# Rate of Change in Lyme Disease Incidence in the United States Exhibits a North-South Gradient Consistent with Climate Change Effect

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**Abstract**

Background: Tick-borne illnesses represent an important class of emerging zoonoses, with climate change projected to increase the geographic range within which tick-borne zoonoses might become endemic. We evaluated the impact of latitude on rate of change of Lyme disease incidence in the United States.

Methods: State-level year-on-year incidence rate ratios (IRR) were estimated using Poisson regression methods, with between-state heterogeneity in IRR evaluated using a random effects meta-analytic approach. State-level characteristics associated with increasing incidence were identified using random effects meta-regression.

Results: Incidence of Lyme disease in the U.S. increased by approximately 80% between 1993 and 2007 (IRR per year 1.049, 95% CI 1.048 to 1.050). There was marked between-state heterogeneity in average incidence of Lyme disease, ranging from 0.008 per 100,000 in Colorado to 75 per 100,000 in Connecticut, and significant between-state heterogeneity in temporal trends ($P$<0.0001). In multivariable meta-regression models, increasing incidence showed a linear association with state latitude and population density. These two factors explained 27% of between-state variation in IRR. No independent association was identified for other state-level characteristics.

Interpretation: Although Lyme disease incidence has increased in the U.S. as a whole over the past two decades, these increases are not uniform. Marked increases have

been identified in northernmost states, while southern states have seen stable or declining rates of Lyme disease. These differences in trends are consistent with expectations under climate change projections, possibly representing the first documentation of a clear relationship between climate change and altered disease epidemiology in the United States.

## Background

Tick-borne illnesses represent an important class of emerging zoonoses (1-3), and are associated with a large burden of morbidity and cost in North America, Europe, and Asia (4, 5). Tick-borne infectious diseases associated with *Ixodes* species, including Lyme disease, babseiosis, and human granulocytic anaplasmosis, have traditionally been regarded as limited to more temperate areas of North America (6, 7); however, reports suggest that their range may have expanded in recent years (8, 9). A key determinant of the range of *Ixodes* ticks that serve as vectors for a variety of tick-borne illnesses of public health importance is the presence of a sufficiently long and warm spring-autumn interval to permit ticks to complete their life cycles (6, 7). The blood meals that precede molting serve to transmit pathogens to mammalian hosts, including humans. Global climate change has resulted in warmer temperatures at northern latitudes (10) and therefore, it is anticipated that *Ixodes* ticks will be able to complete their life cycles at more northerly latitudes. These temperature changes have been projected to increase the geographic range within which tick-borne zoonoses might become endemic (6, 7); models have also suggested that rates of Lyme disease might decrease in southern latitudes in the U.S., due to expanded range of habitat for lizards, which serve as "dead-end" hosts for *Borrelia burgdorferi*, the causative agent of Lyme disease (7). However, to our knowledge, no attempt has been made to develop quantitative indices of the degree to which risk of tick-borne illnesses such as Lyme disease are actually migrating northwards. Such an analysis is complicated by variability in the effectiveness of public health surveillance in different jurisdictions, and by the fact that there is extreme variability in the risk of tick-borne illness.

We sought to overcome these limitations using an approach that evaluated trends in disease by aggregating state-level trend estimates for Lyme disease for the United States. We hypothesized that if climate change is affecting the risk of tick-borne illness, a north-south gradient in year-on-year trends should be seen, such that the most rapid changes in risk are seen in areas that have traditionally been too cold to support robust local Lyme disease transmission.

## Methods

*Data sources*

We estimated state-specific rates of Lyme disease for all 50 U.S. states and the District of Columbia using Lyme disease case counts from 1993 to 2007 obtained from the U.S. Centers for Disease Control and Prevention's National Notifiable Diseases Surveillance System (11), and population denominators derived from the U.S. Census Bureau (12).

We obtained estimates of state characteristics that we thought might, *a priori*, explain a high degree of between-state variability in Lyme disease incidence. State level demographic and economic characteristics, including mean population density (13), proportion of population in rural areas (14), per capita gross domestic product (15), and Gini coefficients (16) (an index of income equality) were derived from the U.S. Census Bureau and the Bureau of Economic Analysis. We used the ratio of protected wilderness lands administered by the U.S. Forest Service to total state area as an index of the abundance of state wilderness areas (17), and used number of issued home construction permits in the year 2000 as an index of growth of suburban areas (18). We assigned approximate geographic coordinates to state centers using the latitude and longitude of state centroids (19). Per capita spending on health-related expenses was derived from the State Government Finance table of the 2002 U.S. Census of Governments (20), and was used as an index of state investment in health. As a humorous article in a major medical journal described an apparent relationship between the geographic distribution of Lyme disease cases and states' candidate choices in the 2004 U.S. presidential election (21), we also categorized states as "Kerry states" and "Bush states" based on 2004 U.S. Presidential election results (22).

*Statistical analysis*

We evaluated trends in crude incidence of Lyme disease at the national and state levels using both tabular methods (with the observation period divided into two approximately equal intervals of 1993-1999 and 2000-2007), and on a year-to-year basis using Poisson regression models. Average crude incidence of Lyme disease, and state-level trends, were explored spatially through geo-mapping. States were categorized as having decreasing, increasing, or stable rates of Lyme disease depending on whether average yearly incidence rate ratios (IRR) were significantly less than 1, greater than 1, or not significantly different from 1, respectively.

Summary estimates of trend in Lyme disease incidence for the United States as a whole were estimated using the random effects meta-analytic approach of DerSimonian and Laird (23), and between-state heterogeneity in trends was evaluated using the meta-analytic *Q*-statistic (23). As significant between-state heterogeneity was observed in state-level trends, we sought to identify sources of heterogeneity through the construction of univariable and multivariable meta-regression models; such models evaluate the contribution of between-category variance to overall variance in measurements (24). Characteristics that were associated with trends at the $P < 0.15$ level in univariable models were considered candidate covariates for multivariable meta-regression models; these models were fit using backwards elimination, with covariates retained in the final model for $P < 0.05$. Interaction between model covariates was evaluated through construction of multiplicative interaction terms.

Several southern U.S. states have undertaken recent educational efforts aimed at reducing physician reporting of southern tick-associated rash illness (STARI), a tick-borne disease transmitted by *Amblyomma americanum*, as Lyme disease, from which it is clinically indistinguishable (25, 26). We explored the possibility that latitude-related effects could have been caused an artifact of such educational campaigns by analyzing southern and northern states separately and then evaluating heterogeneity in effects using the meta-analytic Q-statistic. For the purposes of these analyses "southern" states were defined based on the U.S. Census Bureau's South region (16 states and the District of Columbia) (27).

Statistical analyses were performed with Stata version 9.1 (Stata Corporation, College Station, TX) while maps were created using ArcMap version 9.2 (ESRI Corporation, Redlands, CA).

## Results

*Lyme disease incidence in the United States*

Annualized crude incidence of Lyme disease for the U.S. as a whole was estimated to be 6.2 per 100,000 during the period of observation, but an increase of approximately 40% was observed in overall incidence between the first and second halves of the time series (IRR 1.44, 95% CI 1.43 to 1.45). Poisson regression identified a significant linear increase in Lyme disease incidence for the U.S. as a whole during the period under observation (IRR per year 1.049, 95% CI 1.048 to 1.050) (**Figure 1**).



*State-level changes in Lyme disease incidence*

Marked heterogeneity was identified both with respect to crude Lyme disease incidence per 100,000 in states, which ranged from 0.008 in Colorado to 75 in Connecticut (**Figure 2**), but also in trends in Lyme disease over the period under evaluation. Twenty-one states (and the District of Columbia) showed significant increases in disease incidence over time, 14 states showed a significant decrease, and 15 states showed no significant change (**Figure 3**). Heterogeneity in incidence rate ratios was statistically significant (Q-statistic $1.6 \times 10^4$, on 50 degrees of freedom, $P<0.001$).

*Characteristics associated with trends in state-level incidence*

In univariable meta-regression analyses of state-level characteristics associated with year-on-year trends in Lyme disease occurrence, state latitude was a strong predictor of trends in risk (**Figure 4**). Several other state-level characteristics were also associated with disease trends (**Table 1**). However, in multivariable meta-regression models, only state latitude and mean population density over the study period explained a significant amount of between state variability in disease trends (**Table 2**). Together, these variables explained 27% of between-state variation in trends. There was no statistical evidence for interaction between latitude and population density in either model.

One possible explanation for decreases in Lyme disease incidence in southern and midwestern states is improved diagnosis of southern tick-associated rash illness (STARI), a tick-borne disease transmitted by *Amblyomma americanum* that may cause a rash similar to that observed in Lyme disease (25, 26). We repeated our analyses excluding the southern region of the U.S., where STARI is prevalent. State latitude remained in the multivariable model (β=0.015, 95% CI: 0.006 to 0.02, *P*=0.001) and longitude entered the model (β=0.002, 95% CI: $3.8 \times 10^{5}$ to 0.0039, *P*=0.046); together these variables explained 22% of between-state variation in trends in Lyme disease incidence. When we considered only the southern region, although several state-level characteristics, including latitude, were associated with disease trends in the univariable meta-regression models, only the log of average incidence over the study period (β=0.066, 95% CI: 0.025 to 0.11, *P*=0.002) remained in the multivariable model, explaining 37% of variability in disease trends in these states. However, we found no statistically significant heterogeneity in latitude effects in northern vs. southern states (Q-statistic 0.244, on 1 degree of freedom, *P* = 0.62).

**Interpretation**

The question of whether global climate change will have an important impact on the burden and distribution of infectious diseases generally, and those transmitted by vectors in particular, has received much recent discussion (9, 28, 29). We evaluated trends in the crude incidence of Lyme disease, an important vector-borne disease, in U.S. states and the District of Columbia over the past two decades. Our findings are consistent with the hypothesis that increases in Lyme incidence in recent decades are attributable at least in part to the effects of climate change, with increasing rates of change at more northerly latitudes, and declines in disease incidence in the southernmost states. Indeed, our empirical findings closely match projections made by Brownstein and colleagues using an ecological model published in 2003 (7). Our results are also concordant with the empirical observation that Lyme disease and related vector-borne diseases are now being documented in areas of Canada previously considered too cold to support the *Ixodes* lifecycle (8, 30). Furthermore, although there may have been a decline in reported Lyme disease rates in southern states due to clinician education related to STARI, we found no heterogeneity in effects in southern and northern states, and the effects of latitude remained statistically significant after southern states were excluded from analyses, suggesting that changing classification of STARI does not account for our observations.

Vector-borne diseases are frequently characterized by complex transmission cycles that involve arthropod vectors, higher vertebrate reservoirs, and humans, who may or may not serve as amplifying hosts (i.e., hosts capable of sustaining disease transmission in the absence of a competent animal reservoir). As the distribution, density, and "generation times" of animals involved in these transmission cycles depend on the ecological conditions of habitats, it is reasonable to suppose that changes in temperature, duration of seasons, or precipitation that enhance the abundance of animal reservoirs or insect vectors would result in changes in disease incidence (31). Gradual increases in global mean temperatures due to anthropogenic gas emissions have likely been occurring for more than a century, with an increasing rate of warming over time (10). Climate data have been used to develop risk maps that predict the distribution and expansion of geographic ranges of Lyme disease vectors in the U.S. (32) and Canada (33). In the long term, under the climate change projections of the Intergovernmental Panel on Climate Change, the range of tick vectors (and consequently, Lyme disease) has been projected to expand northwards. However, our findings, and those of other investigators, suggest that these changes are occurring more rapidly than models would project. This may reflect the relatively direct impact of environmental conditions on disease vectors; for example, Subak identified year-to-year shifts in the risk of Lyme disease in high-incidence northeastern U.S. states associated with changes in temperature and precipitation, suggesting that the impact of climate-driven changes in vector and reservoir ecology may be relatively rapid (34).

We also identified an association between increasing state population density and rate of increase in Lyme disease incidence; this effect was independent of latitude. This finding may reflect encroachment of human habitation into wooded areas that support rodents and other animals that serve as reservoir hosts for Lyme disease, which has traditionally been regarded as an important driver of enhanced Lyme disease risk in humans (35, 36). Of note, the idea that woodland fragmentation is a driver of Lyme disease risk in humans, as opposed to density of infection in tick vectors, has recently been disputed by Brownstein and colleagues (35).

Although these data strongly suggest climate-driven changes in the range and burden of Lyme disease in the United States, these analyses are subject to several limitations. We relied on state-level notifiable disease reporting, which is expected to be of variable quality. Many notifiable infectious diseases are thought to be underreported (37). This may have biased our results if the characteristics under consideration were correlated with likelihood of reporting. It is possible that more northern states may have experienced improvements in reporting over time as Lyme disease began spreading northward, compared to southern states with more established Lyme disease surveillance systems. Meta-analytic methods were used to account for this expected between-state heterogeneity. The state-level characteristics under consideration are summary measures that may not fully capture the dynamic nature of some of these variables; as such, our study results should be viewed with the caution necessary in the assessment of any ecological analysis (38). Additionally, although we observed an association between state latitude and Lyme disease incidence, we cannot draw conclusions about causality.

In summary, we have evaluated changes in Lyme disease incidence at the state level and have identified marked increases in northernmost states, while southern states have seen stable or declining rates of Lyme disease. These differences in trends are consistent with expectations under climate change projections, and may indicate that global warming has already substantially impacted the ecology of this important infectious disease, although further confirmatory studies are needed. Public health agencies need to ensure that existing surveillance systems are sufficiently flexible and sensitive to identify climate change-driven changes in infectious disease epidemiology.

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**Table 1.** Univariable Meta-Regression Models Showing Associations Between State Characteristics and State-Level Trends in Lyme Disease

| Characteristic | Univariable models | |
|---|---|---|
| | **β (95% CI)** | ***P*-value** |
| Geography | | |
| Latitude, State Centroid | 0.014 (0.0073 to 0.021) | <0.0001 |
| Longitude, State Centroid | 0.00049 (-0.00084 to 0.0018) | 0.5 |
| Environment | | |
| Percent National Wilderness (2000) | 0.00047 (-0.0041 to 0.0050) | 0.8 |
| New Housing Permits (thousands) (2002) | -0.00060 (-0.0017 to 0.00047) | 0.3 |
| Demography | | |

| | | |
|---|---|---|
| Percent Change in Population between 1990 and 2000 Censuses | -0.0016 (-0.0075 to 0.0042) | 0.6 |
| Population Density (thousands per km$^2$) (2000) | 0.069 (-0.0050 to 0.14) | 0.07 |
| Percent Rural Residents (2000) | 0.00017 (-0.0025 to 0.0028) | 0.9 |
| Politics and Economy | | |
| Log of Per Capita GDP (2000) | 0.19 (-0.022 to 0.41) | 0.08 |
| Kerry vs. Bush, 2004 | 0.10 (0.030 to 0.18) | 0.006 |
| Per Capita Health Spending (per 100 persons) (2002) | 0.00025 (-0.00015 to 0.00065) | 0.2 |
| Gini coefficient (1999) | -1.00 (-2.50 to 0.50) | 0.2 |
| Log of Average Incidence, 1993 – 2007 | 0.026 (0.0081 to 0.044) | 0.004 |

**Table 2.** Final Multivariable Meta-Regression Model Showing Associations Between State Characteristics and State-Level Trends in Lyme Disease

| Characteristic | Multivariable model | |
|---|---|---|
| | β (95% CI) | *P*-value |
| Latitude, State Centroid | 0.014 (0.0075 to 0.021) | <0.0001 |
| Population Density (thousands per $km^2$) | 0.070 (0.0049 to 0.14) | 0.04 |

**Figure Legends**

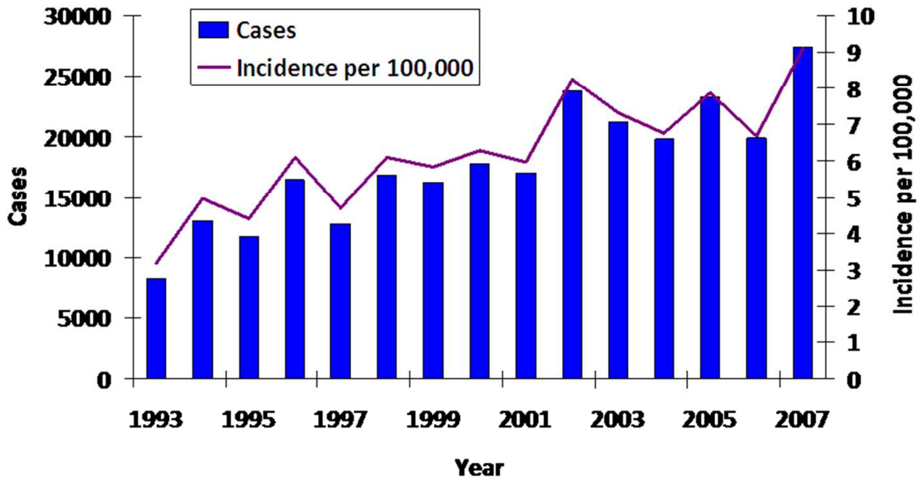
**Figure 1.** Number of cases and incidence rates of Lyme disease in the United States, 1993-2007. The vertical bars depict annual case counts and the solid curve represents incidence per 100,000 population. Incidence approximately doubled over the study period (per year, IRR = 1.049, 95% CI: 1.048, 1.050).

**Figure 2.** Average Lyme disease incidence by State, 1993 to 2007. Rates are per 100,000 person-years. Alaska (0.34) and Hawaii (0.01) are not shown.

**Figure 3.** Temporal trends in Lyme disease incidence by state, 1993 to 2007. States are classified as decreasing, increasing, or unchanged if the average yearly IRR over the study period was significantly less than 1, greater than 1, or not significantly different from 1, respectively. Marked heterogeneity in incidence rate ratios was observed (Q-statistic $1.6 \times 10^4$, on 50 degrees of freedom, $P<0.0001$). Alaska (increasing, IRR = 1.28, 95% CI: 1.15, 1.42) and Hawaii (unchanged, IRR = 0.60, 95% CI: 0.28 to 1.23) are not shown.

**Figure 4.** Correlation between state latitude and average yearly incidence rate ratio. Each circle represents a single U.S. state, with size inversely proportional to standard error in IRR estimates, corresponding to the weight assigned to each state. Latitude is measured using state centroid. States classified as southern (grey) or northern (black)

for subgroup analyses are indicated. Lines represent the association between state latitude and IRR as predicted using univariable meta-regression, with results displayed by northern and southern states and for all states combined. Montana is not shown (IRR = 5.9, 95% CI: 0.99 to 35.5, latitude = 46.60).

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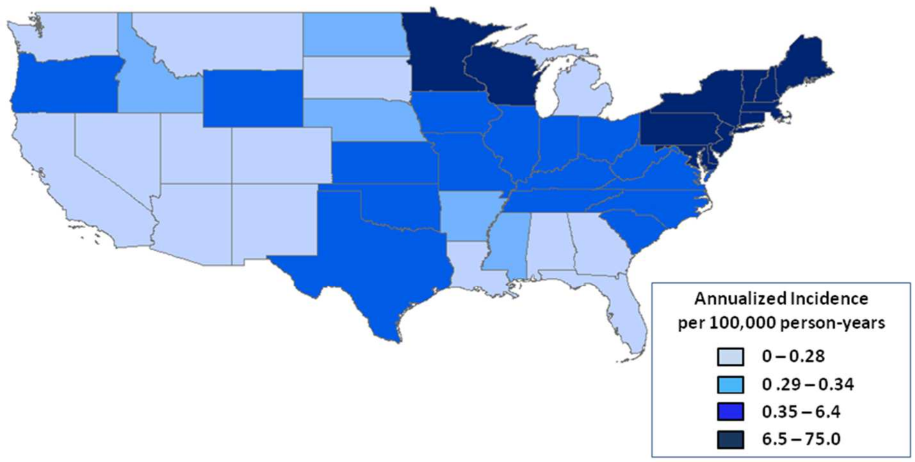


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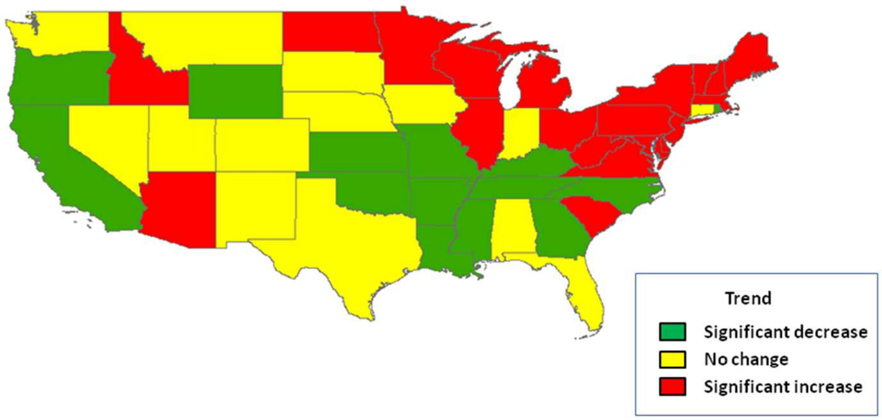


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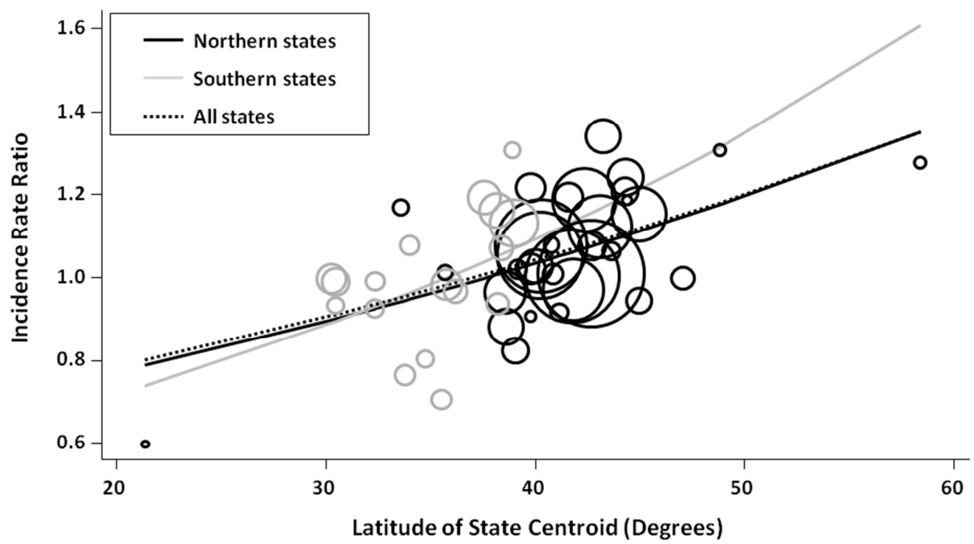


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