



Climate variability and outbreaks of infectious diseases in Europe

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Several studies provide evidence of a link between vector-borne disease outbreaks and El Niño driven climate anomalies. Less investigated are the effects of the North Atlantic Oscillation (NAO). Here, we test its impact on outbreak occurrences of 13 infectious diseases over Europe during the last fifty years, controlling for potential bias due to increased surveillance and detection. NAO variation statistically influenced the outbreak occurrence of eleven of the infectious diseases. Seven diseases were associated with winter NAO positive phases in northern Europe, and therefore with above-average temperatures and precipitation. Two diseases were associated with the summer or spring NAO negative phases in northern Europe, and therefore with below-average temperatures and precipitation. Two diseases were associated with summer positive or negative NAO phases in southern Mediterranean countries. These findings suggest that there is potential for developing early warning systems, based on climatic variation information, for improved outbreak control and management.

Despite a limited knowledge primarily focused on vector-borne pathogens^{1–3}, climate change is commonly predicted to impact the transmission of infectious diseases and their geographical distribution^{4,5}. This may be due to the impact of changes in mean temperature or rainfall⁶, and has been illustrated through statistical evaluation of pathogen dynamic trends and shifts in climatic factors^{7,8}.

Climate variability may also affect outbreaks of infectious diseases⁹. Increase in the transmission of different vector-borne diseases such as Murray Valley encephalitis, bluetongue, Rift Valley fever, African horse sickness, Ross River virus disease, visceral leishmaniasis, dengue and malaria^{5,10–21} have been linked to the El Niño Southern Oscillation (ENSO, an intermittent inversion of Pacific Ocean thermal gradients) driven climate anomalies^{22,23}. Associations with the North Atlantic Oscillation (NAO), another index of climate variability, have also been investigated for several other infectious diseases including Lyme borreliosis²⁴, tularaemia²⁵, and measles²⁶.

Although climate change is a global phenomenon, its effects vary by location, making regional studies of potential impacts important. In Europe, several studies have provided important insights into the consequences of climate change on infectious diseases and evidence for resulting epidemiological changes in individual diseases, such as bluetongue²⁷. However, few studies have taken a comparative approach considering effects upon multiple diseases together^{28,29}, and even fewer have explored the potential links between climate variability and disease outbreaks in Europe as an entity³⁰. While the ENSO index does not seem to be an accurate index of climate variability in Europe, the NAO does^{31,32}.

Positive and negative phases of the NAO reflect patterns of pressure anomalies and are associated with changes in temperature and precipitation patterns extending from eastern North America to western and central Europe. Strong positive phases of the NAO tend to be associated with above-average temperatures and precipitation across northern and central Europe, and above-average temperatures and below-average precipitation over Mediterranean countries (Southern Europe, North African and Middle-Eastern countries). Opposite patterns of temperature and precipitation abnormalities are typically observed during strong negative phases of the NAO (www.cpc.ncep.noaa.gov). However, this pattern seems to be more pronounced in winter and climate variability in Mediterranean countries appears to be linked to the Indian Monsoon³³.

Research covering Europe is limited compared, for example, to the USA. The association between the NAO and the annual incidence rate of 13 viral, bacterial, and protozoan human diseases in the Czech Republic from 1951 to 2003 was investigated by Hubálek³⁰. According to his analyses, toxoplasmosis and infectious mononucleosis were significantly and positively correlated and leptospirosis was negatively correlated with the NAO. For toxoplas-



mosis, it was proposed that the warmer winter associated with a positive NAO, lagged one year (meaning it occurred one year later), would enhance populations of rodents, the intermediate hosts of the protist *Toxoplasma gondii*. For leptospirosis, higher precipitation in negative NAO years, lagged two years, would result in increasing populations of field rodents, the main reservoir of the bacteria *Leptospira interrogans*³⁰. A similar conclusion was reached for hantavirus outbreaks in the USA in relation to El Niño (ENSO), with heavy rains or warm winters boosting mast seeding and thus favouring rodent populations, the reservoirs of hantavirus³⁴. Similar associations were also found for hantavirus in Belgium³⁵.

This study aimed to test the influence of NAO variability upon outbreak occurrences of several infectious diseases across Europe observed over recent decades. Interpretation of the results would also need to consider that non-climate related factors such as an increase in disease reporting over time may be important contributors to observed disease trends.

Results

For eleven diseases, the occurrence of outbreaks was significantly related to the NAO monthly index. These include adenovirus infection, measles, Q fever, Aseptic viral meningitis, enterovirus infection, gastroenteritis, typhoid fever, tularaemia, hantavirus infection, hepatitis A, and shigellosis. A twelfth disease, trichinosis, was associated with the NAO monthly index at a 94% level of statistical certainty. The remaining disease, tuberculosis, was not associated with NAO monthly index.

Mean health expenditure was significantly associated with year (Fig. 1C) (Adjusted $R^2 = 0.967$, $F_{1,47} = 1390$, $P = 0.00001$), as was per capita GDP (Adjusted $R^2 = 0.995$, $F_{1,47} = 9254$, $P < 0.00001$). Per capita GDP and per capita health expenditure across European countries were significantly correlated (Adjusted $R^2 = 0.9598$, $F_{1,47} = 1148$, $P < 0.00001$). We treat per capita health expenditure as a proxy for the effectiveness of surveillance reporting.

We used Generalized Linear Modelling (GLM) to model the association of monthly NAO on the number of outbreaks using smoothed spline fitting function. The best model was selected using the AIC criterion for each infectious disease (ID) studied, given in Table 2.

Of the diseases found to be associated with NAO indices, seven (adenovirus infection, measles, Aseptic viral meningitis, Q fever, gastroenteritis, tularaemia, shigellosis and trichinosis) were associated with the winter positive phases in northern Europe (from November to February), therefore with above-average temperatures and above-average precipitation.

Two diseases were associated with negative NAO at other times of year: enterovirus infection showed an association with the negative summer NAO index in northern Europe; and hantavirus infection was associated with the negative spring NAO index in northern Europe.

Typhoid fever showed an association with positive winter NAO index in southern Europe, which corresponds to below-average temperature and below-average precipitation. Hepatitis A showed an association with negative winter NAO index in southern Europe with above-average temperatures and above-average precipitation.

Discussion

For the majority of the diseases, the detrended number of outbreaks was significantly related to the positive autumn and winter NAO monthly index values in southern countries, or to the negative autumn and winter NAO monthly index values in southern countries. The observed differences in results between northern and southern Europe are in accord with the differential influences of the NAO on Europe, particularly in winter³¹, although climate variability in Mediterranean countries is also influenced by the Indian monsoon³³.

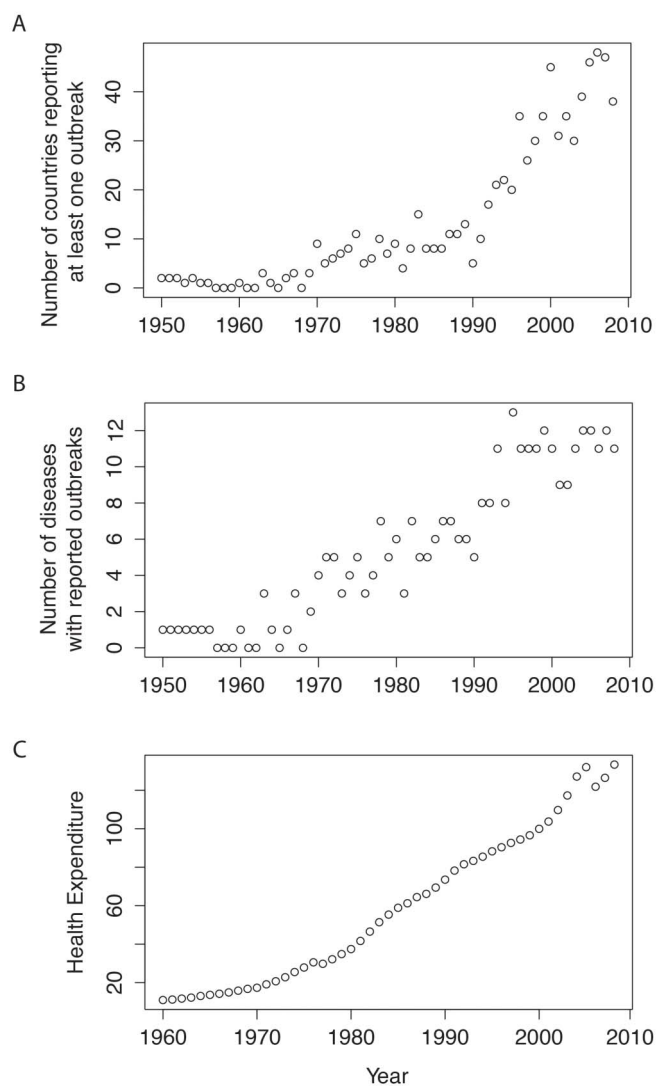


Figure 1 | A. changes in the number of countries reporting at least one outbreak of the diseases of interest in this study from 1950 to 2009 (data from GIDEON, see M&M). B. Changes in the number of diseases having at least one reported outbreak from 1950 to 2009 (data from GIDEON, see M&M). C. Evolution of mean health expenditure in Europe from 1960 to 2009 (data from OECD, see M&M) (base 100 = health expenditure in 2000).

Associations between the occurrence of different infectious diseases and climate variables have been reported worldwide. Evidence of changes in influenza risk attributable to climate variability comes from Choi et al.⁴⁹, who found a lower mortality risk due to influenza during El Niño events compared to periods of normal weather. Sultan et al.⁵⁰ showed that climate variability can also affect the occurrence of meningococcal meningitis, with a correlation found between the onset of meningococcal meningitis epidemics and the winter maximum of an atmospheric index.

In this study, outbreaks of adenovirus infection were associated with positive values of the NAO, which is consistent with other findings in the literature, in which increased precipitation has been reported as boosting the risk of adenovirus infection³⁹. The study also found associations between Q fever and measles with positive values of summer NAO, which are in accordance with previous observations at country level for Q fever in the Netherlands⁴¹ and measles in England and Wales²⁶.

We found three water-borne diseases (enterovirus infection, viral gastroenteritis and shigellosis) were associated with the positive



Table 1 | Infectious diseases and their causative agents investigated in this study with information on transmission routes and potential climate influences on transmission

Infectious disease	Agent	Routes of transmission	Climate influences on transmission	Statistical test	References
Adenovirus	RNA Virus	Air-borne	Correlation between adenovirus infections and precipitation in Brazil	Yes	39
Measles	RNA Virus	Air-borne	Infection cases increased with negative NAO values in England and Wales	Yes	26
Meningitis (viral)	RNA Virus	Air-borne	Outbreak of viral meningitis after El Niño event in Djibouti	No	40
Q fever	Bacterium	Air-borne	Wet soil is associated with decreased risk of Q fever infection in Netherlands	Yes	cited in. 41
Tuberculosis	Bacterium	Air-borne	Seasonal trend in epidemics in Spain, with higher incidence during summer and autumn	Yes	42
Enterovirus	RNA Virus	Water-borne	Increased presence of enteroviruses with heavy rainfall events associated with El Niño in an estuary in Florida	Yes	43
Gastroenteritis -viral	RNA Virus	Water-borne	High temperature and low humidity increase the incidence of rotavirus diarrhoea in Dhaka	Yes	44
Typhoid fever	Bacterium	Water-borne	Increased temperature and precipitation is associated with incidence increase in Nepal	Yes	Unp. report
Nephropathia epidemica (hantavirus infection)	RNA Virus	Air-borne	Increase incidence with increased rainfall associated with strong El Niño in U.S.A.	Yes	34
		Rodent-borne	High summer and autumn temperatures, 2 years and 1 year respectively before NE occurrence, relate to high NE incidence in Belgium	Yes	35
Tularaemia	Bacterium	Vector-borne	2°C increase in monthly average summer temperatures associated with increases in outbreak durations in Sweden	Yes	25
			Low NAO index were associated with high numbers of human cases of tularaemia 2 year later in Sweden	Yes	52
Hepatitis A	RNA Virus	Food-borne	Virus survival increases at reduced temperatures and sunlight (ultraviolet) in U.S.A.	No	45
			Increase incidence warmer and drier conditions associated with El Niño event in Australia	Yes	46
Shigellosis	Bacterium	Food-borne	No association between incidence and strong NAO in Czech Republic	Yes	30
Campylobacter	Bacterium	Food-borne	European and northern American countries with milder winters have peaks of infection earlier in the year. The peak of infection is associated with high temperatures 3 months previously	Yes	47
Trichinosis	Nematode	Food-borne	Warmer temperatures and longer summers increase the number of amplification cycles for parasites and lead to longer summer hunting seasons in Arctic regions	No	48

summer values of the NAO index in northern Europe (wet climate), whereas typhoid fever was correlated with negative values of the NAO in northern Europe and the positive values of the NAO in southern Europe (dry climate). This confirms previous work suggesting that water-borne diseases are affected by climate variability; more specifically heavy rainfall events affecting enterovirus infection in arid tropical regions⁴³, and periods of high temperature affecting viral gastroenteritis⁴⁴ and typhoid fever (Table 1). Further, bacillary dysentery has previously been shown to be affected by climate variations and particularly El Niño⁵¹.

Hantavirus outbreaks in northern Europe were associated with a negative spring NAO with two years lag, which is in agreement with the findings of Tersago et al.³⁵ in Belgium. Heavy rains or warm winters and springs boost mast seeding and, with a certain time lag, favour rodent populations as reservoirs of hantavirus.

Palo et al.⁵² showed that negative values of the NAO index were associated with high numbers of human cases of tularaemia in Sweden. Epidemiological investigations of summer outbreaks of tularaemia in two localities in Sweden showed complex associations with landscape changes (wetland restoration) and recreational activities⁵³. We found the same pattern in our analysis, however at the level of all northern European countries.

Warmer temperatures have been hypothesized to increase the number of amplification cycles for food animal parasites such as *Trichinella* species, which may explain the positive association between the winter NAO phase and trichinosis outbreaks in northern Europe. An alternative explanation might be that these climatic conditions would lead to longer summer hunting seasons and consequently to an increased exposure of humans to the pathogens⁵⁴. The same may also apply to tularaemia. However,



Table 2 | Results of generalized linear regression analyses on detrended infectious disease outbreaks in relation to detrended monthly values of the NAO (North Atlantic Oscillation) (from NAO1: January to NAO12: December) of each year or with one year lag. Best models were selected using a backward-stepwise procedure using AIC and Bonferroni corrections, with only significant, or close to significant ($p < 0.08$) explicative variables indicated

Diseases	Location	Independent variable	Deviance	Sign (P)
Adenovirus	Northern	NAO11	0.76	+0.1 (0.06)
Measles	Northern	NAO8	2.13	+0.3 (0.05)
	Southern	NAO10	0.98	-0.1 (0.03)
Aseptic viral Meningitis	Northern	NAO10	3.82	+0.3 (0.03)
Q fever	Northern	NAO7 (year lag)	<0.01	+0.001 (0.05)
	Southern	NAO12 (year lag)	2.19	-0.2 (0.02)
Tuberculosis				
Enterovirus infection	Northern	NAO6 (year lag)	0.61	+0.1 (0.01)
Gastroenteritis	Northern	NAO9 (year lag)	1.94	+0.02 (0.06)
	Southern	NAO12 (year lag)	1.38	-0.3 (0.03)
Shigellosis	Northern	NAO11 (year lag)	2.42	+0.2 (0.009)
	Southern	NAO5 (year lag)	1.64	-0.2 (0.03)
Typhoid fever	Northern	NAO6 (year lag)	17.15	-0.6 (0.003)
	Southern	NAO12 (year lag)	0.76	+0.2 (0.01)
Hantavirus infection	Northern	NAO12 (year lag)	<0.01	-0.001 (0.005)
	Southern	NAO12 (year lag)	1.27	+0.3 (0.08)
Tularaemia	Northern	NAO3 (year lag)	1.51	-0.2 (0.04)
Hepatitis A	Northern	NAO7 (year lag)	5.41	-0.4 (0.06)
	Southern	NAO9 (year lag)	2.56	-0.2 (0.03)
Trichinosis	Northern	NAO1	<0.01	-0.001 (0.06)

in Europe, most trichinosis infections are associated with wild boar being eaten undercooked and any association with climatic parameters should be evaluated whilst also taking account consumer behaviour.

Climate variability may have a direct impact on pathogens via effects on survival outside of the host, and dissemination. Climate variability may also act indirectly, by acting on other factors which affect the chances of transmission, such as changes in social behaviour, as mentioned above for measles. As emphasized by Randolph⁵⁵ and Evengard & Sauerborn⁵⁶, any increase in disease occurrence can be due to multiple factors. The factors that are most important are not always easy to determine. For infectious mononucleosis for example, which is caused by EB herpesvirus and spreads from person to person by an oropharyngeal route, increasing ambient temperatures are thought to encourage higher than normal outdoor activity and social interactions⁵⁰, which may then increase virus transmission. Similarly, the range of diseases encompassed in this study is likely to be affected by multiple factors, amongst which any NAO variation may act directly on the pathogen or indirectly on the transmission cycle.

Our findings confirm that NAO conditions could have significant implications for European public health. The statistical influences of NAO conditions on outbreak occurrence concern all types of transmission routes: air-borne, water-borne, vector-borne and food-borne. We also showed that increases in outbreak occurrences over the last 50 years for all the diseases investigated are largely related to improvements in disease detection and therefore better reporting. Alternative explanations for the increase are factors linked to disease (re)emergence, increasing urbanization, or immigration from endemic countries⁴², none of them have not been accounted for within this study. For a given disease, a threshold above which policy measures would be engaged could be defined taking into account the economic impact of outbreak occurrence for example. Our results suggest that NAO index may be useful for an early warning system (EWS) at the European regional level, although additional analyses on a selection of highly climate-sensitive diseases should be undertaken.

Methods

Disease outbreaks. Data on 2,058 outbreaks from 114 epidemic infectious diseases (ID) which occurred in 36 countries during the period 1950 to 2009 were extracted from the Global Infectious Diseases and Epidemiology Network (GIDEON) database (www.gideononline.com). A disease outbreak was defined in GIDEON, following the definition of the World Health Organization, as the occurrence of cases of disease in excess of what would normally be expected in a defined community within the current study. GIDEON is a medical database that provides continually updated data on the regional presence and epidemic status of pathogens and it has been used in various recent studies^{36–38}. Records are updated in the GIDEON database using various sources such as WHO and Promed. A subset of 13 infectious diseases was subsequently selected from GIDEON (Table 1), based on whether they had been detected since the early to mid-1950s, and thus sufficient data with which to undertake statistical analysis (i.e. from 1950 to 2009).

Health expenditure was added as a confounding variable to describe any increase in spending on health with time, and a likely intensification in surveillance detection and outbreak reporting. This information was obtained from the Total Economy Database (www.conference-board.org/data/economydatabase/). TED was developed by the Groningen Growth and Development Centre at the University of Groningen (The Netherlands). The aggregated per capita GDP for Europe were used. Per capita health expenditure was obtained from the OECD (<http://www.oecd-ilibrary.org/>, <http://www.cesifo-group.de>). Data on GDP, health expenditure and diseases was acquired for 36 countries.

The number of reported outbreaks of infectious diseases increased from 1950 to 2008 in Europe, as did the number of European countries presenting at least one outbreak of the diseases investigated (Fig. 1A and B). There were marked increasing trends in both the number of outbreaks and number of countries with outbreaks occurring since the early 1960s as well as an increase in health expenditure (Fig. 1C); statistical analyses were consequently undertaken for the period from 1960 to 2008.

North Atlantic Oscillation. Data on the NAO's monthly values were obtained from the National Weather Service of the National Oceanic and Atmospheric Administration (NOAA) (www.cpc.ncep.noaa.gov). The mean value of NAO per year was not correlated to year (Adjusted R² = 0.02, F_{1,47} = 2.046, P = 0.16).

As NAO's values varied greatly according to season (and month) and northern and central or southern Europe (<http://www.cpc.ncep.noaa.gov/products/precip/CWlink/pna/nao.shtml>), the countries within Europe were re-classified as northern European (including Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greenland, Hungary, Iceland, Republic of Ireland, Luxembourg, Netherlands, Norway, Poland, Slovakia, Sweden, Switzerland, Ukraine and United Kingdom) and southern European (including Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Greece, Italy, Macedonia, Malta, Portugal, Romania, Serbia and Montenegro, Slovenia and Spain).

Statistical analysis. In order to minimize any confounding influence of increased surveillance within some countries, which is likely to be related to health expenditure,



we used a cubic smoothing spline as a detrending method for the long-term series of outbreaks using the function `smooth.spline` in the R 2.10 statistical package (<http://www.R-project.org>). The residuals of the trend were calculated by subtracting the value of the trend line from the original value.

We performed Generalized Linear Modelling (GLM) using R 2.10⁴⁹ to identify the likely variables that may explain outbreaks (using detrended values) for each of the selected infectious diseases (ID). Each monthly NAO of the year or of the previous year (one year lag) was included in the model. Best models were selected using a backward-stepwise procedure with reduction in the AIC criterion and Bonferroni corrections were applied due to the use of multiple tests. Analyses were undertaken respectively for northern and southern European countries in order to take into account the differential influences of the NAO on European regions (www.cpc.ncep.noaa.gov).

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Author contributions

S.M. conceived the study and drafted the paper, S.M. and K.O. gathered and analyzed the data, and A.W.-S., K.M.M. and M.B. helped to interpret results and contributed to the writing.



Additional information

Competing financial interests: The authors declare no competing financial interests.

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