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Title	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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Reviewer 1	David Vickers
Institution	Department of Applied Research , University of Saskatchewan, Saskatoon, Sask.
General comments	In my opinion, you have provided a thoughtful statistical model to quantify the degree to which the incidence of Lyme disease appears to be migrating northwards in the United States. In particular, your results do seem to correlate with the predictions of Brownstein et al. (2003) that changes to tick habitats are likely to coincide with changes in climate. However for me, it seemed strange that your model did not include temperature data (such as minimum, maximum, or mean temperatures, or duration spring-autumn intervals) for "northern" and "southern" states over the 15-year period. Instead, it appeared that – even though it is widely-discussed that climate change will bring about warmer temperatures in northern latitudes (as cited in reference 10) – you were using latitude as a proxy indicator of climate, without any actual data to support this correlation. I think you can easily strengthen the support for your hypothesis. For instance, obtaining data on the mean minimum or maximum temperatures in "northern" and "southern" states (for example) will, in my opinion, better-corroborate your hypothesis that the north-south gradient correlates with temperature/climate changes. (I understand that this type of data may not be readily integrated with your model, but could at least provide additional descriptive information in the form of a table or graph that might be informative.) Temperature data may also help you explain-away the decreased rates of Lyme disease in the "southern" states: warmer temperatures can augment both the development and hatching rates of new ticks, but also decrease adult survival, as well as oviposition success (Needham and Teel, 1991 – as cited in Brownstein et al., 2004). Therefore, it may be worth considering the (counter-intuitive) possibility that climate change (over time) might also effectively control the distribution of tick populations in the "south" (Estrada-Pena, 2002; Shope, 1991 – as cited in Brownstein et al., 2004); that is, climate change may redistribute the vector northward, which will lead to more Lyme disease in states that have typically had low (to no) rates of Lyme disease, and thus higher rates in the U.S. overall. However, these increased rates may only be transitional. With climate also getting warmer, the once ideal ecological niches in the south will also likely become less hospitable for the tick vector. Lyme disease rates in the south may continue to decline. References: Estrada-Pena A. Increasing habitat suitability in the United States for the tick that transmits Lyme disease: a remote sensing approach. Environ Health Perspect, 2002; 110:635–640. Needham GR, Teel PD. Off-host physiological ecology of ixodid ticks. Annu Rev Entomol, 1991; 36:659–681. Shope R. Global climate change and infectious diseases. Environ Health Perspect, 1991; 96:171–174.
Reviewer 2	Samira Mubareka MD
Institution	Division of Infectious Diseases, Sunnybrook Health Sciences Centre, Toronto, Ont.
General comments	Tuite and colleagues highlight the importance of climate change on human health in the paper entitled *Rate of change in Lyme disease incidence in the United States exhibits a north-south gradient consistent with climate change effect.* In this study, the authors examine the relationship between certain state-level characteristics and the incidence of Lyme disease for years 1993-2007. Data collected included number of cases of laboratory-confirmed Lyme disease, human population, population density, distribution in rural areas, GDP/capita, healthcare expenditure per capita, ratio of protected wilderness to total state area, urbanization, income equality (Gini coefficient), and politics (Kerry and Bush states). Sources of heterogeneity in this data were sought. The incidence rate ratio (IRR) was used to indicate whether Lyme activity was increasing

	(>1), decreasing (<1) or unchanged (=1). Misreporting of tick-associated rash illness (STARI) as Lyme was controlled for. Important results included an overall increase in Lyme disease (80%), with heterogeneity among states, where latitude was a major predictor of increased Lyme incidence. Mean population density was also significant. After excluding states in the south where STARI was present, longitude and latitude explained 22% of inter-state variation. Range expansion for the Lyme agent vector has been long predicted, however this data underscores the urgency to intervene by demonstrating that Lyme has already expanded its range to the north. Minor comments 1. Increased incidence may be an artifact of testing; the authors should perhaps confirm that case-finding, detection and confirmation methods have not changed during the study period. 2. Although examining area of wilderness protected:state area and home construction permits issued are very informative, they are not direct measures of deforestation and biodiversity or habitat loss, which may be relevant to the spread of Lyme. Understandably these are very difficult data to identify, so a mention of this limitation should probably be made in the discussion. 3. Increased human exposure to Lyme through urbanization and subsequent pet and domestic animal exposure is a plausible factor which is also worthy of mention; unsure whether this data is available but also worth a mention. Major comments 1. Key data relating Lyme disease and vector distribution is lacking. Also, environmental factors suggestive of nefarious climate change are not included. For example, relating disease and tick density with elevated minimum temperatures and rainfall would make the conclusions more robust. Exploration of the relationship between Lyme disease incidence and CO_2 production may also be of interest. In summary, this paper is of interest because it highlights the relationship between climate change and human health through the form of an externality few would have considered in the past during the industrial revolution and the decades that followed. An important take-home message from this paper is the alarming rate of change of Lyme disease incidence. In the absence of an intervention, this and other arthropod-borne transmissible disease will continue to expand their geographic ranges and impact human health substantially.
Author response	Thank you very much for the positive response to our manuscript (which is now) entitled "Effect of Latitude on the Rate of Change in Incidence of Lyme Disease in the United States". We have revised our manuscript to incorporate the suggestions provided in the reviews, as described in detail below. We hope that you find these revisions satisfactory and we look forward to further correspondence related to this manuscript.