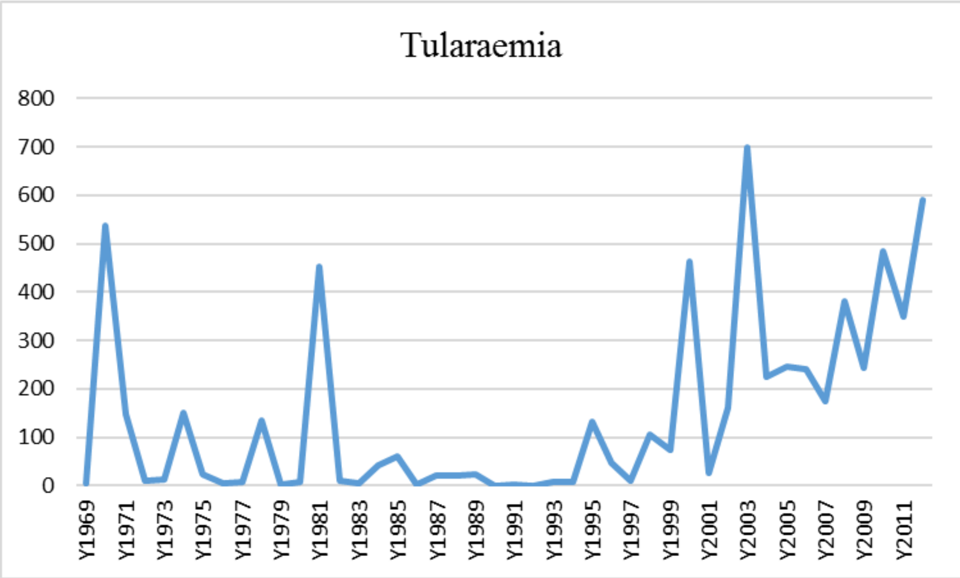

Fig. 3. Prevalence of Tularaemia cases per year in Sweden 1969-2012.

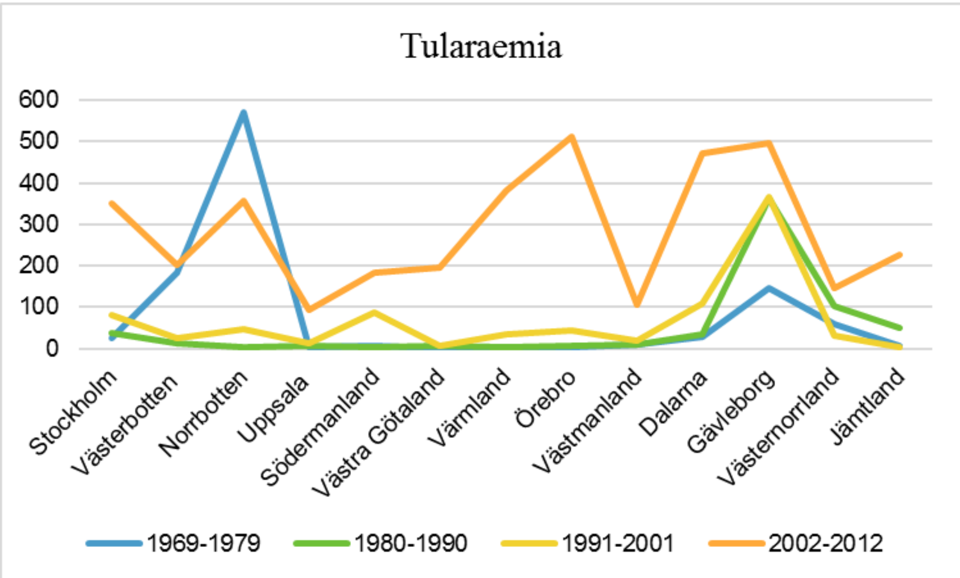

Fig. 4. The counties with highest prevalence of Tularaemia, in different periods.

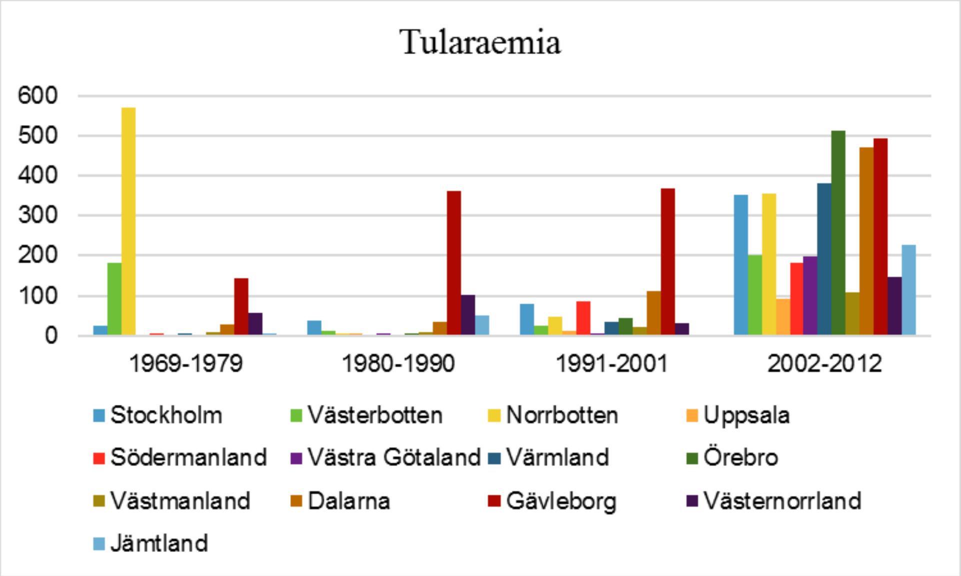

Fig. 5. The counties with highest prevalence of Tularaemia, in different periods presented with staples.

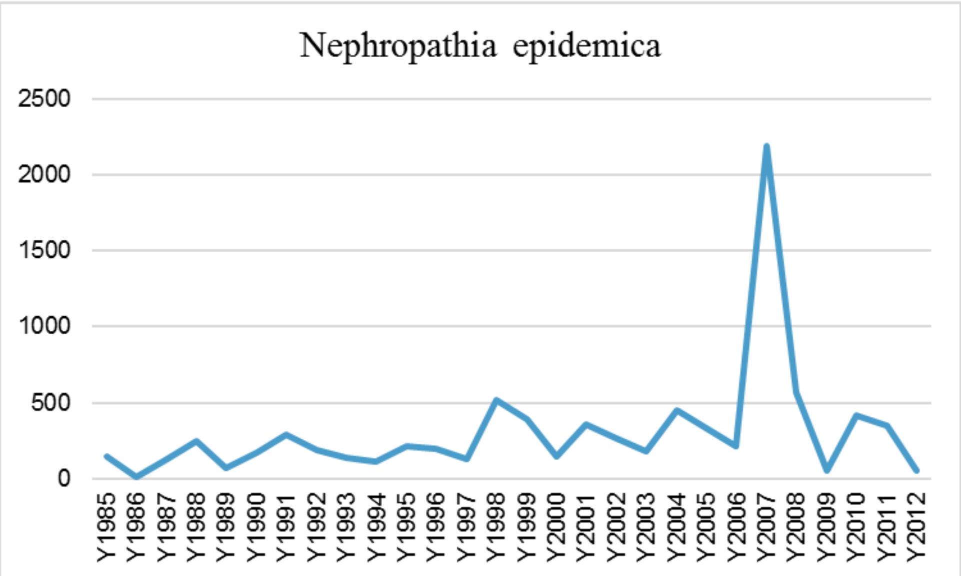

Fig. 6. Prevalence of Nephropathia per year in Sweden 1985-2012.

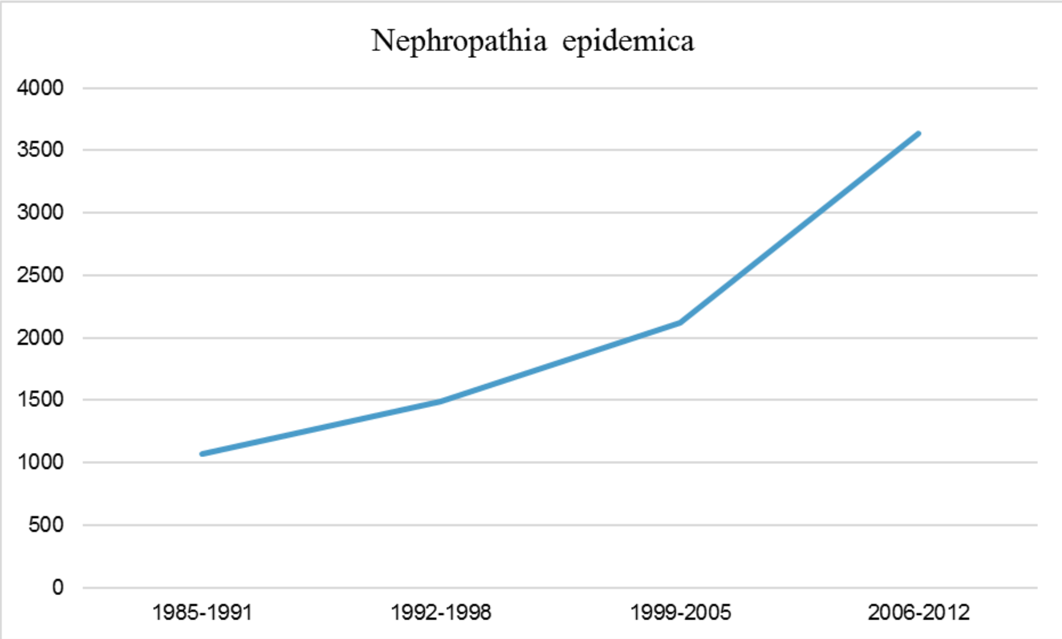

Fig. 7. Prevalence of Nephropathia in Sweden 1985-2012.

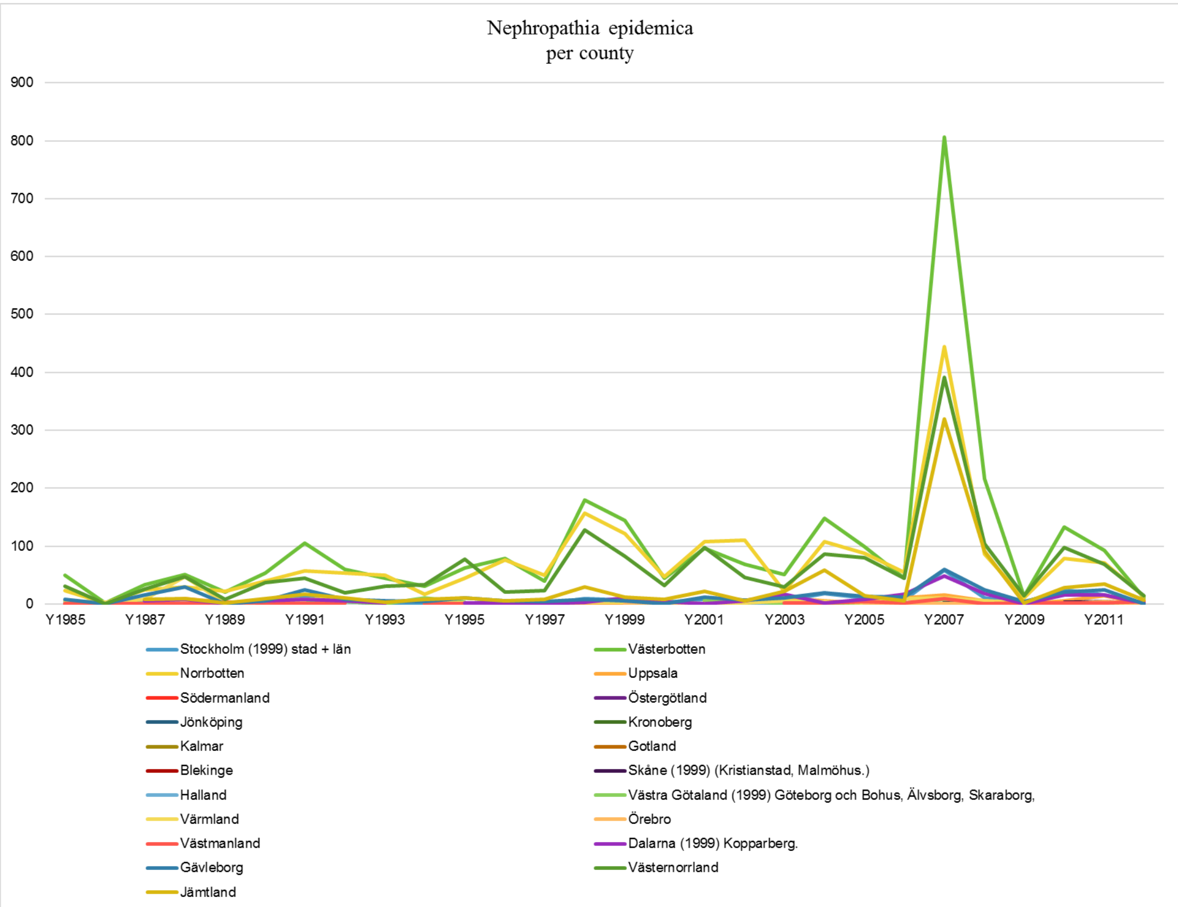

Fig.8. Prevalence of Nephropathia per county 1985-2012.

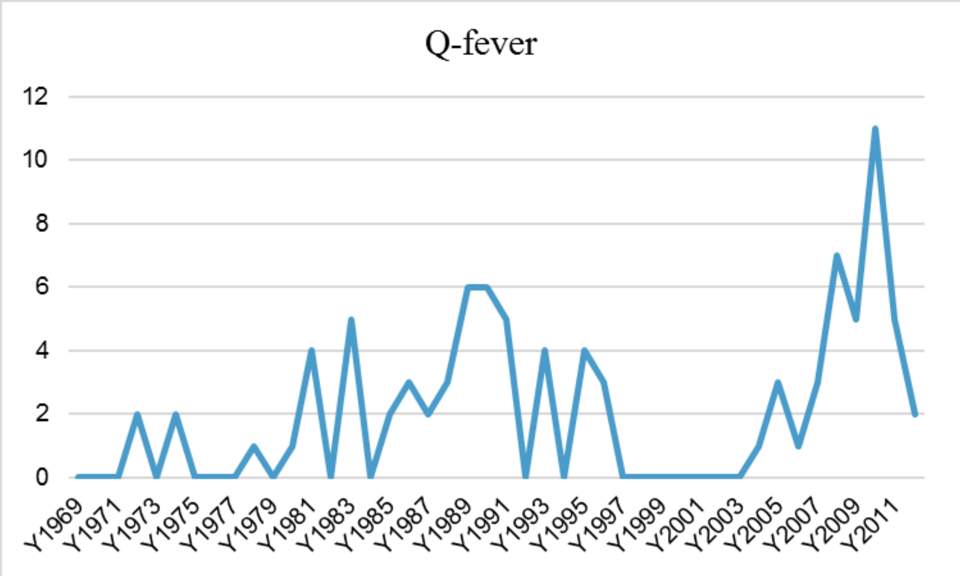

Fig. 9. Prevalence of Q-fever in Sweden 1969-2012.

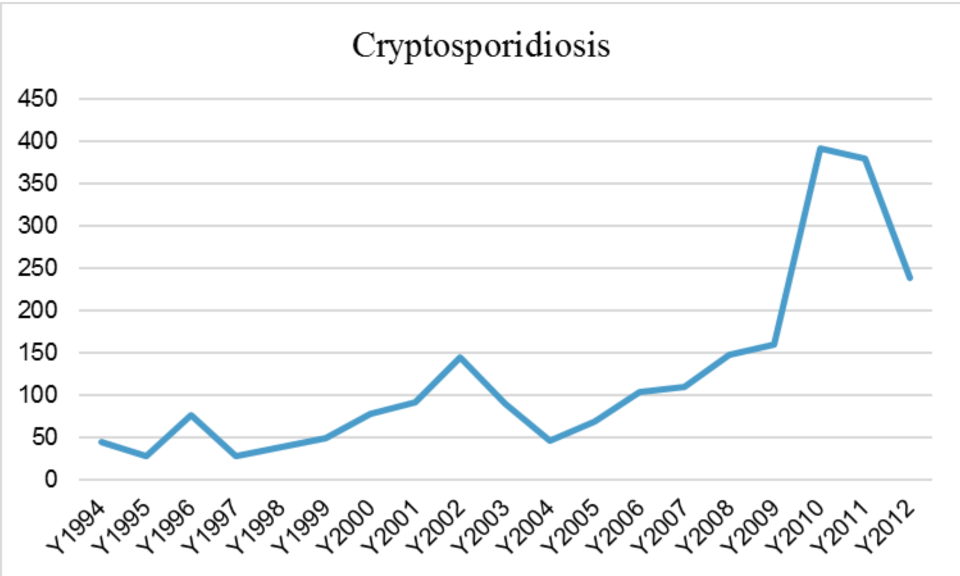

Fig. 10. Prevalence of Cryptosporidiosis in Sweden 1994-2012.

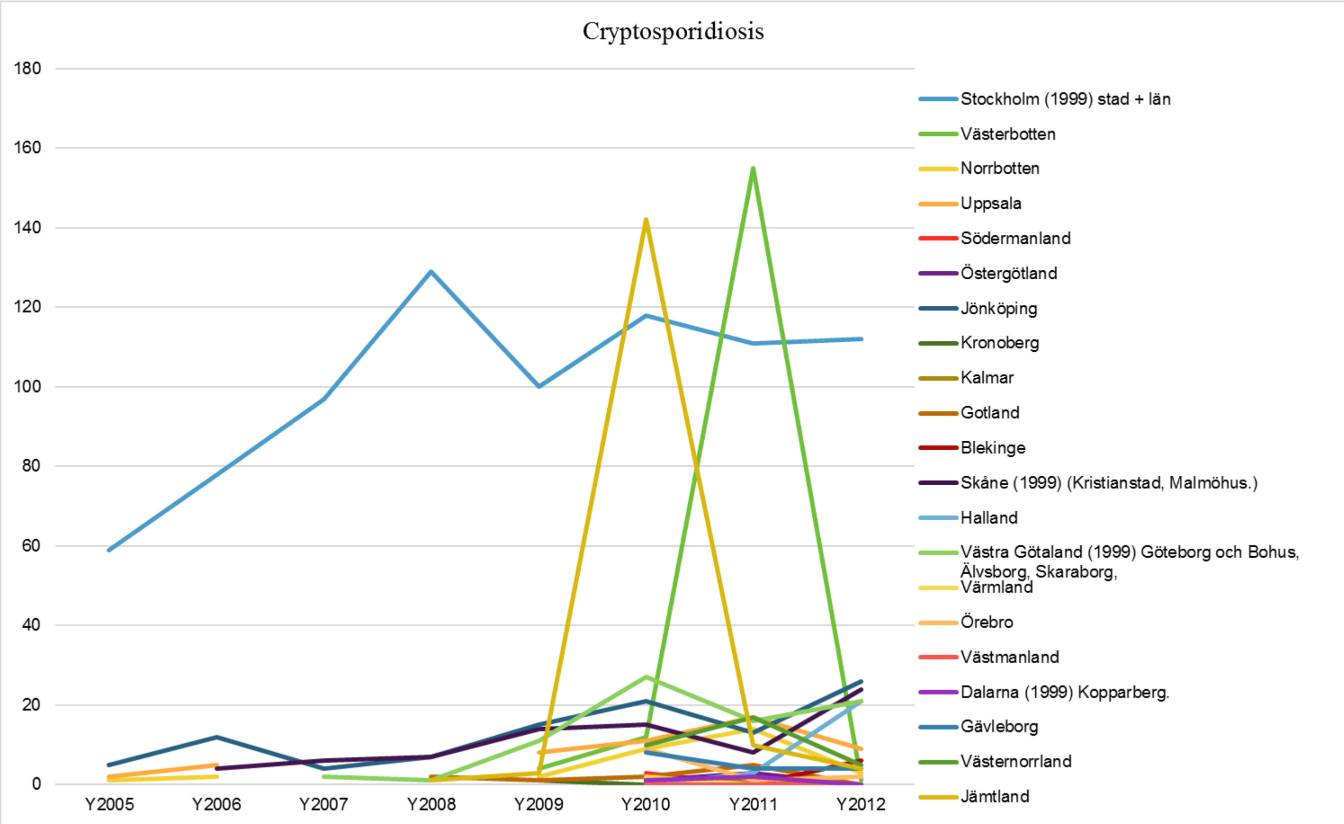

Fig. 11. Prevalence of Cryptosporidiosis per county in Sweden and year 2005-2012.

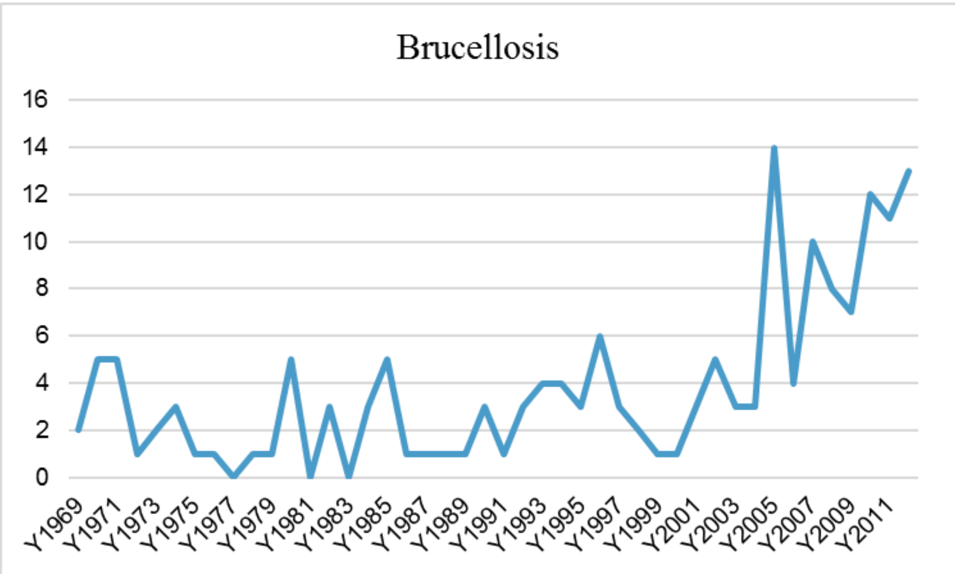

Fig. 12. Prevalence of Brucellosis in Sweden per year 1969-2012.

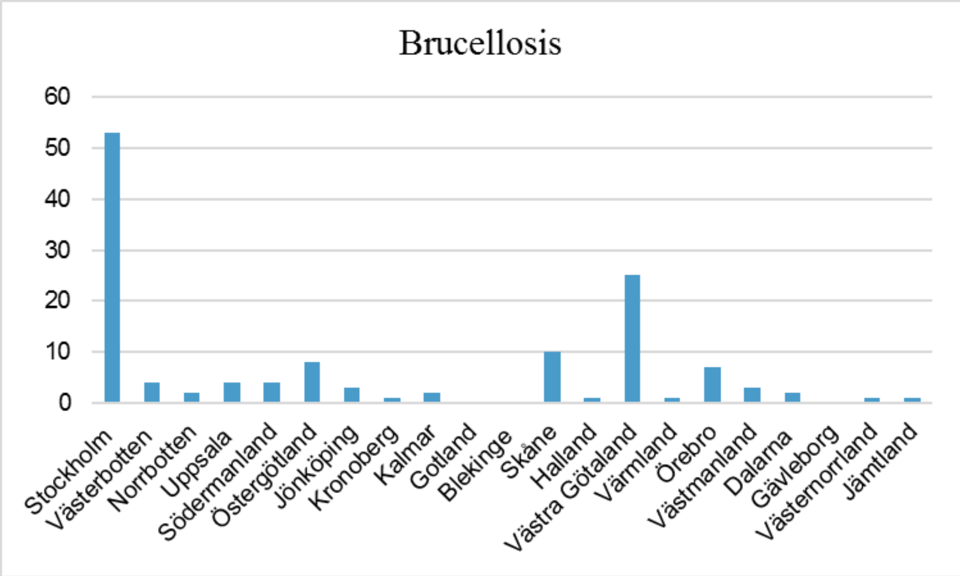

Fig. 13. Prevalence of Brucellosis per county in Sweden, cumulated numbers 1969-2012.

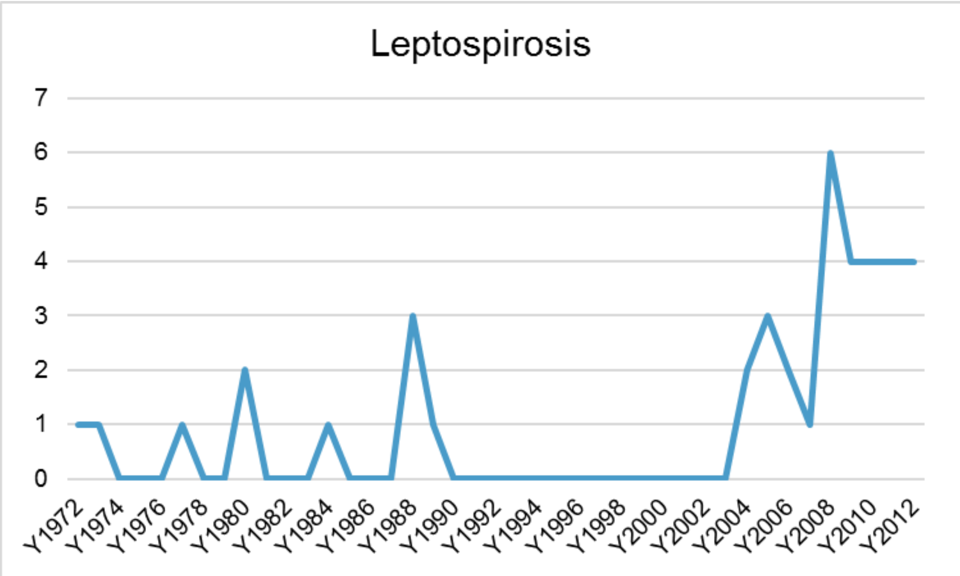

Fig. 14. Prevalence of Leptospirosis in Sweden 1972-2012.

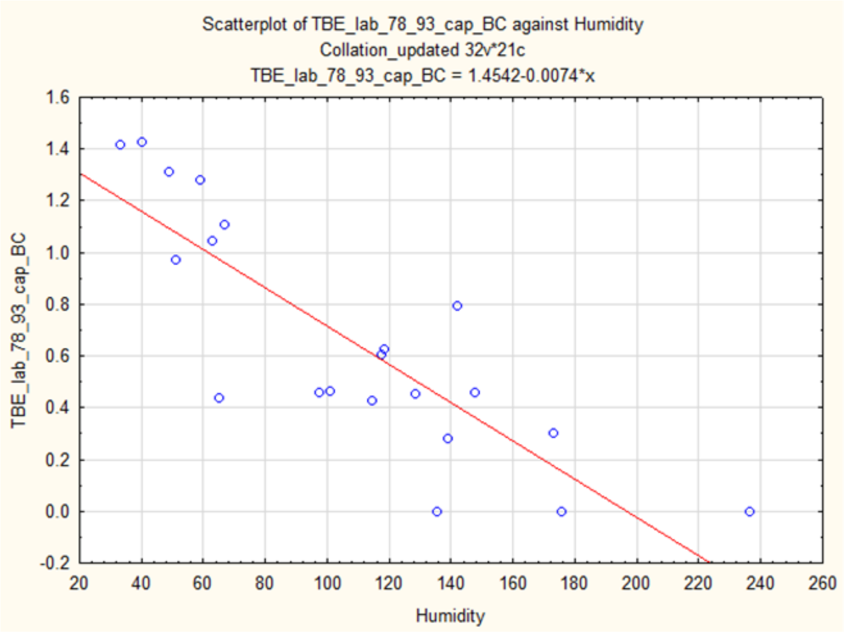

Fig. 15. Correlation between TBE and humidity after Box-Cox transformation.

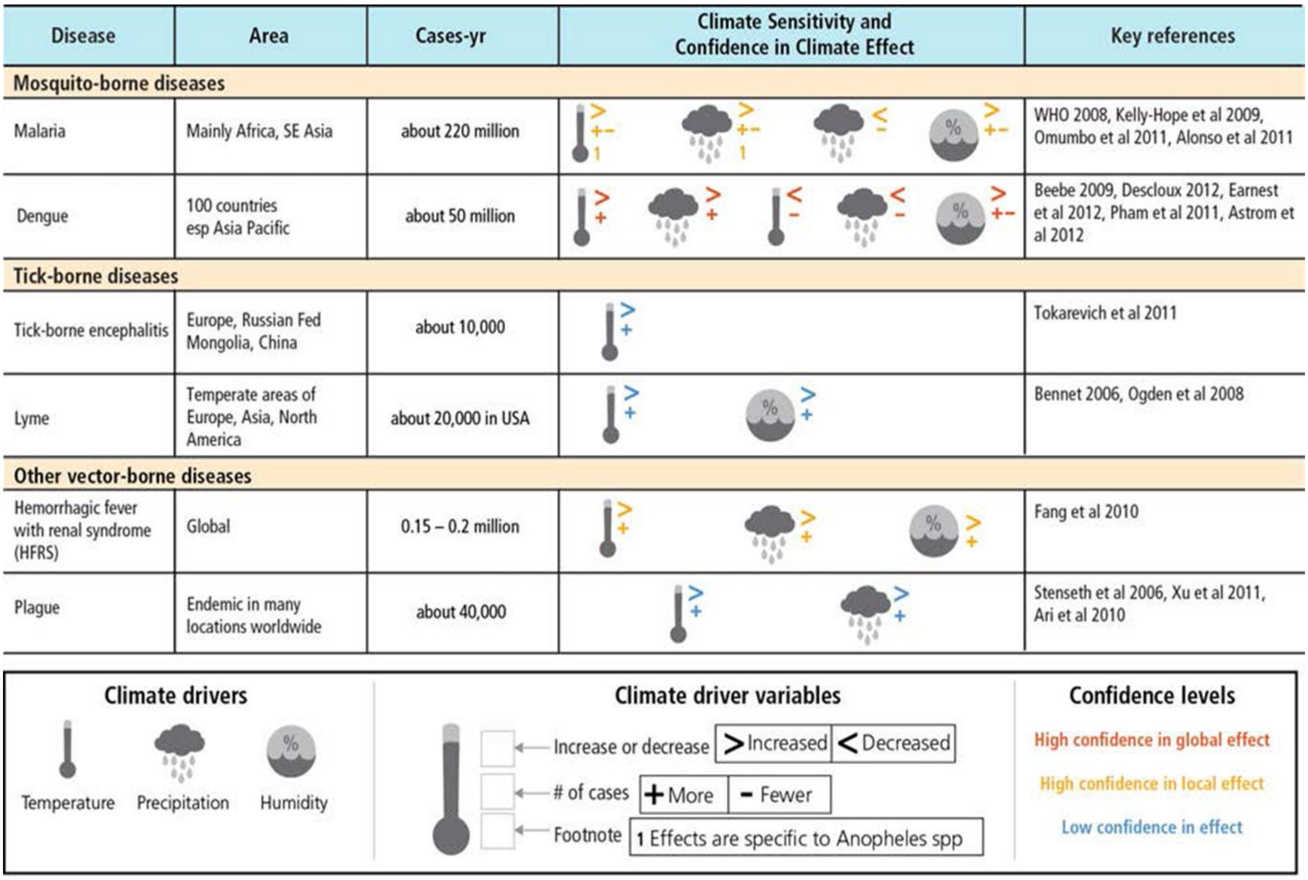

Fig. 16. The association between different climatic drivers and the global prevalence and geographic distribution of selected vector-borne diseases observed over the period 2008-2012. Among the vector borne diseases shown here, only dengue fever was associated with climate variables at both the global and local levels (high confidence), while malaria and hemorrhagic fever with renal syndrome showed a positive association at the local level (high confidence) Source: IPCC ch. 11, 2014.