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The impact of strain-specific immunity on Lyme disease incidence is spatially heterogeneous

Camilo E. Khatchikian [a,b,*], Robert B. Nadelman [c], John Nowakowski [c], Ira Schwartz [d], Gary P. Wormser [c], Dustin Brisson [a,**]

[a] Department of Biology, University of Pennsylvania, PA
[b] Department of Biological Sciences, University of Texas at El Paso, TX
[c] Division of Infectious Diseases, Department of Medicine, New York Medical College, Valhalla, NY
[d] Department of Microbiology and Immunology, New York Medical College, Valhalla, NY

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ABSTRACT

Lyme disease, caused by the bacterium *Borrelia burgdorferi*, is the most common tick-borne infection in the US. Recent studies have demonstrated that the incidence of human Lyme disease would have been even greater were it not for the presence of strain-specific immunity, which protects previously infected patients against subsequent infections by the same *B. burgdorferi* strain. Here, spatial heterogeneity is incorporated into epidemiological models to accurately estimate the impact of strain-specific immunity on human Lyme disease incidence. The estimated reduction in the number of Lyme disease cases is greater in epidemiologic models that explicitly include the spatial distribution of Lyme disease cases reported at the county level than those that utilize nationwide data. strain-specific immunity has the greatest epidemiologic impact in geographic areas with the highest Lyme disease incidence due to the greater proportion of people that have been previously infected and have developed strain-specific immunity.

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Spatial, as well as temporal heterogeneity, is a nearly universal natural phenomenon (i.e. Boulinier et al., 1998; DePuy et al., 2014; Devevey and Brisson, 2012; Kaplan et al., 2010; Khatchikian et al., 2009, 2010, 2011, 2012; MacArthur, 1957; Vazquez-Prokopec et al., 2012; Wang, 2013; Zeman et al., 2015). Such heterogeneity, however, can impede experimental design and analysis and is thus neglected in many studies (e.g. Adler et al., 2001; Grime, 1994; Khatchikian et al., 2015a) which can have both quantitative and qualitative effects on the results (Adalsteinsson et al., 2016; Allen et al., 2012; Becker et al., 2008; Bell and Lechowicz, 1994; Kotliar and Wiens, 1990). For example, the worldwide risk of contracting Ebola in 2015 was 1 in 3,870,000 people (WHO, 2016), far less likely than winning the Spanish *El gordo* Christmas lottery (1 in 100,000) or being struck by lightning (1 in 1,190,000). However, the incidence of Ebola on local scales, the scale most relevant to public health, was greater than 1 in 2 persons in some locations (Osterholm et al., 2015). Assessing incidence rates at spatial scales that are relevant to the heterogeneity in the system are more likely to provide an accurate assessment of the true disease risk (Kotliar and Wiens, 1990). The ubiquity of spatial and temporal heterogeneity implies that analytical inferences are often imprecise if resolution of spatial data is insufficient to describe the heterogeneity in the system.

Lyme disease, caused by the bacterium *Borrelia burgdorferi*, is extremely heterogeneous in incidence across geographic space. Although it is the most common vector-borne disease in North America, nearly all human cases are reported from the Northeastern (71%) or the Midwestern (15%) United States (CDC, 2016). Despite such heterogeneity, a previous study estimated the epidemiological impact of strain-specific immunity (see Khatchikian et al., 2014) using the overall prevalence of Lyme disease in the United States (Khatchikian et al., 2015a). This study reported that strain-specific immunity, which provides temporary immunity (lasting at least 5 years) to one of the many *B. burgdorferi* strains due to prior infection with that strain, has a real but moderate epidemiological impact on human Lyme disease incidence. In that report, it was estimated that the number of avoided cases ranged between 11 and 4100, depending on the model assumptions (Khatchikian et al., 2015a).

In this analysis, we estimate the reduction in human Lyme disease cases due to strain-specific immunity using recently reported county-level incidence data. The goal of the present study is to estimate the effect that spatial heterogeneity in Lyme disease incidence has on the epidemiological impact of strain-specific immunity. Here we compare the epidemiological impact of strain-specific immunity estimated from models that aggregate incidence data across different spatial scales.

* Corresponding author. Tel.: +1-915-747-8640; fax: +1-915-747-5844.
** Corresponding author. Tel.: +1-215-746-1731; fax: +1-215-573-9454.
E-mail addresses: ckhatchikian@utep.edu (C.E. Khatchikian), dbrisson@sas.upenn.edu (D. Brisson).

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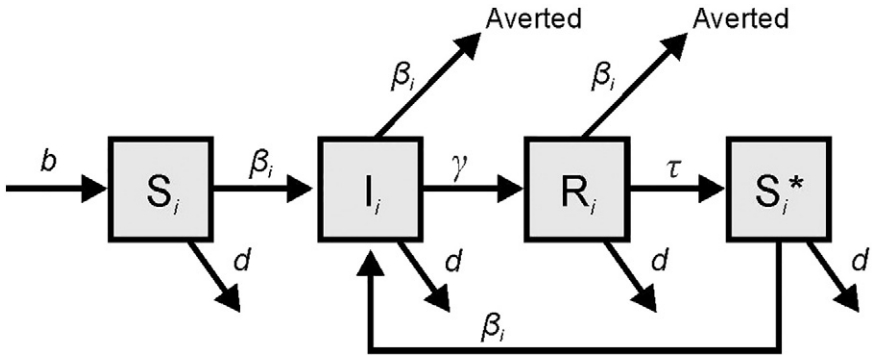

Fig. 1. A schematic representation of the modified SIRS* model used to estimate the annual number of averted Lyme disease cases. The total population in each county is equal to the sum of the susceptible (S), infected (I), recovered (R), and susceptible but previously infected (S^*) individuals. Individuals enter the population (b) in the susceptible state and individuals in all states leave the population at the same rate ($d = b$), resulting in a constant population size. Individuals susceptible to strain i (S_i) transition to the infected state (I_i) at rate β_i, transition to the recovered state (R_i) at rate γ, where they remain immune to a subsequent infection from strain i until they transition back to the susceptible state (S_i^*) at rate τ. Thus, the number of new infections with strain i is equivalent to the proportion of susceptible individuals that encounter a tick infected by strain i ($\beta_i{}^*(S_i + S_i^*)$). Similarly, the number of infections with strain i averted due to strain-specific immunity is equivalent to the proportion of immune individuals that encounter a tick infected by strain i ($\beta_i{}^*(I_i + R_i)$).

The analyses suggest that a far greater number of human Lyme disease cases are averted each year due to immunity than previously reported (Khatchikian et al., 2015a). Interestingly, the greatest reductions in human Lyme disease incidence caused by strain-specific immunity is likely to occur in areas where *B. burgdorferi* infections are most prevalent.

1. Methods

1.1. Incidence rate data

We expanded the equilibrium dynamic model previously described (Khatchikian et al., 2015a), which calculates the annual number of Lyme disease cases averted due to strain-specific immunity across the US population (homogeneity model), to explicitly include spatial heterogeneity at the state and county levels (heterogeneity models). To accurately compare the impact of incorporating spatial heterogeneity in the analyses with previously reported estimates, we used 2 Lyme disease incidence datasets as was done previously (Khatchikian et al., 2015a). The *observed* incidence rates were calculated as the average number of cases reported per year between 2010 and 2014 in each US county (Appendix A) (CDC, 2016). The *estimated* incidence rates were calculated assuming that only 10% of all human cases from each county are reported to the CDC (Hinckley et al., 2014; Nelson et al., 2015). The observed re-infection incidence rate, or the incidence rate in patients that had been previously diagnosed with Lyme disease, of 3% was used in models analyzing both the observed and the estimated incidence rates. The models that explicitly include spatial heterogeneity assess each county independently using county-level incidence rates derived from either the *observed* or the *estimated* incidence as described above.

1.2. Equilibrium dynamic model

The equilibrium dynamic model is a modified SIRS* model in which patients susceptible to strain i (S_i) become infected (I_i), recover (R_i), and then return to the susceptible state (S_i^*) after a set duration of strain-specific immunity (τ) following:

$$\frac{dS_i}{dt} = b - S_i{}^*(d + \beta_i) \tag{1}$$

$$\frac{dI_i}{dt} = (S_i + S_i^*)^*\beta_i - I_i{}^*(d + \gamma) \tag{2}$$

$$\frac{dR_i}{dt} = I_i{}^*\gamma - R_i{}^*(d + \tau) \tag{3}$$

$$\frac{dS_i^*}{dt} = R_i{}^*\tau - S_i^{**}(d + \beta_i) \tag{4}$$

where the birth rate (b) equals the death rate (d). In this model, patients transition from susceptible to strain i (S_i) to infected by strain i (I_i) at rate β_i, which is equivalent to the annual incidence rate of strain i (Fig. 1). The incidence rate for each strain is scaled to the total incidence rate for all *B. burgdorferi* strains using the frequency at which each strain is found in human infections (Khatchikian et al., 2015a; Nadelman et al., 2012). Patients transition from the infected state (I_i) to the resistant state (R_i) at a rate of $\gamma = 1$. Patients are assumed to transition from the resistant state (R_i) to the susceptible but previously infected with strain i state (S_i^*) in 5 years ($\tau = 0.2$). A 5-year duration of strain-specific immunity ($\tau = 0.2$) is a conservative estimate according to previously published analyses (see Khatchikian et al., 2014, 2015a). The equilibrium numbers of people in each disease state for each strain type i ($\widehat{S}_i, \widehat{I}_i, \widehat{R}_i, \widehat{S}_i^*$) was calculated at the national-level, within each state, and within each county as:

$$\widehat{S}_i = {}^{b}\Big/_{(d+\beta_i)} \tag{5}$$

$$\widehat{I}_i = {}^{(\beta_i{}^*b^*(d+\tau))}\Big/_{(d^*(d+\gamma)^*(d+\tau)+\beta_i{}^*d^*(d+\gamma+\tau))} \tag{6}$$

$$\widehat{R}_i = {}^{(\beta_i{}^*\gamma^*d)}\Big/_{(d^*(d+\gamma)^*(d+\tau)^*\beta_i{}^*d^*(d+\gamma+\tau))} \tag{7}$$

$$\widehat{S}_i^* = {}^{(\beta_i{}^*\gamma^*d^*\tau)}\Big/_{(d^*(\beta_i+d)^*((d+\gamma)^*(d+\tau)+\beta_i{}^*(d+\gamma+\tau)))} \tag{8}$$

The annual number of Lyme disease cases within each county, state, or in the US is equivalent to the product of the number of people susceptible to each strain ($\widehat{S}_i + \widehat{S}_i^*$) and the incidence rate of strain i in each area (Eq. (9)). The number of cases averted due to strain-specific immunity was estimated as the number of individuals in the infected or resistant states ($\widehat{I}_i + \widehat{R}_i$) that are exposed to strain i (Eq. (10)). Appendix B includes a step-by-step derivation of the model.

$$Incidence = \sum_{i=0}^{n} \beta_i{}^*\left(\widehat{S}_i + \widehat{S}_i^*\right) \tag{9}$$

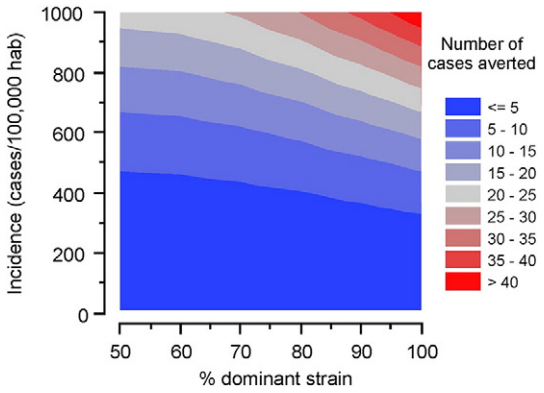

Fig. 2. The number of averted cases is a function of both the local incidence rate and the local diversity of strains. At low incidence rates, few cases are averted due to strain-specific immunity regardless of the percentage of the *B. burgdorferi* population that consists of the dominant strain in a system with 2 strains. At greater local incidence rates, the number of averted cases increases with decreasing diversity in the *B. burgdorferi* populations (increasing percentage of the dominant strain). The greatest number of averted cases is predicted in locales with the lowest strain diversity and the highest overall incidence. The empirically-observed reinfection rate of 3% was assumed in these estimates.

$$Averted = \sum_{i=0}^{n} \beta_i{}^{*} \left(\hat{I}_i + \hat{R}_i \right) \tag{10}$$

The equilibrium dynamic model relies on several assumptions. The probability of exposure to each of the *B. burgdorferi* strains was assumed to remains constant in the United States, as was previously assumed (Khatchikian et al., 2014, 2015a). The probability of exposure to each strain was estimated from the frequency that each strain was detected in skin biopsy samples of 200 early Lyme disease patients in the Lower Hudson Valley region of New York State (Khatchikian et al., 2014; Wormser et al., 2008). These patients, who had no prior history of Lyme disease, were diagnosed between 1991 and 2005 and constitute the largest existing sample from human patients (Appendix A) (Khatchikian et al., 2014; Wormser et al., 2008). The sensitivity of the results to this assumption were assessed by allowing the probability of exposure to each strain in Midwestern populations to be equivalent to the frequency each strain was cultured from 56 patients in Wisconsin diagnosed between 1993 and 2003 (Hanincova et al., 2013). The populations in counties outside the Midwestern US were assumed to encounter each strain at rates similar to the Northeastern US due to an absence of empirical data to make more accurate estimates. Additional assumptions include that all patients attain strain-specific immunity after infection, strain-specific immunity provides no cross protection against other strains, and that the duration of strain-specific immunity is the same for all strains. We assessed the overall effect (benchmark) of strain heterogeneity on the predicted number of averted cases (Fig. 2) by exploring a simple case consisting of 2 strains with varying prevalence in the system from equal prevalence (0.5) to only one strain present (1.0). In addition, we assessed the sensitivity of the model to the duration of strain-specific immunity, the rate of reinfection, the distribution of strains, and biases in under-reporting of Lyme disease (Appendix B).

2. Results

Explicitly including spatial heterogeneity in the analyses results in a substantially greater estimate of the epidemiological impact of strain-specific immunity than estimates derived from models that do not consider the spatial heterogeneity in disease incidence. The estimated number of Lyme disease cases averted per year has a limited impact on the total Lyme disease incidence in models that do not consider spatial heterogeneity (Table 1). However, the estimated annual number of averted Lyme disease cases is 7-fold greater in models that explicitly considering the spatial heterogeneity among counties in Lyme disease incidence. The analyses including county-level spatial heterogeneity suggest that strain-specific immunity may reduce the incidence rate among previously infected patients by up to 27%, depending on the parameter values employed (Appendix B, Table 1).

The number of locally averted Lyme disease cases is strongly correlated with the local incidence rates observed (Fig. 3A). The majority of averted cases (79%) were derived from counties in the Northeastern US, followed by counties in the Midwest (15%), comparable to the spatial heterogeneity in Lyme disease incidence (Fig. 3B). Counties within each region differed considerably in incidence rates and in the number of averted cases (data for counties in the state of Connecticut are presented in Table 2). Reducing the spatial resolution of the analyses by aggregating data at the state or national level substantially reduces the impact of strain-specific immunity on the proportion of averted Lyme disease cases. Using the observed county level data, the estimated proportion of re-infections cases that are averted annually reaches 7.80%, drops to 4.2% when data are aggregated at the state level and to 1.0% when data are aggregated at the national level.

Model results are highly sensitive to the population turnover rate parameter and the duration of strain-specific immunity. The population turnover rate (birth and death rate) has a large effect on the proportion of the population that are exposed to multiple infectious tick bites over their lifetime, which in turn affects the re-infection rate and the rate of averted infections (Appendix C, Figs. 1, 2). Models with a high population turnover rate contain very few people in the previously infected state, thus reducing the potential impact of strain-specific immunity. The primary results reported here use models with the birth and death rate parameters adjusted such that the reinfection rate was 3%, equal to the reinfection rate observed in the US population, was achieved in in a human dataset. Similar to previous reports, the duration of strain-specific immunity was strongly correlated with the number of averted cases, especially in models with population turnover rates similar to those observed from the data. Model results are relatively insensitive to the distribution of strains in different regions and to potential biases in the under-reporting of Lyme disease cases (Appendix C, Table 1). Including the distribution of strains reported in Midwestern patients to estimate the equilibria in Midwestern counties has only a minor effect on the number of cases averted (Appendix D). For example, the number of infections averted, using the county-wide observed dataset, changes from 30 to 28. Similarly, assuming that county-level incidence is correlated (either negatively or positively) with under-reporting of human Lyme disease cases results in minor changes in model results (Appendix C, Table 1). Systematic under-reporting from low-incidence counties exacerbates heterogeneity among counties leading to greater estimates of the impact of strain-specific immunity while systematic under-reporting from high-incidence counties effectively homogenizes among-county incidence leading to lower estimated impacts of strain-specific immunity.

3. Discussion

Lyme disease incidence continues to rise over time and expand geographically in the United States (e.g. Khatchikian et al., 2015b; Leo et al., 2017). The results of this study suggest that, without strain-specific immunity, there would be as many as 2516 additional human Lyme disease cases per year in the United States. The increased estimates of the effects of strain-specific immunity (Khatchikian et al., 2015a) reported in this study result from the explicit consideration of spatial heterogeneity in human Lyme disease risk (Table 1). Analyses that explicitly include spatial heterogeneity suggest that 8–27% of patients who would have otherwise suffered a second bout of Lyme disease were protected due to strain-specific immunity, far greater than previous estimates of ~3.5% (Khatchikian et al., 2015a). Further, these data suggest that the nationwide Lyme disease rate would have been as much as 0.85% greater in the absence of strain-specific immunity using the *estimated*

Table 1
Summary of statistics using either the observed dataset or the estimated dataset and considering different levels of spatial aggregation of the US population, either as a single group including all habitants (homogeneity model) or discriminating data at the state or county levels (heterogeneity models).

	Observed dataset (31,123 cases/year)		Estimated dataset (311,234 cases/year)	
	Averted cases	% re-infections reduced	Averted cases	% re-infections reduced
US-wide scale	9.4	1.0	364.3	3.9
State-wide scale	39.3	4.2	1429.0	15.3
County-wide scale	73.0	7.8	2516.5	27.0

dataset. In areas with high human Lyme disease incidence, strain-specific immunity may result in as much as 5.3% fewer Lyme disease cases and 34.3% more re-infection cases per county per year than would have occurred in the absence of strain-specific immunity.

Explicitly including the spatial heterogeneity in Lyme disease incidence results in spatial variation in the proportion of people in the resistant state and substantially greater estimates of the epidemiological impact of strain-specific immunity than in homogenous models. Areas with high Lyme disease incidence have a large proportion of people in the resistant state and are the areas where the majority of infectious tick bites occur (Fig. 4). Thus, the majority of infectious tick bites occur in areas where the concentration of people in the resistant state is highest, leading to many averted Lyme disease cases. By contrast, most of the population in low incidence areas are in the susceptible state and are rarely exposed to *B. burgdorferi* such that cases are rarely reported and very few averted cases are expected. The clustering of resistant individuals into areas with many infectious ticks and of susceptible people into areas with few infectious ticks, which occurs by including spatial heterogeneity, explains the greater reduction in human Lyme disease incidence due to strain-specific immunity than was estimated from homogeneous models.

The epidemiologic impact of strain-specific immunity on Lyme disease incidence is limited by the relatively small group of previously-infected individuals who can benefit from its protection. It is currently estimated that ~3% of all Lyme disease cases annually occur in individuals who have been previously diagnosed with Lyme disease (Khatchikian et al., 2014; Nadelman et al., 2012). However, re-infection risk is greatest in high incidence areas, which is positively correlated with the proportion of people who are expected to be in the resistant states ($\hat{I}_i + \hat{R}_i$). Thus, the areas where re-infections are most likely are also the areas where the majority of averted cases are likely to occur (Fig. 3A). The current analyses suggest that up to 27% of the potential cases of re-infection are averted each year. This figure is not substantially lower than the reduction in re-infections expected in Columbia County, NY (31%), the county with the highest expected reduction in re-infections caused by strain-specific immunity. The estimated reduction in re-infection in the county-level dataset is driven by areas with high Lyme disease incidences where most of the total cases occur (Appendix E).

Numerical estimates of the impact of strain-specific immunity are likely underestimates of the true impact, as there is undoubtedly relevant spatial heterogeneity in Lyme disease risk within counties. Increased clustering of people in the resistant state would result in even greater epidemiological impacts of strain-specific immunity. Additionally, the risk of exposure to each strain was calculated from patients across a large geographic area, which removed spatial heterogeneity in strain-specific risk among areas. Greater biases in strain-specific risk increase the probability of repeated exposure to the same strain, resulting in greater epidemiological impacts of strain-specific immunity (Fig. 2). For example, when the more homogeneous strain probabilities observed in Midwestern patients (Hanincova et al., 2013) are used to estimate averted cases in Midwestern counties, only a very slight

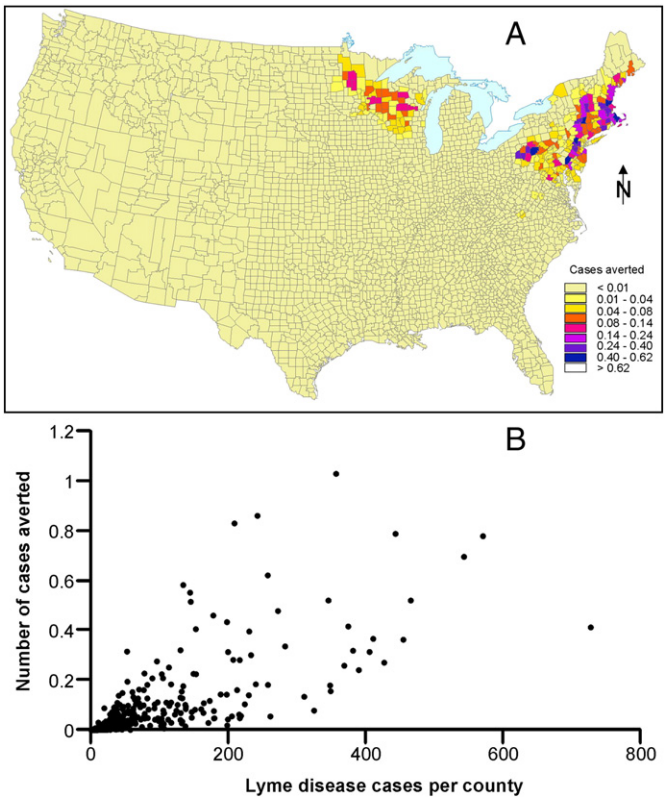

Fig. 3. A) Estimated number of Lyme disease cases averted each year due to strain-specific immunity are concentrated in the northeastern and upper-Midwestern counties. The number of averted Lyme disease cases per county per year was estimated assuming that strain-specific immunity lasted 5 years, a reinfection rate of 3%, and an annual nationwide incidence rate of 311,234. The relative geographic distribution of averted cases was equivalent when using the *observed* dataset. B) The estimated number of averted cases and the observed number of Lyme disease cases in each county are correlated ($p < 0.05$, $R^2 = 0.64$).

Table 2
The population size, average number of Lyme disease cases (2010–2014), and estimated number of averted Lyme disease per year in multiple counties in the state of Connecticut. Lyme disease incidence is reported as cases per 100,000 people.

County	Population size	Lyme disease cases	Lyme disease incidence	Averted (estimated dataset[1])	Averted (estimated dataset[2])
Fairfield	933,835	348.2	37.29	0.372	12.83
Hartford	897,259	215.2	23.98	0.148	5.10
Litchfield	187,530	125.6	66.98	0.241	8.32
Middlesex	165,602	132.6	80.07	0.304	10.50
New Haven	862,813	309.8	35.91	0.319	11.00
New London	274,170	345	125.83	1.246	42.91
Tolland	151,539	199	131.32	0.750	25.83
Windham	117,599	148.8	126.53	0.540	18.61

[1] Observed dataset - 31,123 cases per year.
[2] Estimated dataset - 311,234 cases per year.

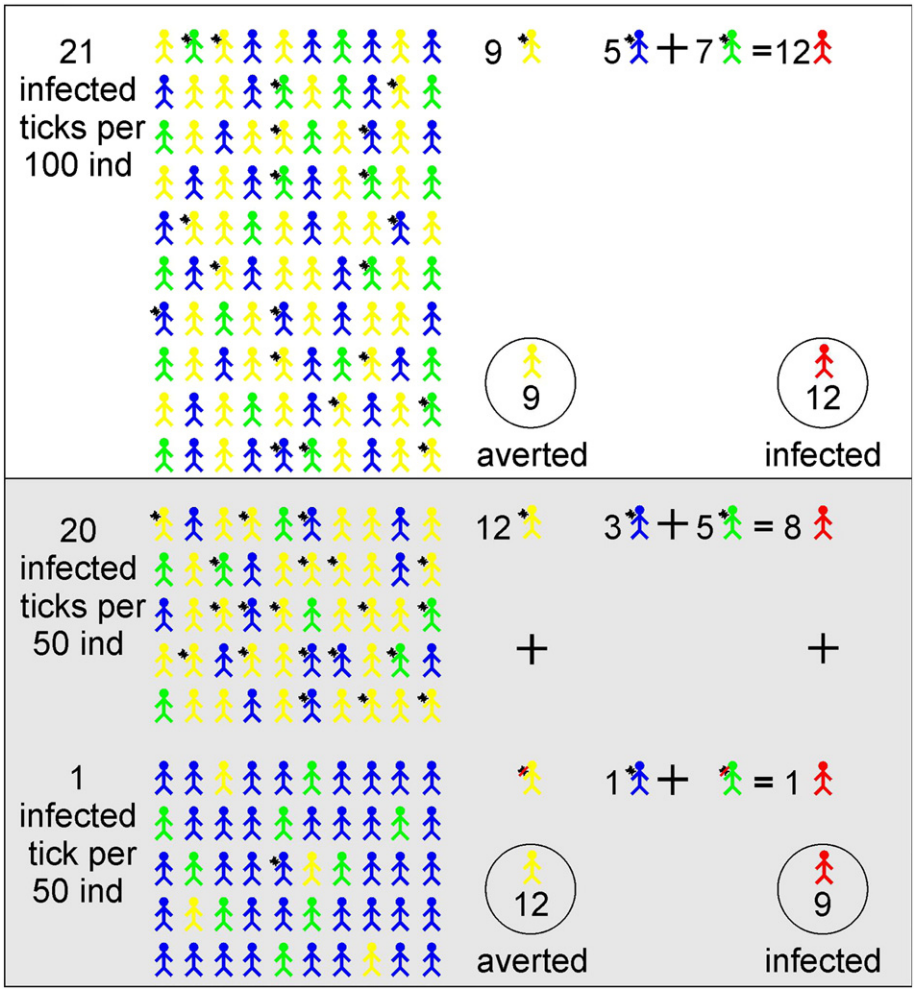

Fig. 4. Schematic representation of the effects of including spatial heterogeneity on model estimates. In 2 communities (50 people each) that collectively receive 21 infectious tick bites per year, 20 infectious tick bites occur in one community while 1 infectious tick bite occurs in the second community. If one does not consider the spatial heterogeneity in risk (100 individuals and 21 infectious tick bites per year), 24% of the people are expected to be in the susceptible state (blue), 33% in the previously infected but no longer resistant state (green), and 44% in the resistant state (yellow) each year given the parameters of the model. Thus, approximately 9 of the 21 infectious tick bites are expected to occur on a resistant individual, resulting in averted cases. Including spatial heterogeneity in risk, the higher incidence community (20 infectious ticks per year) is expected to have 60% of the people in the resistant state (yellow) leading to approximately 12 of the 20 infectious tick bites occurring on a resistant individual. The low incidence community has few individuals in the resistant state, but with only one infectious tick per year there will be at most 1 case. Thus, explicitly considering the spatial heterogeneity in incidence prevents underestimates of individuals in the resistant state in areas where there are many infectious ticks (high incidence areas). These underestimates in the proportion of people in the resistant state in high incidence areas result in underestimates of the public health impact of strain-specific immunity.

reduction in the number of averted cases is observed (Appendix D). Additionally, relaxing the assumption that strain-specific immunity is restricted to a single strain, and thus allowing partial protective cross-immunity, would result in an even greater estimated impact of strain-specific immunity, whereas relaxing the assumption that it is 100% protective would decrease its estimated impact. Although there is likely some error in each of these assumptions, none negate the importance of spatial heterogeneity in Lyme disease risk on the epidemiological impact of strain-specific immunity.

4. Conclusions

Recent data demonstrated that nearly every recurrence of Lyme disease in human patients was caused by a different strain of *B. burgdorferi* than that which caused the original infection (Nadelman et al., 2012), suggesting that initial infections may result in strain-specific immunity lasting at least 5 years (Khatchikian et al., 2014). An initial investigation using Lyme disease incidence data aggregated across the US suggested a real but moderate public health impact of strain-specific immunity (Khatchikian et al., 2015a). The current analysis, using finer spatial-resolution incidence data, suggests that the public health significance of strain-specific immunity is likely to be 7-fold greater than previously reported (Khatchikian et al., 2015a).

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diagmicrobio.2017.08.015.

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