

Efficacy of antibiotic prophylaxis for the prevention of Lyme disease: an updated systematic review and meta-analysis

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Background: The clinical value of antibiotic prophylaxis in preventing Lyme disease remains uncertain, owing to a meta-analysis lacking sufficient power to demonstrate efficacy and a more recent trial showing effectiveness but lacking precision. Our objective was to update our prior meta-analysis on antibiotic prophylaxis for the prevention of Lyme disease, to obtain a more precise estimate of treatment effect.

Methods: Clinical trials were identified by searching MEDLINE, Embase, the Cochrane Library and trial registries, and by an assessment of the bibliographies of retrieved articles and reviews. Trials were selected if their patients were randomly allocated to a treatment or placebo group within 72 h following an *Ixodes* tick bite and had no clinical evidence of Lyme disease at enrolment. Details of the trial design, patient characteristics, interventions and outcomes were extracted from each article. Study quality was assessed using the Jadad scale.

Results: Four placebo-controlled clinical trials were included for review. Among 1082 randomized subjects, the risk of Lyme disease in the placebo group was 2.2% [95% confidence interval (CI), 1.2%–3.9%] compared with 0.2% (95% CI, 0.0%–1.0%) in the antibiotic-treated group. Antibiotic prophylaxis significantly reduced the odds of developing Lyme disease compared with placebo (pooled odds ratio=0.084; 95% CI, 0.0020–0.57; $P=0.0037$).

Conclusions: The available evidence to date supports the use of antibiotic prophylaxis for the prevention of Lyme disease in endemic areas following an *Ixodes* tick bite. Pooled data from four placebo-controlled trials suggests that one case of Lyme disease is prevented for about every 50 patients who are treated with antibiotics.

Keywords: *Borrelia burgdorferi*, borreliosis, *Ixodes*, primary care, tick bites

Introduction

Lyme disease is the most commonly reported vector-borne infection in the USA, with 27 444 reported cases in 2007.¹ In the USA, the disease is caused by transmission of the spirochaete *Borrelia burgdorferi* following an *Ixodes* spp. tick bite. The most common clinical manifestation is an expanding skin lesion, erythema migrans, which usually occurs at the site of the tick bite after 7–14 days. Subsequent extracutaneous features may develop in untreated patients, which include certain neurological, cardiac and musculoskeletal conditions. Despite the goals set by the US Department of Health and Human Services to target a 44% reduction in the incidence of Lyme disease,² the number of reported cases has continued to increase, prompting a renewed interest in prevention strategies.

For the primary prevention of Lyme disease, the 2006 Infectious Diseases Society of America guidelines recommend

avoiding tick-infested areas.³ When in such areas, they suggest the use of protective clothing, tick repellents and routine personal inspection, with prompt removal of attached ticks. The role for Lyme disease prevention by antibiotic prophylaxis following a documented *Ixodes* tick bite, however, remains controversial.³ In 1996, we published a meta-analysis⁴ of three randomized placebo-controlled trials^{5–7} that included 600 patients with *Ixodes* tick bites. The analysis lacked sufficient power to demonstrate treatment efficacy of antibiotic prophylaxis for Lyme disease after an *Ixodes* tick bite in endemic areas [odds ratio (OR)=0.0; 95% confidence interval (CI), 0.0–1.5; $P=0.12$]. Since then, a larger clinical trial has been published that established the treatment efficacy of prophylaxis with a single dose of doxycycline.⁸ This latest trial estimated a relative risk reduction of 87%, but lacked precision due to a wide CI (95% CI, 2.9%–100%).⁸ In view of the uncertain clinical value of prophylaxis after an *Ixodes* tick bite, we sought to obtain

a more precise estimate of the effectiveness of chemoprophylaxis by conducting a follow-up meta-analysis that includes all of the evidence to date.

Methods

Data sources and study selection

To identify controlled trials on antibiotic prophylaxis for Lyme disease published after our prior meta-analysis,⁴ we searched MEDLINE, Embase and the Cochrane Central Register of Controlled Trials from 1 January 1995 to 1 April 2009 using the keyword combination '(Lyme or borreliosis) and (prophylaxis or prevention)', without language restrictions. We retrieved full-length texts of all articles potentially pertaining to Lyme disease chemoprophylaxis after a review of titles and abstracts from our search. References of obtained articles were reviewed to identify additional studies for retrieval. To minimize publication bias, we searched for unpublished trials in the metaRegister of Controlled Trials⁹ and in the NIH registry¹⁰ using the search term 'Lyme disease'.

We applied similar eligibility criteria to the retrieved articles as in our prior meta-analysis.⁴ Trials were included if their patients were randomly allocated to a treatment or placebo group, enrolled within 72 h following an *Ixodes* tick bite and had no clinical evidence of Lyme disease at enrolment. We did not restrict trials based on the antibiotics used, age of the patients enrolled, length of patient follow-up or the outcomes observed.

Data extraction

Using our prior protocol,⁴ the following data were extracted from the eligible trials: the year of publication; patient demographics; the number of patients enrolled and completing the trial; the antimicrobial agent used (including dose, schedule and duration of therapy); and the duration of patient follow-up. We also extracted details of the trial design, including inclusion and exclusion criteria, patient and physician blinding, randomization procedures, compliance with taking the antimicrobial agent, adverse reactions to antibiotics, dropout and exclusion rates, the percentage of ticks infected, and laboratory methods for the detection of *B. burgdorferi* antibody in human serum. Outcome data were extracted from each trial for the number of subjects that experienced an unfavourable event in each arm of therapy. An unfavourable event was defined as the development of erythema migrans at the site of the tick bite or an objective manifestation compatible with early extracutaneous Lyme disease (e.g. seventh cranial nerve palsy) or late Lyme disease (e.g. arthritis) confirmed by seroconversion. Other clinical outcomes, such as an acute viral-like illness without erythema migrans, were not included as unfavourable events for statistical analysis. Data were extracted independently by two of the authors (S. W. and G. P. W.), and disagreements were resolved through discussion and consensus.

Validity assessment

Validity assessment was performed using methods described by Jadad *et al.*¹¹ for the evaluation of randomized clinical trials. A quality score was assigned to each study based upon the responses to five yes-or-no questions (maximum score of 5). A point was awarded if the study was described as randomized. An additional point was awarded if the method of randomization was clearly described and appropriate. A point was awarded if the study was described as double-blind. An additional point was awarded if an identical-appearing placebo was used. A point was given if the reasons for withdrawal were provided for all persons who did not complete the follow-up period or were not included in the final analysis. Trials with a total score of three or greater were considered to be of superior quality.¹² Blinded assessment

of each trial was performed independently by two reviewers (L. K. F. and D. H. L.) and disagreements were resolved through discussion.

Quantitative data synthesis

An exact stratified analysis, using StatXact, Version 3.0.2 (Cytel Software Corp., Cambridge, MA, USA, 1996) computer software, was used to: perform conditional maximum likelihood estimates (CMLEs) for the OR and the 95% CI for each trial; calculate the CMLEs for the pooled OR and its 95% CI; and perform an exact test of homogeneity to observe the consistency between the results of the four trials. A *P* value of >0.1 was used to define homogeneity. The overall risk of infection for the antibiotic prophylaxis and placebo groups was calculated as the sum of the unfavourable events divided by the total number of subjects in each group. The 95% CIs of these risks were computed with StatXact using an exact binomial method.

The number needed to treat (NNT) to prevent one case of Lyme disease was calculated using the formula:

$$\text{NNT} = 1/[\text{baseline risk} \times (1 - \text{relative risk})],$$

where the overall risk of infection on placebo was used as the baseline risk, and the relative risk was calculated from the OR using the formula:¹³

$$\text{relative risk} = \text{OR}/[(1 - \text{baseline risk}) + (\text{baseline risk} \times \text{OR})]$$

The 95% CI estimates for NNT were computed using the 95% CIs of the OR.

Results

Literature search and selection of trials

Figure 1 summarizes the process of trial selection. Our database search identified 1316 unique references (available on request), of which 1175 references were excluded after review of their titles and abstracts, because they did not pertain to Lyme disease chemoprophylaxis. The remaining 141 full-text articles were retrieved and 10 additional studies were identified upon review of the references of the obtained articles. Upon further review of the 151 full-text articles, 140 were excluded because they did not report original data (were not clinical studies). Of the 11 remaining studies,^{8,14-23} 1 study⁸ met our eligibility criteria to be added to our prior meta-analysis. Thus, our meta-analysis was based on four randomized trials.⁵⁻⁸

Trial design and study characteristics

Table 1 summarizes the study design of the four randomized, double-blind, placebo-controlled trials included for analysis. All four trials were conducted in areas where Lyme disease is endemic and all trials enrolled patients with an *Ixodes scapularis* tick bite within the preceding 72 h. In all four trials, the blinding of patients was performed by giving them identical-appearing tablets, capsules or liquid suspensions. The success of patient blinding was assessed in only one study.⁶ In all four trials, physicians were reported to be 'blinded' to the treatment allocation. However, no trial reported how physician blinding was assessed. Two trials assessed patient compliance: the first⁶ measured patient compliance by assessing the antimicrobial activity of patient urine; and the other⁸ asked subjects to swallow the single-dose regimen under direct observation by study personnel.

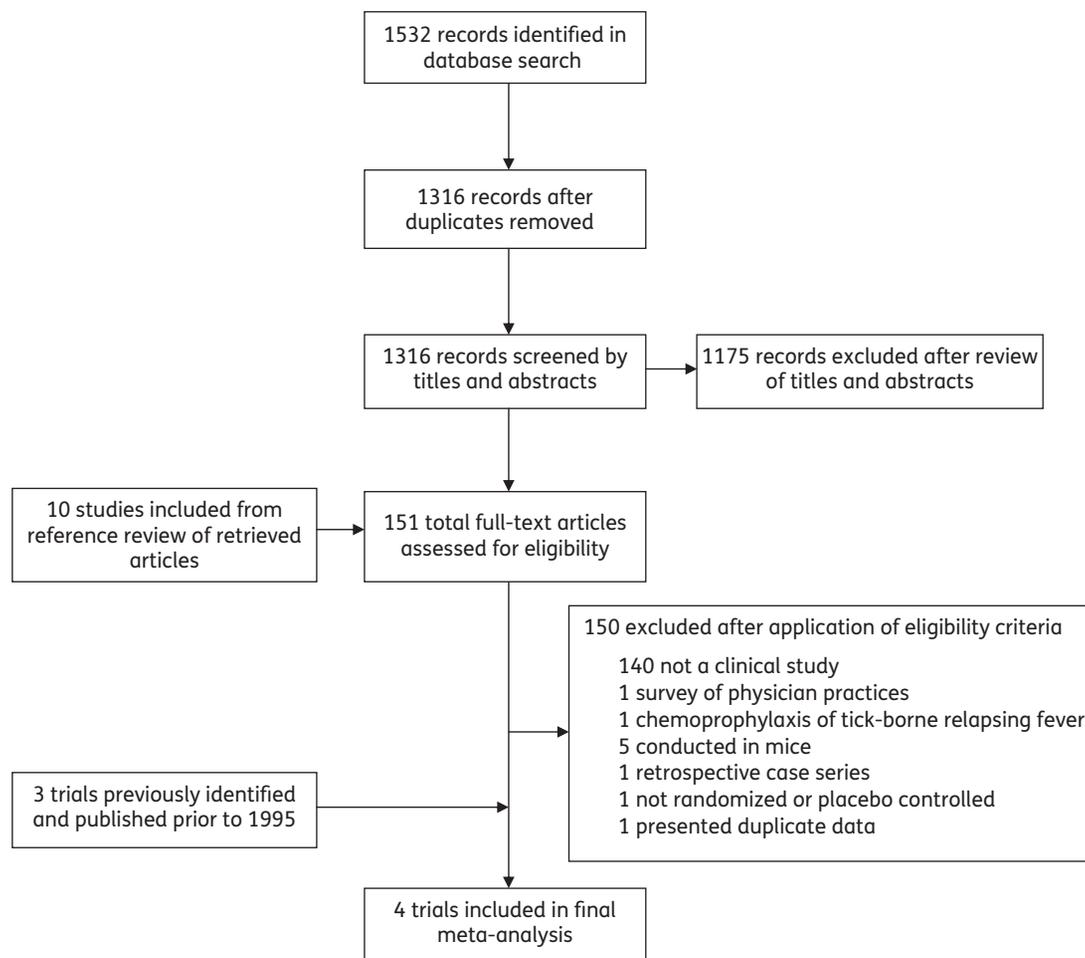


Figure 1. Literature search and study selection flowchart for the meta-analysis.

All of the four clinical trials^{5–8} used the development of erythema migrans or symptoms of extracutaneous Lyme disease as their primary outcome for statistical analysis. All trials measured serum antibodies against *B. burgdorferi* at presentation and upon follow-up. Only two trials^{6,8} confirmed equivocal or positive results with immunoblot assays.

Table 2 summarizes the study characteristics of the four trials included for analysis. A total of 1145 patients were enrolled in the four trials. The total number included in the final data analysis was 1082: 543 in the antibiotic prophylaxis group and 539 in the placebo group.

Dosage, duration and types of antibiotics tested varied among trials. In three trials,^{5–7} a 10 day course of treatment was administered. In the other trial,⁸ subjects were given two 100 mg capsules of doxycycline as a single dose.

In the antibiotic-treated groups, 4% of patients developed a rash to penicillin,⁵ 1% developed a rash to amoxicillin,⁶ no patients developed an allergic reaction to penicillin or tetracycline⁷ and 0% developed a rash due to doxycycline.⁸ The trial using doxycycline reported a 15% incidence rate of nausea in their treated patients.⁸ Serious adverse reactions, such as anaphylaxis, were not reported in any of the trials.

Exclusion and dropout rates of patients were generally low. In one trial,⁵ 18% of patients were excluded from analysis for

failure to return for follow-up venepuncture. In another trial, 4% of patients dropped out of the study primarily for refusing repeat venepuncture and 2% were excluded from analysis after randomization because they had serological evidence of past infection with *B. burgdorferi* (IgG ELISA).⁶ In a third trial, 3% were excluded from analysis because four patients with an inter-current illness were treated with antibiotics and one patient refused repeat venepuncture.⁷ In the most recent trial, 5% of patients were excluded from analysis after randomization because they were bitten by ticks other than *I. scapularis*.⁸ The patients lost to follow-up (11%), however, were included in the final data analysis.

In all four trials, cases of erythema migrans were reported; however, none of the patients in the trials developed an objective extracutaneous manifestation of Lyme disease. Two of the four trials reported patients who developed an acute viral-like illness without erythema migrans but with putative laboratory evidence of *B. burgdorferi* infection.^{7,8} One trial reported a patient in the placebo group who developed an influenza-like illness without erythema migrans but with a ‘weakly positive’ immunofluorescence assay (IFA) titre after 6 weeks (immunoblot testing was not performed).⁷ Another trial reported three patients who developed an acute viral-like illness without erythema migrans.⁸ Two patients were in the placebo group:

Table 1. Study design of included trials

Trial, year	Study location and state	Inclusion criteria	Exclusion criteria	Method of randomization	Method of blinding	Primary outcome
Costello <i>et al.</i> , 1989 ⁵	multiple practice sites, Madison, CT	age ≥ 5 years, <i>I. scapularis</i> tick bite within 72 h	current antibiotics, pregnancy, penicillin allergy, clinical signs of Lyme disease	not reported	double-blind, identical placebo	erythema migrans or symptoms of extracutaneous Lyme disease ^a
Shapiro <i>et al.</i> , 1992 ⁶	single site, Middletown, CT	<i>I. scapularis</i> tick bite within 72 h	tick bite between 3 and 42 days prior to study, penicillin allergy, pregnancy, antimicrobial use, positive IgG Lyme disease titre at enrolment	table of random numbers	double-blind, identical placebo	erythema migrans or symptoms of extracutaneous Lyme disease with seroconversion ^b
Agre and Schwartz, 1993 ⁷	one paediatric practice, Westchester County, NY	age 3–19 years, <i>I. scapularis</i> bite within 72 h	none reported	predetermined by coin flip	double-blind, identical placebo	erythema migrans or symptoms of extracutaneous Lyme disease ^c
Nadelman <i>et al.</i> , 2001 ⁸	two hospitals, Westchester County, NY	age ≥ 12 years, <i>I. scapularis</i> tick bite within 72 h	clinical signs of Lyme disease, current antibiotics, pregnancy, lactation, prior vaccination	randomized list in 1:1 ratio	double-blind, identical placebo	erythema migrans at site of tick bite ^d

^aSecondary outcome was *B. burgdorferi* seroconversion determined by IgM or IgG ELISA drawn at 3 weeks and at 6 months.

^bSeroconversion was determined by IgM or IgG ELISA, confirmed by western immunoblot drawn at 3 weeks and at 6 months.

^cSecondary outcome was seroconversion determined by IFA drawn at 6 weeks.

^dSecondary outcomes were erythema migrans at a site other than the tick bite or laboratory evidence of *B. burgdorferi* seroconversion in the absence of erythema migrans. Seroconversion was determined by IFA or ELISA, confirmed by IgM immunoblot drawn at 3 weeks and at 6 weeks.

Table 2. Study characteristics of included trials

Trial	Patients enrolled (completed), N (n)	Patient characteristics	% Male	Antibiotics used	Daily dose (mg/day)	Therapy duration (days)	Follow-up period (months)	Dropout rate ^a
Costello <i>et al.</i> ⁵	68 (56)	adults and children enrolled at multiple practice sites	35.7	penicillin	1000	10	6–12	17.6%
Shapiro <i>et al.</i> ⁶	387 (365)	adults and children enrolled at one site	42.6	amoxicillin	750	10	12	5.6%
Agre and Schwartz ⁷	184 (179)	children enrolled at one paediatric practice	49.2	penicillin or tetracycline ^b	1000	10	12–36	2.7%
Nadelman <i>et al.</i> ⁸	506 (482) ^c	adults and children enrolled at two hospitals	53.3	doxycycline	200	1	1.5	11% ^d

^aDefined as the percentage of patients who were randomized but did not complete or were excluded from the study.

^bPatients ≥ 9 years of age received tetracycline; younger patients received penicillin.

^cTwenty-four patients of the 506 who were randomized were excluded from analysis because they were bitten by ticks other than *I. scapularis*. Fifty-one patients who did not return for all follow-up visits were included in the analysis.

^dDropout rate does not include 24 patients who were randomized but not included in the final analysis because they were bitten by ticks other than *I. scapularis*.

Table 3. Quality scoring by the Jadad method

	Costello <i>et al.</i> ⁵	Shapiro <i>et al.</i> ⁶	Agre and Schwartz ⁷	Nadelman <i>et al.</i> ⁸
Study described as randomized?	yes ^a	yes	yes	yes
If randomized, is the method described and appropriate?	no ^b	yes	yes	yes
Study described as double blind?	yes	yes	yes	yes
If double blind, is the method described and appropriate?	yes	yes	yes	yes
Appropriate description of withdrawals and dropouts?	yes	yes	yes	no ^c
Total Jadad quality score	4	5	5	4

^aRandomization of treatment assignments was confirmed by personal correspondence with an author from the trial.

^bThe method of randomization was not specified.

^cBreakdown of withdrawals and dropouts by treatment group was not reported.

one with an equivocal ELISA and a positive IgM immunoblot; and the other with a negative ELISA and a positive blood culture for *B. burgdorferi*. The third patient was in the treatment group, and had a positive ELISA and a negative immunoblot. Three of the four trials reported that none of their patients seroconverted without symptoms.^{5,6,8} In one trial, two asymptomatic patients in the placebo group developed 'weakly positive' IFA titres after 6 weeks (immunoblot testing was not performed).⁷

In two of the four trials, the ticks that were presented to or removed by the physician were tested for the presence of *B. burgdorferi* by immunofluorescence or PCR.^{5,6} Of the examinable ticks, 29%⁵ and 15%⁶ were infected. One trial noted engorgement status and estimated the duration of attachment of both nymphal and adult ticks; the trial reported that all nine of their cases of erythema migrans were from partially engorged nymphal stage ticks.⁸ In untreated subjects who had removed partially engorged nymphal stage ticks, 10% developed erythema migrans, and in subjects with untreated bites from nymphal ticks that fed for ≥ 72 h, 25% developed erythema migrans. No untreated patient developed erythema migrans from an adult tick bite.

Validity assessment

The results of quality scoring are shown in Table 3. Of the four trials described as randomized, three trials provided an adequate description of their randomization procedure,⁶⁻⁸ and three studies were judged to have adequate allocation concealment.^{5,7,8} The Costello study did not describe its method of sequence generation, but was judged to have adequate allocation concealment.⁵ The Shapiro trial had an appropriate sequence generation, but its method of allocation concealment was not described.⁶ All four trials' methods of double-blinding were described and were judged to be appropriate. Three studies provided an adequate description of dropouts and withdrawals.⁵⁻⁷ Only two studies had a completion rate of $>90\%$ after randomization^{6,7} and only one study⁸ conducted its analysis as intention to treat. All four trials met the criteria for high quality as described by Khan *et al.*¹²

Quantitative data synthesis

The risk of acquiring Lyme disease among subjects who received antibiotic prophylaxis ranged from 0% in three trials⁵⁻⁷ to 0.4%

in the largest trial,⁸ while the risk of infection among the placebo groups ranged from 1.1%⁷ to 3.4%.⁵ The overall risk of Lyme disease infection following an *I. scapularis* tick bite in the placebo group was estimated at 2.2% (95% CI, 1.2%–3.9%) and the overall risk of infection with Lyme disease in the prophylaxis group was estimated at 0.2% (95% CI, 0.0%–1.0%). A Forest plot illustrating the ORs of the individual trials and the pooled data is shown in Figure 2. The ORs for three individual clinical trials⁵⁻⁷ were estimated to be 0.00 (in favour of therapy), none of which achieved statistical significance ($P > 0.05$ for all three trials), while the latest and largest trial⁸ estimated an OR of 0.13 (95% CI, 0.003–0.97), which achieved statistical significance ($P = 0.045$). The pooled OR that included 1082 patients from the four trials was estimated at 0.084 (95% CI, 0.0020–0.57; $P = 0.0037$). The test of homogeneity of the OR was determined to be homogeneous across all four trials ($P = 1.00$). The NNT to prevent one case of Lyme disease was estimated to be 49 (95% CI, 45–106).

Discussion

Meta-analysis of these four studies strongly suggests that the use of antibiotic prophylaxis for the prevention of Lyme disease after an *I. scapularis* tick bite is effective. Patients who received antibiotic prophylaxis were shown to be less likely to acquire Lyme disease than those given placebo, consistent with a relative risk reduction (RRR) of 91% (95% CI, 42%–100%). These findings contrast with our prior meta-analysis,⁴ whose results did not achieve statistical significance owing to the small number of unfavourable events found in the three included trials.⁵⁻⁷ These three trials achieved an RRR of 100%; however, their estimates were very imprecise due to the rarity of events (four in total) and their small sample sizes.

The Nadelman *et al.*⁸ study, which was published after our first meta-analysis, is the only clinical trial to demonstrate a large and significant treatment effect of antibiotic prophylaxis (RRR = 87%; $P = 0.045$). Their point estimate of treatment efficacy, however, had a wide 95% CI, thus limiting the study's clinical value. Our meta-analysis not only found a greater effect of treatment (RRR of 91% versus 87%), but also raised the lower bound of the 95% CI to 42%. In addition, our findings are consistent with trials demonstrating the efficacy of doxycycline prophylaxis for the prevention of disseminated

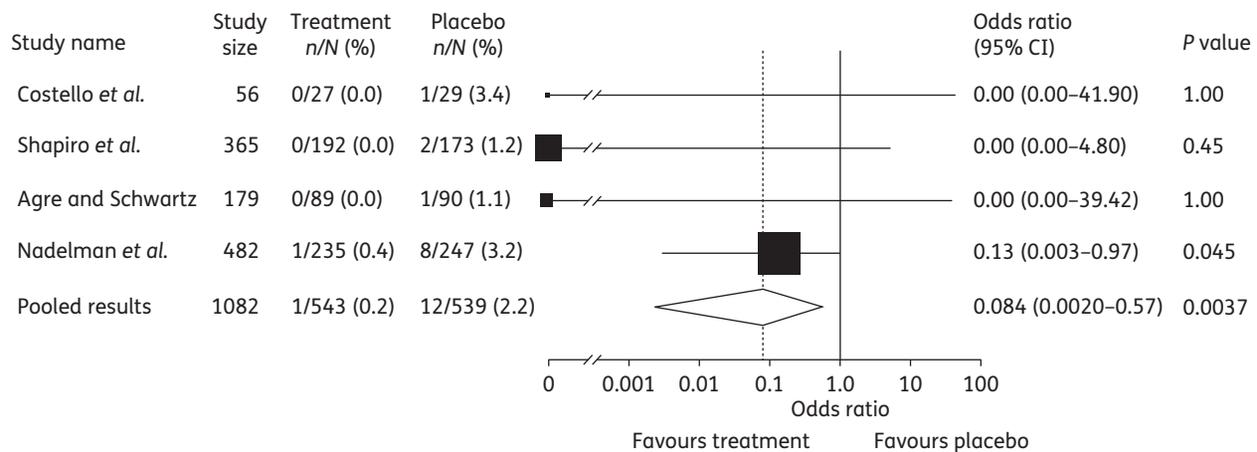


Figure 2. Forest plot of odds ratios of antibiotic treatment versus placebo for prophylaxis of Lyme disease. Black squares with horizontal bars indicate odds ratios and 95% confidence intervals (CIs) for individual studies. The size of each square is proportional to the size of the trial. The pooled odds ratio is represented by the white diamond; the width of the diamond represents the pooled 95% CI. The ratio n/N is defined as the number (n) of Lyme disease cases that developed among the total number (N) of study patients allocated to treatment or placebo.

B. burgdorferi infection in mice that were bitten by infected *I. scapularis* ticks.^{18,20}

In highly endemic areas for Lyme disease, we estimate that 49 patients (95% CI, 45–106) would need to be treated (NNT) with antibiotic prophylaxis to prevent one case of Lyme disease. This number could be substantially reduced to just 11 patients (95% CI, 10–25) if chemoprophylaxis was restricted to individuals whose ticks were visibly engorged with blood.⁸ Several studies have demonstrated that the risk for developing Lyme disease is negligible if the tick has fed for <36 h, because of the intrinsic delay in transmission of *B. burgdorferi* after a tick bite, with the highest risk in humans^{8,24} and experimental animals^{25–27} occurring after 72 h of tick feeding. In the Nadelman *et al.*⁸ study, of the 448 ticks for which engorgement status was available, 223 (49.8%) were partially engorged. Similarly, in another study from Long Island, NY,²⁴ of the 193 *I. scapularis* ticks evaluated, only 71 (36.8%) had fed for >24 h. These data suggest the use of chemoprophylaxis is unnecessary in the majority of persons bitten by ticks, even in highly endemic areas for Lyme disease. The use of prophylaxis in lower-risk geographical areas (where the *B. burgdorferi* infection risk of the local tick populations is typically low) would similarly affect the risk-to-benefit ratio by inflating the NNT.³

While antibiotic prophylaxis may be worthwhile, the risks of antibiotic treatment should be considered, which range from side effects, such as rash or nausea, to the small but serious possibility of anaphylaxis. We estimate that for every 100 patients treated, two cases of Lyme disease are prevented, but four cases of rash would occur following a course of amoxicillin⁴ and 15 cases of nausea would occur following a 200 mg dose of doxycycline.⁸

Since antibiotic treatment of recognized erythema migrans is very effective (~95% effective),²⁸ the risk of developing serious sequelae of Lyme disease after a tick bite is extremely low. However, a cost-effectiveness analysis by Magid *et al.*²⁹ estimated that up to 30% of patients who developed early Lyme disease did not detect or receive treatment for erythema migrans. Additionally, they estimated that ~83% of these

untreated cases would develop late sequelae of Lyme disease (neurological, rheumatological and cardiac). Thus, based on these figures and our baseline risk of 2.2%, we calculate that treating ~160 tick bites with antibiotic prophylaxis will prevent one case of late sequelae. We note, however, that no cases of late sequelae developed on placebo in any of these prevention trials. We believe that under the close supervision of the trials' protocols, all erythema migrans cases were detected and treated.

If an acute viral-like illness without erythema migrans but with the development of *B. burgdorferi* antibodies was also considered to be an adverse outcome, such cases would account for 20% (3 of 15 patients) of early Lyme disease events in the pooled placebo group. This result is similar to the proportion of cases of an acute viral-like illness without erythema migrans but with laboratory evidence of *B. burgdorferi* infection found in the placebo group of a large prospective vaccine trial for prevention of Lyme disease (26%, 38 of 144 patients).³⁰ Our meta-analysis did not include such cases in our primary analysis for two reasons. First, tick bites are common in endemic areas; subjects could have developed antibodies from additional unrecognized tick bites after prophylactic antibiotics (or placebo) were given.⁸ Second, we did not believe that serological tests are accurate enough to definitively establish a diagnosis of Lyme disease in these patients. For example, if the two-step ELISA and western blot approach has a sensitivity of 53% and a specificity of 98%,³¹ the positive predictive value of the combined tests is 37%, assuming the prevalence of Lyme disease is 2.2%. Therefore, 63% of positive results would be false positives, implying that many of the reported cases of acute viral-like illness without erythema migrans but with *B. burgdorferi* seroconversion are not actual cases of Lyme disease.

Our study has certain limitations. Although many features of the trial design were similar and statistical homogeneity was demonstrated, we note that our analysis combined trials enrolling both adults and children. We believe that the clinical features of Lyme disease between adults and children are likely to be similar; thus, not affecting the results in any substantive

manner. Also, we combined three trials with a 10 day antibiotic regimen⁵⁻⁷ with a trial with a 1 day regimen of doxycycline.⁸ We believe that the universal use of these antibiotic regimens for chemoprophylaxis soon after exposure to an *I. scapularis* tick bite (when the bacterial load is extremely low) is more important than their differences in antibiotic type and duration. It is also known that all of these antibiotics are effective treatments for erythema migrans and topical application of all four has been shown to be effective prophylaxis for Lyme disease in mice.¹⁶

While we intended to include European studies in this meta-analysis, the studies by Maraspin *et al.*²¹ and Korenberg *et al.*²² did not meet our inclusion criteria. Although the Korenberg *et al.*²² study was not randomized or placebo-controlled, it found that among patients who were bitten by infected ticks, those who received doxycycline prophylaxis had a significantly lower risk of developing Lyme disease as compared with the control group. The Maraspin *et al.*²¹ study was a retrospective, uncontrolled analysis of 5000 patients with tick bites treated with antibiotic prophylaxis, which reported only seven cases (0.14%) of Lyme borreliosis. This infection risk is comparable to our risk estimate of 0.2% for the pooled treatment group. We note, however, that while many of the clinical features of European and North American Lyme disease are similar,³² the dynamics of *Borrelia* transmission are quite different;²² thus, limiting the applicability of our results to European borreliosis. In Europe, the spirochete may be transmitted to the host within 24 h of tick attachment, while in North America the risk of transmission is unlikely before 36 h.³ Further randomized controlled trials are needed to establish a precise treatment effect of prophylaxis in Europe.

Although our meta-analysis supports the role of antibiotic prophylaxis in patients who were bitten by an *I. scapularis* tick within 72 h in a highly endemic area, clinicians may have difficulty identifying *I. scapularis* among the different types of ticks in the area by visual inspection. Also, patients may not have the tick upon presentation to the physician, thereby limiting the applicability of our findings. Our findings are applicable to the Middle Atlantic States, Northeast and North Central regions of the USA where Lyme disease is highly endemic and often >20% of *I. scapularis* are infected with *B. burgdorferi*.

Since one dose of 200 mg of doxycycline was found to be effective, it should be used in non-allergic patients ≥ 8 years of age, who are not pregnant or lactating. In young children or pregnant patients, a 10 day course of amoxicillin is likely to be effective, although the precise benefit has not been established. In addition, even if antibiotic prophylaxis is given, it is important for persons to continue to inspect the site of the tick bite for erythema migrans, since prophylaxis is not 100% effective in preventing infection. Nevertheless, it is important to emphasize that Lyme disease has an excellent prognosis, especially when treated early.³

In summary, our meta-analysis provides supporting evidence for a role of antibiotic prophylaxis within 72 h after a recognized *I. scapularis* tick bite in an endemic area. The data suggest that the clinical benefit increases with the duration of tick attachment or the degree of engorgement. Areas of future research could include an investigation of the efficacy of shorter courses of penicillin or amoxicillin and additional trials correlating the effectiveness of prophylaxis to the duration of tick bite attachment.

Furthermore, the efficacy of prophylaxis of doxycycline or penicillin on co-infection by babesiosis or human granulocytic anaplasmosis is unknown and cannot be assumed.

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Transparency declarations

None to declare.

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