Systematic Review and Meta-analysis of Lyme Disease Data and Seropositivity for *Borrelia burgdorferi*, China, 2005–2020

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Since its initial identification in 1986, Lyme disease has been clinically diagnosed in 29 provinces in China; however, national incidence data are lacking. To summarize Lyme disease seropositivity data among persons across China, we conducted a systematic literature review of Chinese- and English-language journal articles published during 2005–2020. According to 72 estimates that measured IgG by using a diagnostic enzyme-linked assay (EIA) alone, the seropositivity point prevalence with a fixed-effects model was 9.1%. A more conservative 2-tier testing approach of EIA plus a confirmatory Western immunoblot (16 estimates) yielded seropositivity of 1.8%. Seropositivity by EIA for high-risk exposure populations was 10.0% and for low-risk exposure populations was 4.5%; seropositivity was highest in the northeastern and western provinces. Our analysis confirms Lyme disease prevalence, measured by seropositivity, in many Chinese provinces and populations at risk. This information can be used to focus prevention measures in provinces where seropositivity is high.

Lyme disease is a tickborne zoonosis caused by genospecies of *Borrelia burgdorferi* sensu lato that occur primarily in the Northern Hemisphere, including North America, Europe, and some countries in Asia (*1*). In China, Lyme disease has been an emerging disease since the first human case was documented in Heilongjiang Province in 1986 (*2*). Multiple genospecies of *B. burgorferi* have been identified in China, although only *B. garinii*, *B. afzelii*, and *B. valaisiana*–related genospecies have been reported to cause disease in humans (*3*,*4*).

B. burgorferi is transmitted to humans by *Ixodes* ticks and in China specifically by *I. persulcatus*, *I. sinensis*, and *I. granulatus* ticks (*5*–*7*). Of those species, *I. persulcatus* ticks are regarded as the most competent vectors and are frequently identified in northeastern and select western, central, and eastern provinces (*6*). Lyme disease is widely distributed across China, and cases have been documented in 29 provinces across the country, several of which show endemicity in certain regions, specifically the northeastern provinces (*5*).

During the past several decades, Lyme disease has emerged as a public health issue for China; however, lack of information about disease burden makes it difficult for national and local governments to effectively develop and implement prevention strategies. No national Lyme disease surveillance exists in China, and no estimates of national disease incidence have been published. Thus, the only available approach for quantifying disease risk is human *B. burgorferi* seroprevalence, which reflects the proportion of persons in the population with positive serum test results for the pathogen. During 1987–1996, seroprevalence summarized from 22 provinces indicated an average seropositivity rate of 5.06% (*8*). Most of those early investigations focused on persons employed in forestry and were geographically limited to the northeastern provinces. Subsequently, human seropositivity data have been reported for provinces across all of China: in populations for which tick exposure varies, in populations in different

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DOI: https://doi.org/10.3201/eid2812.212612

occupations and age groups, and by using different diagnostic testing approaches (*9*).

To summarize published human Lyme disease seropositivity data for 2005–2020, we reviewed data from the literature. We provide updated summary estimates of seropositivity for individual exposure risk, by distinct provinces and for China overall, based on diagnostic testing approaches to determine exposure to *B. burgorferi*.

Methods

Search Strategy and Selection Criteria

We conducted a global systematic literature review across 5 databases, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (*10*). We tailored the search to each database accessed: PubMed, EMBASE, CABI direct, China National Knowledge Infrastructure, and Wanfang Data (Appendix Table 1, https://wwwnc.cdc.gov/EID/article/28/12/21-2612-App1.pdf); we limited the search to articles published from January 1, 2005, through December 31, 2020. After performing the keyword search and reviewing the abstracts of retained articles, we assessed full-text articles to confirm their eligibility for inclusion. Articles were included only if they reported numerator (clearly indicating the number of seropositive persons) and denominator (the population tested) and had a diagnostic testing strategy that included an enzyme immunoassay (enzyme-linked assay [EIA] or ELISA), immunofluorescence assay (IFA), or Western immunoblot (WB). We excluded articles that did not describe the sample population for the study. We used a snowball technique to identify additional eligible articles in the reference lists of excluded literature review articles.

The protocol for the English-language literature review was published in the PROSPERO database (registration CRD42021236906, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021236906). The search and extraction of the Chinese-language databases (China National Knowledge Infrastructure and Wanfang Data) occurred independently of the English-language literature review.

Variables

In China, human serum is analyzed for the presence of *Borrelia*-specific IgM or IgG with either an EIA (or ELISA) or an IFA (*11*). If the EIA or IFA result is positive or equivocal, a more specific WB (or line blot) is subsequently conducted; this method is referred to as a standard 2-tier testing approach. This approach emphasizes sensitivity initially with the first-tier test and then with the second-tier test (*12*). However, this approach is not consistently used in China (*13*). In general, diagnostic assays were not well characterized in many of the included articles because there was limited information on diagnostic performance data, standardization criteria for all genospecies, and consistency in assay specifications (e.g., antigens and reagents used).

The primary analytical strategy prioritized IgG measurements based on a single-tier EIA or IFA test. Although IgM-based tests are useful for clinical diagnosis of an early infection, they are also more likely than IgG-based tests to yield false-positive results; consequently, a sensitivity analysis was conducted for seropositivity estimates derived from an EIA or IFA that did not distinguish the results as either IgM or IgG positive. A second diagnostic sensitivity analysis was performed for estimates reporting 2-tier testing (EIA or IFA followed by WB), which may serve as a truer indicator of seropositivity. Neither sensitivity analysis included estimates used for the primary analytical strategy. We conducted subgroup analyses for estimates reported by exposure, sex, age group, and province based on an IgG measurement as determined by an EIA or IFA, similar to the primary analysis.

To adequately reflect potential variation in exposure to ticks and transmission of *Borrelia*, we characterized exposed populations. The study populations within reviewed articles were categorized into 2 broad categories: by clinical suspicion (sample identified from hospital or clinic settings, which is an unknown reflection of risk) or by exposure risk (risk for exposure to natural foci of Lyme disease, either by location or by occupation). Clinical suspicion cases are identified in hospital or clinic settings from persons with a history of suspected tick bites or with a clinical suspicion of Lyme disease (e.g., arthritis, nervous system disease, or early symptoms). To reduce biasing the risk assessment, we assessed exposure risk groups before performing statistical analyses. We categorized low exposure risk as persons who worked or lived in either nonforested plains areas or urban environments or who had minimal or no exposure to tick-infested habitats, medium exposure risk as persons whose work or location exposed them to tick-infested habitats but whose exposure was neither frequent nor prolonged, and high exposure risk as persons whose work or location frequently exposed them to forested areas or other areas where prolonged exposure to tick-infested habitat might have occurred.

Statistical Analyses

We descriptively summarized all articles for this meta-analysis and calculated fixed-effects summary estimates. Although the reviewed studies may be sufficient for drawing conclusions about the relationship between exposure and the outcome from the fixed-effects model, the studies themselves could be highly variable. Therefore, we conducted tests of homogeneity for the study samples for all studies. We assumed the variable "province" to be random and re-evaluated seropositivity to assess the robustness of the estimates by using the mixed-effects model. We considered a fixed-effects meta-analysis to be an appropriate method for summarizing seropositivity data for Lyme disease as the primary analytical strategy for the sensitivity analyses.

We used the number of available seropositivity estimates to calculate the overall least square mean summary estimate, SE, and lower and upper 95% CIs by using PROC Mixed in SAS (SAS Institute Inc., https://www.sas.com), in which the response term was the outcome (seropositivity) and the class term was province. We developed odds ratios to estimate the odds of an association between high-exposure risk group seropositivity and low-exposure risk group seropositivity, including corresponding 95% CIs. Given the paucity of data and variables available from each article, we made no adjustment for confounding in the fixed-effects models. We used forest plots to display the distribution of seropositivity and heterogeneity of the summarized seropositivity results. All analyses were conducted by using SAS version 9.4.

Results

Our literature review identified 3,657 articles that focused on China; 48 articles met the selection criteria (Figure 1), of which 42 articles met the criteria for the primary analytical strategy. In total, these 42 articles provided 72 estimates of seropositivity that we extracted for analysis. Some articles produced seropositivity estimates for multiple provinces or years (Appendix Table 2). Six articles did not meet the criteria for the primary analytical strategy; thus, they contributed data to only the 2 diagnostic sensitivity analyses. From the included studies, we compiled a description of estimates by subgroup (Table 1), by exposure group and province (Table 2), and by province (Figures 2, 3).

For the primary analytical strategy, the reported IgG seropositivity estimates based on a single-tier test (EIA or IFA) ranged from 0% to 37%; the fixed-effects modeled summary estimate was 9.1% (95% CI 7.5%–10.7%) (Table 1). When the random-effects model was used

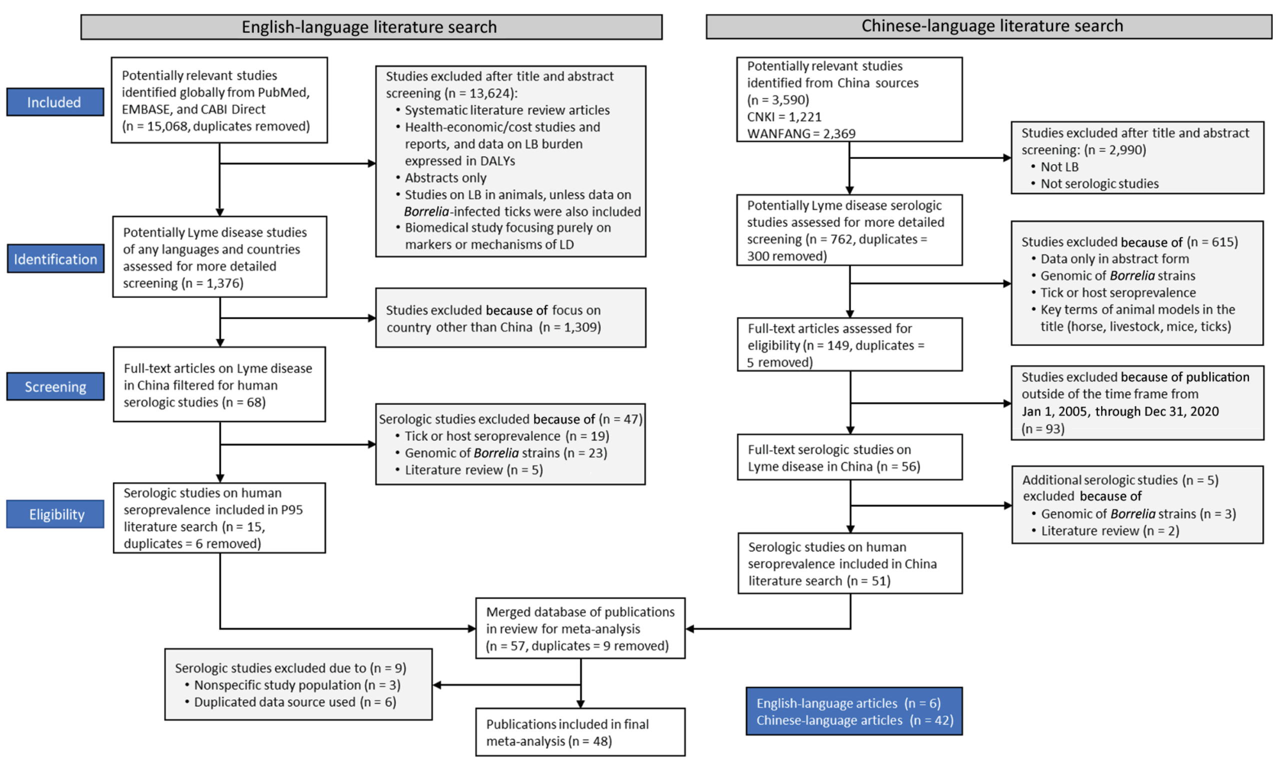

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (*10*) flow diagram of the 2 literature searches performed in review of seropositivity for *Borrelia burgdorferi* in China, 2005–2020. DALY, daily adjusted life years; LB, Lyme borreliosis; LD, Lyme disease.

Table 1. Modeled estimates of seropositivity for *Borrelia burgdorferi* sensu lato in China, 2005–2020*

Variable	Seropositivity estimates, no. (study denominator sample size)†	Modeled seropositivity, % (95% CI)
Primary analysis: IgG only	72 (34,719)	9.1 (7.5–10.7)
Sensitivity analysis		
IgM and IgG	35 (9,446)	14.5 (11.8–17.2)
EIA‡ + WB	16 (8,837)	1.8 (0.9–2.7)
Exposure group		
Clinical suspicion	10 (3,982)	7.1 (6.4–8.0)
Low risk	10 (5,245)	4.5 (3.9–5.1)
Moderate risk	12 (5,300)	6.1 (5.4–6.7)
High risk	40 (20,192)	10.0 (9.6–10.4)
Sex		
F	21 (7,542)	10.0 (6.6–13.2)
M	21 (8,223)	9.4 (6.2–12.6)
Age group, y		
<20	13 (1,420)	12.0 (4.4–19.6)
20–29	11 (1,416)	12.3 (6.3–18.4)
30–39	11 (1,734)	14.5 (5.9–23.1)
40–49	11 (1,757)	14.2 (8.5–20.0)
50–59	11 (1,434)	13.1 (8.5–17.7)
≥60	12 (1,429)	12.6 (6.6–18.5)

*EIA, enzyme immunoassay; WB, Western blot.
†Positive test results: primary analysis = 2,859; sensitivity analysis IgM and IgG = 1,260; sensitivity analysis EIA + WB = 147.
‡First-tier test was either an ELISA or immunofluorescence assay.

for the primary analytical strategy, neither estimate nor variance differed. The total sample size producing this summary estimate was 34,719 (Table 1).

Fewer articles and estimates were available for the diagnostic sensitivity analyses. For the sensitivity analysis based on 35 estimates (sample size of 9,446 obtained from 5 articles) that did not distinguish between IgG and IgM results, seropositivity was 14.5% (95% CI 11.8%–17.2%). For the sensitivity analysis that used a 2-tier testing system (16 estimates obtained from 6 articles with a sample size of 8,837), seropositivity was 1.8% (95% CI 0.9%–2.7%) (Table 1).

Seropositivity for the clinical suspicion sample was 7.1% (95% CI 6.4%–8.0%). Lyme disease seropositivity estimates by exposure risk populations were 4.5% (95% CI 3.9%–5.1%) for low risk, 6.1% (95% CI 5.4%–6.7%) for medium risk, and 10.0% (95% CI 9.6%–10.4%) for high risk (Table 1). The odds ratio of high exposure risk seropositivity compared with low exposure risk seropositivity was 2.4 (95% CI 2.1–2.7) and of moderate exposure risk seropositivity compared with low exposure risk seropositivity was 1.4 (95% CI 1.2–1.6).

Variation by province was substantial; the highest seropositivity estimates were 23.1% for Heilongjiang Province and 16.2% for Neimenggu (Inner Mongolia) Province (Figure 2). Moreover, variation across provinces was substantial (Figure 3). There was no discernable trend over time for seropositivity (data not shown).

Discussion

Our systematic literature review of *B. burgdorferi* seropositivity in China generated summary estimates by diagnostic test, exposure risk, sex, age group, province, and year. Depending on the testing algorithm applied, the seropositivity ranged from 1.8% to 14.5%, reflecting Lyme disease endemicity in the population. Combined with the widespread distribution of *Ixodes* ticks, specifically *I. persulcatus* ticks in many provinces, this analysis reinforces that Lyme disease is a public health problem in China.

The summary estimates of 9.1% among EIA/IFA positive samples and 1.8% among samples confirmed with WB fell within the range identified in Europe. In Germany, the nationwide, population-based cross-sectional KiGGS study estimated seropositivity among children and adolescents of 4.8% by single-tier ELISA testing (4% when confirmed by line blot) (*14*). A similar nationwide, population-based, cross-sectional study among adults in Germany (DEGS) reported overall seropositivity of 9.4%, confirmed by line blot (*15*). A cross-sectional health survey among a representative sample of adults in Finland reported seropositivity of 3.9% according to 2-tier testing (*16*). A representative sample of healthy blood donors from the Tyrol region of Austria reported a seropositivity range of 1.5%–7.2% from samples confirmed by line blot (*17*). A regional study in Turkey among healthy volunteers revealed seropositivity of 4.1% by single-tier testing with ELISA and 2.2% confirmed by WB (*18*).

In China, results of the diagnostic sensitivity analyses were consistent with expectations based on Lyme diagnostic testing limitations. Several studies did not adequately delineate the results by IgM or IgG positivity, and this joint numerator resulted in a substantially higher estimate than IgG seropositivity alone. IgM responses to *Borrelia* may persist over time, although IgM reactivity alone without isotype switching to IgG may reflect a false-positive result (*12*,*19*). False-positive results may provide an explanation for the higher seropositivity found when including results that did not distinguish between IgM and IgG. Testing results were further complicated in many studies by assays that used a whole-cell sonicate; such a lysate generates multiple antigens that can increase the likelihood that cross-reactive IgG or IgM creates a false-positive result compared with newer EIAs that focus on a reduced set of well-defined purified antigens specific to *B. burgdorferi* genospecies (*12*).

In many countries in Europe and in the United States, a 2-tier testing system for Lyme disease is used for clinical diagnosis and seroprevalence assessments. The sensitive first-tier test uses an ELISA, or less often an IFA, followed by a highly specific, second-tier WB if the ELISA is positive or equivocal. Diagnostic sensitivity can vary widely, with estimates ranging from as low as 14% during the early stages of disease to 100% as symptoms and manifestations evolve (*12*). The value of this standard 2-tier testing approach is improved specificity compared with ELISA or IFA alone (*9*,*20*). Specificity in all clinical phases is robust at ≥99% after the second-tier test. Recently, a modified 2-tier testing system based on 2 EIAs, which substitutes an EIA for the second-tier WB, has been implemented. Third-generation EIAs focus on select antigens; as a result, pairing with different EIAs enables substantial orthogonality that improves sensitivity while maintaining specificity (*12*). Neither of those 2-tier testing approaches has been widely adopted in China (*13*), where studies reporting the seropositivity of antibodies to *B. burgdorferi* relied primarily on the first-tier EIA or IFA and less often on the confirmatory, specific WB.

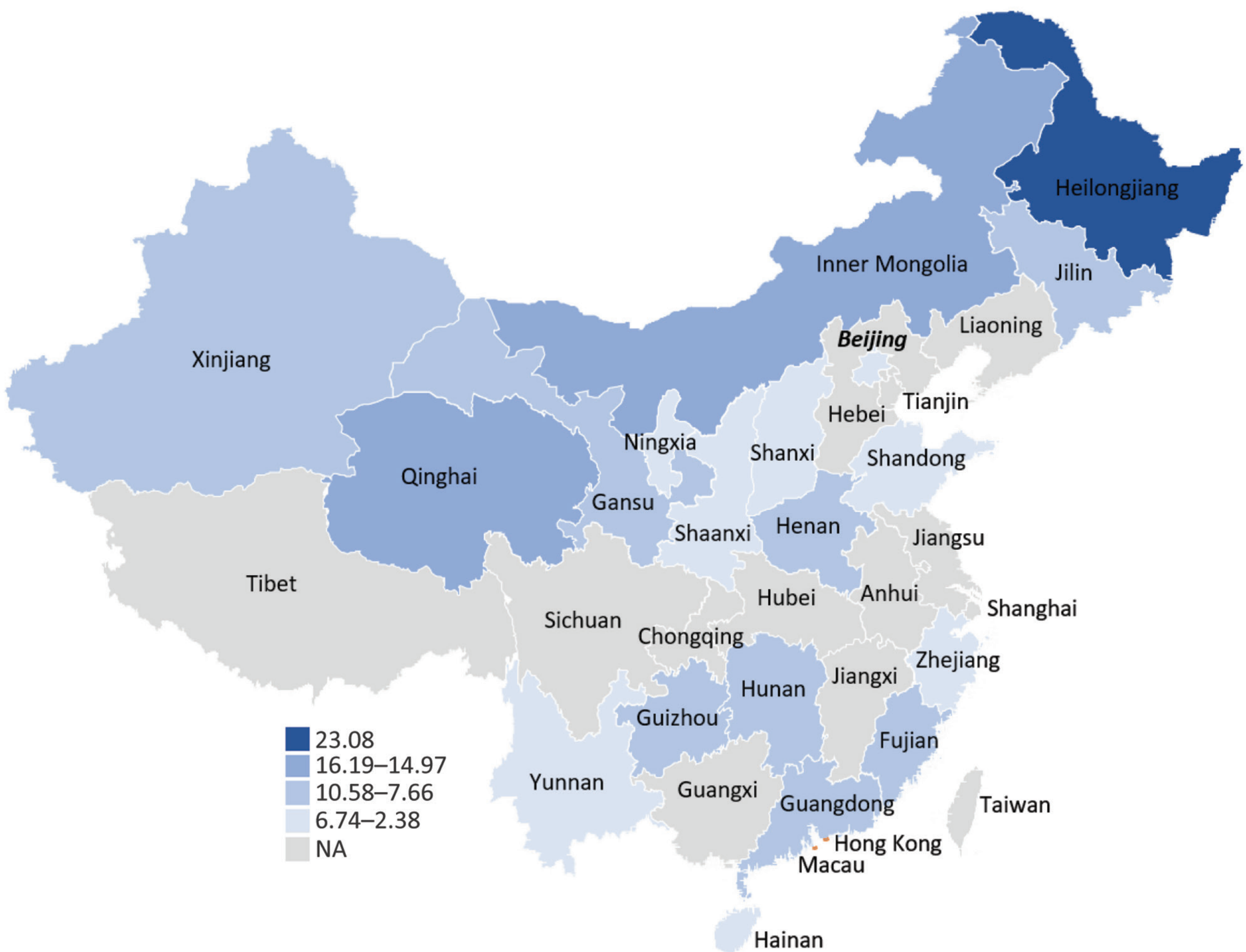

Figure 2. Estimated seropositivity for *Borrelia burgdorferi,* by province, China, 2005–2020. *Ixodes persulcatus* ticks, among the most frequently identified ticks in China, have been found across the northeastern and select western, central and eastern provinces. *I. sinensis* and *I. granulatus* ticks are the main identified vectors in the southern and eastern regions of the country. Variations in seropositivity reflect differences in tick competency, tick bite risk, and diagnostic tests. Numbers in key are percentages. NA, not applicable.

Furthermore, diagnostic performance data are not readily available from China, particularly across the range of testing procedures used. Some studies acknowledged use of reagents provided by the China Centers for Disease Control and Prevention, others used local commercial test kits, a few used nondomestic test kits, and several others did not describe the assays used. The China Centers for Disease Control and Prevention described criteria for standardization of a WB based on lysates of *B. garinii* bacteria; the assay used a single band for IgG or IgM, a criterion that differs from guidelines in Europe and the United States that require at least 2 of 3 bands by IgM or 5 of 10 bands by IgG to be classified as positive by WB (*12*,*13*). In addition, interpretation criteria were not consistent across associated articles. The few articles from our review that reported seropositivity with a confirmatory WB result led to a summary estimate substantially lower than the single-tier test (1.8% vs. 9.1%). The limited information on quality of assays, accreditation, and validation remains a major limitation of analytic interpretability. Nevertheless, the sampling for the 2-tier testing strategy occurred in 4 provinces across all types of exposure categories, providing some evidence of a representative seroprevalence estimate (Appendix Table 2).

Seropositivity was higher for populations that had been assessed as having a higher risk for exposure to a natural foci of Lyme disease, either by occupation or by location. These data were consistent with targeted samples of higher risk occupational groups from other countries. For instance, IgG seropositivity among farmers was 5.5%–9.7% in Belgium (*21*) and 10%–13.7% in Poland (*22*,*23*). Forestry workers are among the most sampled high exposure risk occupational groups; reported seropositivity was 14% in Lithuania (*24*), 31% in Hungary (*25*), 7.8% in Italy (*26*), 11.8% in Serbia (*27*), 10.9% in Turkey (*28*), 21.6% in Belgium (*29*), and 14%–34% in Poland (*22*,*30*). Likewise, increased seropositivity seen in medium to high exposure risk populations in China and consistency with data from Europe provide initial confidence in the overall estimates provided in this report.

The summary estimate in the clinical suspicion sample, which reflected a mixture of studies focused on history of a suspected tick bite or clinical suspicion of Lyme disease, was 7.1%. The TBD STING study in Sweden and Finland reported seroconversion after a tick bite for 3.5% of participants (*31*). Nonetheless, seroconversion does not necessarily reflect clinical infection because Lyme disease manifestation during the 3-month follow-up period did not develop for 57.6% of the *Borrelia*-infected persons who seroconverted. Among the seroconversions that resulted in clinical manifestations, these included erythema migrans (85%), *Borrelia* lymphocytoma (3%), nervous system disease (6%), or nonspecific symptoms of Lyme disease (6%). A study conducted in China documenting clinical manifestations after tick bite reported a lower proportion of erythema migrans (69%) and a higher proportion of nervous system disease (21%) and arthralgia (21%), among other manifestations (*32*). In the United States, a randomized controlled trial of a vaccine candidate documented an asymptomatic proportion of <10%, potentially arising from the shorter duration of follow-up for symptoms compared with that in Europe (*33*). Notwithstanding, differences in asymptomatic proportions and clinical

Table 2. Distribution of estimates of seropositivity for *Borrelia burgdorferi* sensu lato, by exposure group and province, China, 2005–2020

Province	Total no. estimates, n = 72	Clinical suspicion estimates, n = 10	Exposure group		
			Low risk, n = 10	Moderate risk, n = 12	High risk, n = 40
Beijing	6	2	1	1	2
Fujian	2	0	1	0	1
Gansu	4	0	0	0	4
Guangdong	2	0	0	1	1
Guizhou	3	0	1	1	1
Hainan	4	4	0	0	0
Heilongjiang	3	2	0	0	1
Henan	2	0	0	0	2
Hunan	2	0	0	0	2
Jilin	7	0	1	1	5
Neimenggu	4	1	1	0	2
Ningxia	1	0	0	0	1
Qinghai	2	0	0	0	2
Shaanxi	1	0	0	0	1
Shandong	1	0	0	0	1
Shanxi	2	0	0	0	2
Tianjin	2	0	1	0	1
Xinjiang	18	0	2	8	8
Yunnan	1	0	1	0	0
Zhejiang	5	1	1	0	3

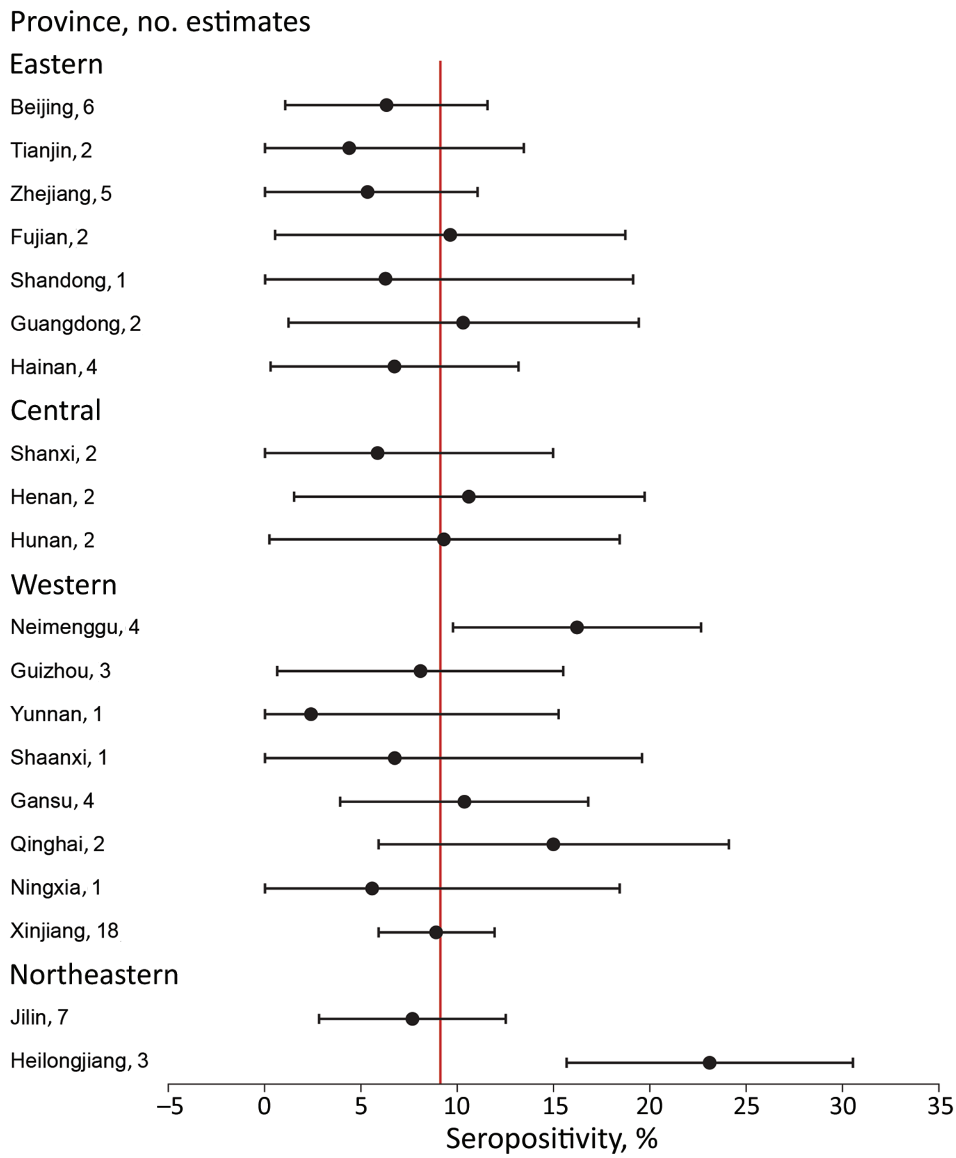

Figure 3. Forest plot illustrating seropositivity estimates for *Borrelia burgdorferi*, by province, China, 2005–2020. The red horizontal line indicates the summary estimate based on the primary analysis; error bars indicate 95% CIs. For 7 estimates, the lower bound of the 95% CI was <0 (a negative value); those values were fixed at 0% for interpretation.

manifestations between studies and countries may reflect differences in study design, duration of follow-up, diagnostic quality, timing of postinfection treatment, antibody waning, and circulating genospecies.

The highest summary seropositivity estimates were detected in 2 provinces in northeastern China (Heilongjiang Province, 23.1%) and western China (Neimenggu Province [Inner Mongolia], 16.2%). *I. persulcatus* ticks are among the most frequently identified ticks in China and have been found across the northeastern and select western, central, and eastern, provinces (*6*). Several other provinces that border Heilongjiang and Neimenggu Provinces have frequently reported the presence of *I. persulcatus* ticks, although the reported seropositivity has been lower (7%–10%). The lower calculated estimates within these provinces could reflect differences in the sampled exposure groups because studies from Heilongjiang and Neimenggu Provinces largely focused on populations for which higher infection prevalence was expected (e.g., forest residents and forestry workers). In addition, no samples from Heilongjiang and Neimenggu Provinces were tested by using the more conservative 2-tier testing strategy, which probably would have resulted in lower seropositivity estimates. Alternatively, lower seropositivity in border regions could reflect true differences in exposure risk. Other regions of China, particularly those in the southern and eastern regions, reported somewhat lower seropositivity (2%–10%). The distribution of *I. persulcatus* ticks is limited in these regions, although *I. sinensis* and *I. granulatus* ticks have been reported and are considered to be the main vectors in these provinces. However, demonstration of vector competency and efficiency of *I. sinensis* and *I. granulatus* ticks as vectors of *B. burgorferi* is unclear (*5*,*7*).

Other caveats to consider include the possibility that seropositivity may be driven by persons who become infected in higher incidence regions but reside in regions without efficient local transmission, because their limited awareness of Lyme disease precludes appropriate personal prevention measures. Another consideration is the local prevalence of Lyme disease for such persons. Despite good specificity of the test, a low a priori probability of disease will lead to a lower positive predictive value for true disease (*12*). Regardless of these caveats, increasing tick distributions across China has been attributed to planned reforestation and changing land use patterns leading to suitable environments to maintain the tick enzootic cycle and ultimately *Borrelia* transmission (*3*).

Among the study limitations, there were substantial variations in populations sampled (including persons seeking clinical care, or convenience samples), in risk exposure population targeting, and in varying study designs (none of the studies were designed to be nationally representative). More than half of the studies were conducted among a higher risk exposure population that probably elevated the summary estimate. With additional information on the percentage of the country's population at different levels of risk, a weighted average could be obtained, although this type of data is difficult to quantify. Second, the included studies used a range of testing methods that may not be comparable. For example, IFA was widely used to estimate seropositivity, but this traditional, manual method relies on the experience of the technician, leading to potentially lower specificity compared with enzyme immunoassay (EIA or ELISA) (*9*,*20*). In addition, 2-tier testing was not uniformly used, which could have resulted in potentially higher rates of false-positive results. Third, exposure risk may have been misclassified because an accurate description of specific testing populations may be missing from source manuscripts. Fourth, although *B. garinii* and *B. afzeli* have been reported as the predominant circulating genospecies, other circulating nonpathogenic genospecies may cause a false-positive result (*3*,*4*). Last, seropositivity estimates reflect exposure risk for infection regardless of clinically apparent disease; therefore, these summary estimates should not be interpreted as reflecting risk for clinical disease. Collectively, these limitations portend to overestimate seropositivity compared with other results as noted in Europe.

In conclusion, the results from this meta-analysis demonstrate seropositivity to *B. burgorferi* in China over the past several decades, particularly in certain provinces and in high exposure risk populations. By itself, however, the utility of this information for driving public health policy is limited because it gives no indication of clinical burden, either overall or by severity, and may not accurately represent geographic variations in risk. The expanding geographic range of infected ticks and increased likelihood of contact with humans will continue to present a public health challenge for China.

Acknowledgments

We thank Jennifer Moisi for her critical review of the manuscript. Editorial support was provided by Judith Kandel and funded by Pfizer Inc.

This study was supported and jointly funded by Valneva and Pfizer as part of their co-development of a Lyme disease vaccine.

J.H.S., J.C.Z., S.R.V., J.L., K.P., M.A.F., L.J., and B.D.G. are employees of Pfizer and may hold stock or stock options. X.L. declares no conflict of interest. L.B. is an employee of P95, which was contracted by Pfizer to conduct the research described in the article.

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Article DOI: https://doi.org/10.3201/eid2812.212612

Systematic Review and Meta-analysis of Lyme Disease Data and Seropositivity for *Borrelia burgdorferi*, China, 2005–2020

Appendix

Appendix Table 1. Search strategies and results by database

Database	Search strategy	Results
PubMed	Borreliosis OR lyme OR borrelia Filters: Full text, from 2005/1/1 - 2020/12/31	8,537
EMBASE	(((borrelia AND (2005:2020[pdat])) OR (lyme AND (2005:2020[pdat]))) OR (borreliosis AND (2005:2020[pdat]))) Filters: Date: Publication years 2005 – 2020; Pub. Types: Article, Data Papers, Review	10,445
Global Health (CABI Direct)	((borrelia OR lyme OR borreliosis) AND yr:[2005 TO 2020]) AND (((item-type:(("Journal article")))))	6,348
CNKI	Topic: Lyme disease (vague) OR Topic: Borrelia burgdorferi (vague) OR Topic: Lyme disease AND Serum (vague) Publication time: 1st Jan 2005 - 31st Jan 2020	2,032
Wanfang Data	All (vague): Lyme disease; All (vague): Borrelia burgdorferi; All (vague): Lyme disease AND Serum Publication time: 1st Jan 2005 - 31st Jan 2020	3,658

Appendix Table *2*. Studies included in systematic literature review contributing to seropositivity analyses and associated data points

Study	Year(s) of data collection	Province of data collection	Diagnostic test(s)	Antibody*	Sero-positivity, (%)†	Study Denominator	Exposure category	Study population details
Chen et al. (*1*)	2011	Beijing	ELISA	IgG	4.6%	549	Moderate exposure risk	Mountain residents of randomly selected survey sites in Miyun, Beijing, with history of defined field activities within one year. No specific forestry exposure mentioned.
Cui et al. (*2*)	2003–2006	Zhejiang	IFA	IgG	11.9%	932	High exposure risk	Forestry (forest farms) workers and mountain residents in three districts of Hangzhou, Zhejiang.
Dong et al. (*3*)	2004	Neimenggu (Inner Mongolia)	IFA	IgG	1. 10.4% 2. 33.3%	1. 671 2. 84	1. High exposure risk 2. Clinical suspicion	1. Forestry residents from forest farms of Greater Khingan, Neimenggu 2. Hospitalized psychiatric patients in the forestry area of Greater Khingan, Neimenggu
Dou et al. (*4*)	2013	Beijing	ELISA + WB	IgG	5.1%	801	Moderate exposure risk	Mountain residents lived near Miyun Reservoir in the northern suburb of Beijing. No specific forestry exposure mentioned.
Du et al. (*5*)	2010	Henan	IFA	IgG	10.3%	126	High exposure risk	Local residents in the mountain regions of Henan with high vegetation coverage and high risk of tick exposure during animal contact.

Study	Year(s) of data collection	Province of data collection	Diagnostic test(s)	Antibody*	Sero-positivity, (%)†	Study Denominator	Exposure category	Study population details
Geng et al. (*6*)	2001–2006	Multiple Provinces	IFA + ELISA	IgG & IgM	16.3%	827	Clinical suspicion	Serum samples from healthcare-seeking patients with clinical suspicion of Lyme disease (unclear forestry exposure)
Geng et al. (*7*)	2007	Jilin	IFA	IgG	10.8%	545	High exposure risk	Forestry residents from the forest region of Changbai and Tonghua counties, Jilin.
Geng et al. (*8*)	2007–2008	Multiple Provinces	IFA + ELISA	IgG & IgM	15.2%	105	Clinical suspicion	Serum samples from healthcare-seeking patients with clinical suspicion of Lyme disease (unclear forestry exposure)
Geng et al. (*9*)	2009	Heilongjiang	IFA	IgG	17.0%	342	Clinical suspicion	Healthcare seeking patients identified from Mudanjiang Forestry Central Hospital.
Gong et al. (*10*)	2002–2004	Zhejiang	1. IFA 2. IFA 3. ELISA 4. ELISA	IgG	1. 0.1% 2. 0.0% 3. 4.7% 4. 9.8%	1. 958 2. 162 3. 86 4. 430	1. High exposure risk 2. Clinical suspicion 3. Low exposure risk 4. High exposure risk	1. Forestry workers, mountain farmers, and other residents in the forestry area of Kaihua county and Tiantai county, Zhejiang 2. Suspected Lyme disease cases identified from community health centers. All surveyed individuals were local farmers. No specific forestry exposure mentioned. 3. Urban or suburb residents from Lishui, Zhejiang 4. Forestry (forest farms) workers and farmers from Lishui, Zhejiang
Gu et al. (*11*)	NA	Heilongjiang	ELISA	IgG	33.9%	498	High exposure risk	Forestry residents from multiple forest farms of Xiao Hinggan Mountains, Heilongjiang
Hao et el (*12*).	NA	Multiple Provinces	IFA	IgG	10.3%	3,669	High exposure risk	Human population in forest areas of 8 provinces in China, covering a wide area of the country from north to south. Investigation sites were chosen based on clear evidence of ticks in the environments. Study population had lived in the forest areas and often worked in the fields.
Ji (*13*)	1. 2013 2. 2014	Neimenggu (Inner Mongolia)	1. IFA 2. ELISA	IgG	1. 16.9% 2. 4.1%	1. 136 2. 98	1. High exposure risk 2. Low exposure risk	1. Individuals from mountain region, forestry area 2. Individuals from plains area
Li et al. (*14*)	2008	Yunnan	ELISA	IgG	2.4%	42	Low exposure risk	University students. A convenient sample taken from health checks in a university in Yunnan. No forestry exposure mentioned.
Li et al. (*15*)	2008–2009	Shaanxi	IFA	IgG & IgM	6.7%	194	High exposure risk	Forestry workers, mountain farmers, and other local residents with long-term residency (greater than 5 years) in three forestry areas of Shaanxi.

Study	Year(s) of data collection	Province of data collection	Diagnostic test(s)	Antibody*	Sero-positivity, (%)[†]	Study Denominator	Exposure category	Study population details
Li et al. (*16*)	2013	Hainan	1. IFA 2. IFA + WB	IgG	1. 12.4% 2. 2.8%	1. 251 2. 251	Clinical suspicion	Healthcare-seeking patients identified from a hospital in Hainan. Suspected cases were defined as patients with clinical diagnosis of neurological symptoms.
Li et al. (*17*)	2015	Hainan	1. IFA 2. IFA + WB	IgG	1. 3.3% 2. 1.5%	1. 1,334 2. 1,334	Clinical suspicion	Healthcare-seeking patients identified from multiple hospitals in Hainan. Suspected cases were defined as patients with clinical diagnosis of arthritis and/or neurological disease suspected of Lyme disease (excluding rheumatoid arthritis and other related diseases).
Lin (*18*)	NA	Jilin	ELISA	IgG	8.3%	218	High exposure risk	Forestry residents from multiple forest farms of Changbai mountain, Jilin
Lin et al. (*18*)	2007	Fujian	IFA	IgG	17.1%	269	High exposure risk	Forestry workers, mountain farmers, and other local residents of the north forest area (Wuyi Mountain) in Fujian.
Liu et al. (*19*)	2006	Hunan	IFA	IgG	10.2%	914	High exposure risk	Forestry workers, mountain farmers, and other local residents in the mountain forestry areas of Shandong
Liu et al. (*20*)	2010–2011	Heilongjiang	IFA	IgG	18.3%	180	Clinical suspicion	Healthcare-seeking patients with recent tick bite in the past 2 months identified from Mudanjiang Forestry Central Hospital, Heilongjiang. The participants usually presented with tick-borne disease related clinical symptoms.
Long et al. (*21*)	2013–2014	Xinjiang	IFA	IgG	5.7%	637	Low exposure risk	Voluntary blood donors (urban residents) in People's Hospital of Xinjiang Uygur Autonomous Region. Most of the urban residents were not exposed to forestry or pastoral environments.
Song et al. (*22*)	2000–2003	Tianjin	IFA	IgG	1. 6.9% 2. 1.8%	1. 735 2. 170	1. High exposure risk 2. Low exposure risk	1. Local residents from mountain regions or mid-levels of Tianjin 2. Local residents from plains areas of Tianjin
Sun et al. (*23*)	1998–2003	Xinjiang	IFA or ELISA	IgG & IgM	13.0%	7,956	Moderate exposure risk	Workers and other local residents of Xinjiang prospecting bureau of Henan oil field, in natural foci of Lyme disease in Xinjiang.
Sun et al. (*24*)	2002–2004	Gansu	IFA	IgG	12.9%	240	High exposure risk	Forestry (forest farms) workers in both protected natural forests and nursey forests.
Tan et al. (*25*)	1999–2004	Xinjiang	1. IFA 2. IFA + WB	IgG	1. 12.1% 2. 3.1%	1. 223 2. 223	High exposure risk	Natural population (including residents and forestry workers) in natural foci of Lyme disease in Southern Mountainous Area of Urumqi, Xinjiang. The survey sites are exposed to high level of forests, pastures, wild animals and plants.

Study	Year(s) of data collection	Province of data collection	Diagnostic test(s)	Antibody*	Sero-positivity, (%)†	Study Denominator	Exposure category	Study population details
Tan et al. (*26*)	2000–2004	Xinjiang	IFA + WB	IgG	NA‡	NA‡	1. High exposure risk 2. Moderate Exposure Risk	1. Natural population in natural foci of Lyme disease in six districts of Xinjiang, including forestry workers, pastoral workers, and border soldiers. Individuals with no clinical suspicion of Lyme disease were randomly surveyed from hospitals and out-patient clinics of Xinjiang as comparison group. No specific forestry exposure mentioned but noted this region in Xinjiang is endemic to Lyme disease.
Tan et al. (*27*)	1. 2002 2. 2006	Xinjiang	WB	IgG	1. 0.3% 2. 37.0%	1. 1,406 2. 119	1. Moderate exposure risk 2. Moderate exposure risk	1. Human population in natural foci of Lyme disease in Xinjiang were selected. 2. Individuals in natural foci of Lyme disease in Xinjiang with negative test results in the previous epidemiologic study in 2002.
Wang et al. (*28*)	1990	Shandong	IFA	IgG	6.3%	1,934	High exposure risk	Forestry (forest farms) workers and local residents of multiple regions in Shandong.
Wang et al. (*28*)	1990–2003	Guizhou	IFA	IgG	5.0%	139	Moderate exposure risk	Workers and other residents (including mostly agrarian population and selective forestry workers) living in agricultural county.
Wang et al. (*29*)	2005	Beijing	IFA	IgG	1. 9.5% 2. 3.0% 3. 8.5%	1. 370 2. 331 3. 47	1. Moderate exposure risk 2. Low exposure risk 3. Clinical suspicion	1. Local residents and pastoral workers in the natural foci of Lyme disease in Miyun district, Beijing. No forestry exposure mentioned. 2. Local residents engaged in tourism reception work at home. Had low or minimal risk of tick exposure. 3. Local residents with neurologic disorders identified from local mental health care facility.
Wang et al. (*30*)	2006	Jilin	IFA	IgG	6.6%	617	Moderate exposure risk	The mountainous area and the border area in conjunction with North Korea. Survey sites in Tonghua, Ji'an, and Changbai counties of Jilin are selected, which are representative of Lyme disease-endemic area in Jilin. No specific forestry exposure mentioned.
Wang et al. (*31*)	2003–2008	Jilin	IFA	IgG	5.0%	909	Low exposure risk	Local residents from the plains regions of five districts in Jilin
Wang et al. (*31*)	NA	Jilin	ELISA	IgG	7.0%	1,002	High exposure risk	Local residents from the mountainous forest region of Jilin county and Yanbian county, Jilin. These regions have high forestry coverage

Study	Year(s) of data collection	Province of data collection	Diagnostic test(s)	Antibody*	Sero-positivity, (%)†	Study Denominator	Exposure category	Study population details
								and Lyme disease-endemic area.
Wu et al. (*32*)	2016	Xinjiang	ELISA	IgG	4.1%	1,500	Low exposure risk	Individuals participated in health checks in the urban region of southern Xinjiang. No forestry exposure mentioned.
Xia et al. (*33*)	NA	Jilin	ELISA	IgG	6.8%	281	High exposure risk	Forestry residents from multiple forest farms of Tonghua county, Jilin.
Xie et al. (*34*)	NA	Guangdong	IFA or ELISA	IgG	1. 10.3% 2. 10.3%	1. 1,191 2. 993	1. High exposure risk 2. Moderate exposure risk	1. Natural population in living in forestry area (forest farms) of Meizhou, Guangdong (natural foci of Lyme disease). 2. Natural population living in non-forestry area of Meizhou, Guangdong (natural foci of Lyme disease).
Yang et al. (*35*)	2016	Beijing	ELISA + WB	IgG	9.3%	140	Clinical suspicion	Healthcare-seeking patients identified from 10 community health centers in Lyme disease natural foci of Miyun, Beijing. Suspected cases were defined as patients with clinical diagnosis of arthritis (excluding rheumatoid arthritis and other related diseases).
Ye et al. (*36*)	2005	Fujian	IFA	IgG	2.1%	239	Low exposure risk	Individuals participated in health checks (including pregnant women and drug users) in the urban region of Xiamen, Fujian. No specific forestry exposure mentioned.
Yu et al. (*37*)	2006	Gansu	IFA	IgG	10.9%	522	High exposure risk	Forestry (forest farms) workers and local residents of Diebu county, Gansu.
Yue & Shi (*38*)	NA	Qinghai	IFA	IgG	15.1%	1,108	High exposure risk	Forestry workers, farmers, and other forestry residents in agricultural or pastoral county.
Zhang et al. (*39*)	2005	Shanxi	IFA	IgG	6.2%	227	High exposure risk	Forestry workers and mountain residents in Shanxi
Zhang et al. (*40*)	2009	Multiple Provinces	IFA	IgG	7.0%	725	High exposure risk	Forestry residents of four provinces in northern China, including Xinjiang, Gansu, Ningxia, and Shaanxi
Zhang et al. (*41*)	2013	Hainan	1. IFA 2. IFA+ WB	1. IgG & IgM 2. IgG & IgM	1. 16.6% 2. 2.3%	1. 259 2. 259	Clinical suspicion	Healthcare-seeking patients identified from a hospital in Hainan. Suspected cases were defined as patients with clinical diagnosis of arthritis or neurological disease suspected of Lyme disease.
Zhao et al. (*42*)	2012	Xinjiang	ELISA	IgG	1. 5.9% 2. 2.9%	1. 101 2. 34	1. High exposure risk 2. Moderate exposure risk	1. Border guard soldiers stationed in mountain/forest habitats in northern Xinjiang. 2. Border guard soldiers stationed in the Gobi/desert habitats in northern Xinjiang. Indicated occupational risk of tick exposure.
Zhu et al. (*41*)	2013	Hainan	1. IFA 2. IFA+ WB	IgG	1. 7.7% 2. 1.3%	1. 542 2. 542	Clinical suspicion	Healthcare-seeking patients identified from a hospital in Hainan. Suspected cases were defined as patients with

Study	Year(s) of data collection	Province of data collection	Diagnostic test(s)	Antibody *	Sero-positivity, (%)†	Study Denominator	Exposure category	Study population details
Zhu et al. (*43*)	2015	Hainan	1. IFA 2. IFA+ WB	IgG	1. 3.4% 2. 1.4%	1. 900 2. 900	Clinical suspicion	clinical diagnosis of arthritis or neurological disease suspected with B. burgdorferi infection (excluding related diseases). Healthcare-seeking patients identified from two hospitals in western region, Hainan. Suspected cases were defined as patients with clinical diagnosis of arthritis or neurological disease suspected of Lyme disease (excluding rheumatoid arthritis and other related diseases).
Zhuang et al. (*44*)	2006	Guizhou	1. IFA 2. IFA+ WB	IgG	1. 5.3% 2. 1.1%	1. 1,233 2. 1,233	Low exposure risk	Rural population of 8 counties in Guizhou (alpine, mainly plains area). No specific forestry exposure mentioned.

*Antibody measured reflects data used for analysis. For IgG and IgM, results were presented collectively without separation. ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; IgG, immunoglobulin G; IgM, immunoglobulin M; WB, Western immunoblot.
†Multiple estimates from same source presented as the total estimate.
‡Multiple data points available in Supplementary Table 1.

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