Comparative Effectiveness and Toxicity of Oral Antibiotics for Early Lyme Disease Associated with Erythema Migrans: A Systematic Review and Network Meta-analysis

A thesis submitted by

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Abstract

Background: Lyme disease (LD) is caused by transmission of *Borrelia burgdorferi* bacteria through a tick bite. About 60-70% of patients with early LD develop Erythema migrans (EM). Though many antibiotics are available to treat early LD, it is difficult to pinpoint the best treatment due to a limited number of RCTs comparing different antibiotics head-to-head. We therefore conducted a network meta-analysis to compare effectiveness and toxicity of oral antibiotics in patients with early Lyme with erythema migrans.

Material/methods: We searched relevant database from inception to March 2016. We included all RCTs which involved patients with early LD presenting with EM and compared two or more oral antibiotics. We categorized antibiotic treatments by therapeutic class: cephalosporins, macrolides, penicillins, and tetracyclines. Our outcomes were acute treatment response (defined as the resolution of EM and LD symptoms at the end of treatment and within1 month post-treatment) and dissemination of LD (defined as the presence of objective findings of LD at ≥6 months). We performed network meta-analysis using a Bayesian random effects model with non-informative priors.

Results: We identified 16 studies comprising 1,659 patients aged between 0.5 and 83 years. The proportion of males ranged from 44% to 62%. In achieving acute response, cephalosporins were comparable with macrolides, penicillins, and tetracyclines. Macrolides were significantly less effective in achieving acute response compared to penicillins (Odds Ratio: 2.72 [95% Credible Interval:1.14, 6.65]), but were not different from tetracyclines. Penicillins showed a small, but statistically significant, benefit over tetracyclines (OR: 0.28 [95% CrI: 0.09, 0.94]). The majority of patients recovered

completely within 6 months. None of the treatments were statistically significantly different with regard to the number of patients reporting dissemination of LD.

Conclusions: Our results showed that penicillins demonstrate a significant benefit over macrolides and tetracyclines with regard to rapidity of treatment response in patients with early LD and EM, and that they generally had a more favorable safety profile than all other classes. We found that different therapeutic classes of oral antibiotics were similarly effective in preventing disease dissemination. These results could prove valuable to clinicians in selecting appropriate first-line treatments for early LD patients.

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List of Abbreviations

AE	Adverse event
CI	Confidence interval
CrI	Credibility interval
EM	Erythema migrans
GI AE	Gastrointestinal adverse event
OR	Odds Ratio
RCT	Randomized controlled trial
TAE	Treatment-related adverse event

Chapter 1. Introduction

1.1. Lyme Disease

Lyme disease, or Lyme borreliosis, is caused by the spirochete *Borrelia burgdorferi* and is transmitted to humans through an *Ixodes* species tick bite. The estimated annual incidence of Lyme disease cases between 2005 and 2010 was 107 cases per 100,000 persons and this is about 329,000 Lyme cases annually in the United States (1). The most common clinical manifestation of early Lyme is erythema migrans. It is an annular erythematous skin lesion that expands around the site where *B. burgdorferi* is deposited by an infected tick and develops in about two thirds of infected patients approximately one to two weeks after tick bite (2). Lyme carditis and Lyme meningitis and other manifestation of early neurologic Lyme disease, such as radiculopathy, cranial nerve palsy, and lymphocytic cerebrospinal fluid pleocytosis, may occur during the early stage of Lyme with or without erythema migrans (3-6).

In the late stage of Lyme disease, patients present with Lyme arthritis, neurologic Lyme disease affecting the central or peripheral nervous systems, and acrodermatitis chronica atrophicans (an unusual progressive fibrosis skin process). In addition to the late stage Lyme disease symptoms, some patients experience persistent symptoms after treatment for Lyme disease, as known as, post-treatment Lyme disease syndrome. Symptoms include muscle or joint pain, fatigue, depression, and neurocognitive symptoms [7]. However, the existence and incidence of post-treatment Lyme disease syndrome is still controversial, and its pathogenesis remains unknown [8-10].

1.2. Treatment of Lyme Disease

To prevent the complications from late stage Lyme disease, it is critical to treat patients presenting with early Lyme associated with erythema migrans. An observational study examining the antibiotic treatment patterns among patients with newly-diagnosed Lyme disease in the US showed that the majority of patients received doxycycline (73%), followed by amoxicillin (22%), cefuroxime (4%), azithromycin (3%), and ciprofloxacin (1%) [11]. Despite the wide acceptance of doxycycline as a standard of care [7], there is limited evidence of its impact on clinical outcomes in comparison with other antibiotics, because there is no financial incentive for pharmaceutical companies to test their drug against others after a product is already approved.

The Infectious Diseases Society of America (IDSA) guidelines recommend doxycycline, amoxicillin, or cefuroxime as first line therapies and azithromycin, clarithromycin, or erythromycin as second line therapies for the treatment of adult patients and pediatric patients older than 8 years old with early localized and disseminated Lyme disease associated with erythema migrans [2]. However, these recommendations were based on the results from traditional meta-analyses and RCTs which were limited in their comparisons, power, and precision to detect differences between multiple treatments. An enhanced method for comparing efficacy and toxicity profiles of all available oral antibiotics would be of significant value, especially when there are a limited number of studies comparing different antibiotics head-to-head.

1.3. Experimental Approach: Network meta-analysis

Network meta-analysis is a method for comparing three or more interventions, even when they have not been evaluated directly head-to-head in the same study [13]. With network meta-analysis, one can compare several treatment options simultaneously in a single study using both direct evidence from the comparisons of interventions within RCTs and indirect evidence from the comparisons across trials based on an intermediate comparator. By integrating direct evidence with indirect evidence, network meta-analysis provides more power and precision to detect differences between several interventions. It also permits ranking of these treatments based on their efficacy and safety profiles, which assists in the development of a hierarchy of treatments for a condition. Furthermore, it allows estimates of the differences between treatments which have never been compared against each other in an RCT.

1.4. Study Objectives

We aimed to conduct a systematic review and network meta-analysis to examine the comparative efficacy and toxicity of oral pharmacological treatments for early Lyme disease associated with erythema migrans. The objectives of this study are the following.

1. **Aim 1** - To estimate the comparative effectiveness of oral antibiotics used to treat early Lyme disease in achieving acute phase response
2. **Aim 2** - To estimate the comparative efficacy of oral antibiotics used to treat early Lyme disease in preventing dissemination of Lyme disease

3. **Aim 3 -** To compare the incidences of adverse effects associated with oral antibiotics used for early Lyme disease

Chapter 2.

Comparative Effectiveness and Toxicity of Oral Antibiotics for Early Lyme Disease Associated with Erythema Migrans: A Systematic Review and Network Meta-analysis.

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ABSTRACT

Background: Approximately two thirds of patients with early Lyme develop erythema migrans. Though many antibiotics are available to treat early Lyme, it is difficult to pinpoint the best treatment due to a limited number of RCTs comparing different antibiotics head-to-head.

Purpose: To compare effectiveness and toxicity of oral antibiotics in patients with early Lyme with erythema migrans.

Data Source: MEDLINE, EMBASE, Web of Science, Google Scholar, and the Cochrane Database from inception to January 2017.

Study Selection: Sixteen RCTs of patients with erythema migrans comparing oral antibiotics with regard to acute treatment response, dissemination of Lyme at 6 months or beyond, or treatment-related adverse events.

Data Extraction: Study data were extracted by two independent reviewers.

Data Synthesis: Network meta-analyses showed that compared with penicillins, macrolides and tetracyclines were significantly less effective in achieving acute treatment response (Odds ratio: 0.37 [95% Credible interval: 0.15, 0.88] and 0.28 [0.09, 0.94], respectively). Most patients (96%) recovered completely within 6 months. None of the treatments were significantly different with regard to the number of patients reporting disease dissemination. More patients experienced treatment-related adverse events from cephalosporins and tetracyclines compared with penicillins (OR: 4.41 [1.50, 17.76] and 6.54 [2.31,24.15], respectively). Patients taking tetracyclines were more likely to report adverse events compared with macrolides (OR: 4.00 [1.19, 14.75]).

Limitation: Most of the studies had high risk of bias.

Conclusion: Penicillins demonstrated a significant benefit over macrolides and tetracyclines with regard to acute treatment response and a more favorable safety profile than cephalosporins and tetracyclines. All therapeutic classes were similarly effective in preventing disease dissemination. These findings should guide the selection of therapy for patients with erythema migrans.

Primary Funding Source: None.

Introduction

Lyme disease is caused by the spirochete *Borrelia burgdorferi* and is transmitted to humans through an *Ixodes* species tick bite. The estimated annual incidence of Lyme disease cases between 2005 and 2010 was 107 cases per 100,000 persons and this is about 329,000 Lyme cases annually in the United States (1). The most common clinical manifestation of early Lyme is erythema migrans. It is an annular erythematous skin lesion that expands around the site where *B. burgdorferi* is deposited by an infected tick and develops in about two thirds of infected patients (2). Lyme carditis and Lyme meningitis and other manifestation of early neurologic Lyme disease, such as radiculopathy, cranial nerve palsy, and lymphocytic cerebrospinal fluid pleocytosis, may occur during the early stage of Lyme with or without erythema migrans (3-6). In the later stages of Lyme, patients present with Lyme arthritis, Lyme neuroborreliosis, and acrodermatitis chronica atrophicans (an unusual progressive fibrotic process in the skin).

To prevent complications from late stage Lyme disease, it is important to treat patients presenting with early Lyme with erythema migrans. The Infectious Diseases Society of America (IDSA) guidelines recommend doxycycline, amoxicillin, or cefuroxime as first line therapies and azithromycin, clarithromycin, or erythromycin as second line therapies for the treatment of adult and pediatric patients older than 8 years with early localized and disseminated Lyme disease associated with erythema migrans (2). However, these recommendations were based on the results from traditional meta-analyses and RCTs which were limited in their comparisons, power, and precision to detect differences between multiple antibiotic treatments. An enhanced method for comparing

the efficacy and toxicity profiles of all available oral antibiotics would be of significant value, especially when there are a limited number of studies comparing different antibiotics head-to-head.

Network meta-analysis is a method for comparing three or more interventions in a single study using both direct comparisons of interventions within RCTs and indirect comparisons across trials based on a common comparator (7). By integrating direct evidence with indirect evidence, network meta-analysis provides more power and precision to detect differences between several interventions. Furthermore, it allows estimates of the differences between treatments which have never been compared against each other in an RCT.

Therefore, a systematic review and network meta-analysis of RCTs in patients with early Lyme disease associated with erythema migrans was conducted. The objectives of this study are to compare efficacies of oral antibiotics in achieving acute treatment response and preventing dissemination of Lyme disease and to compare the occurrences of treatment-related adverse events. Our findings could prove valuable to clinicians selecting appropriate first-line treatments for early Lyme patients with erythema migrans.

Methods

Data Sources and Searches

We searched MEDLINE, Embase, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials from inception through March 22, 2016 (Table 4.1). In addition, we hand-searched the references of included studies and reviews or meta-analyses on similar topics, as well as conference abstracts. The search was updated on January 4, 2017.

Study Selection

All randomized controlled trials of patients of any age who had early Lyme disease associated with erythema migrans were included. Studies were selected based on our PICO criteria: i) participants - studies were included if patients with early Lyme associated with erythema migrans were enrolled, ii) intervention/comparators – studies were included if two or more oral antibiotics listed in Table 4.2 were compared, and iii) outcomes - studies were included if acute treatment response, dissemination of Lyme disease, or treatment-related adverse effects were reported. In keeping with the IDSA guidelines, RCTs identifying patients with erythema migrans diagnosed by clinical findings were included, and the confirmation with positive serologic testing was not required. (Appendix Section 4.1)

Acute treatment response was defined as the resolution of erythema migrans and associated signs and symptoms of Lyme at the end of treatment and up to one month post-treatment. Dissemination of Lyme disease was defined as the occurrence of objective findings of the manifestations of Lyme disease, such as arthritis, carditis, meningitis, or neurologic Lyme disease at 6 months and beyond. Treatment-related adverse events were defined as any newly reported symptoms during the treatment until one month post-

treatment that did not present at the time of entry into the study. These included gastrointestinal adverse events (e.g. diarrhea, nausea/vomiting, and abdominal pain), allergic reactions (e.g. rash/drug eruption, photosensitivity, and hypersensitivity reaction), severe adverse events (e.g. any life-threatening adverse events that resulted in hospitalization or death) and patient withdrawals from the study due to the development of adverse events.

For the outcomes of acute treatment response and treatment-related adverse events, studies were required to follow up patients at the end of treatment (up to 1 month post-treatment). For the outcome of dissemination of Lyme disease, studies were required to have a follow up time of at least 6 months. For the studies reporting dissemination of Lyme at multiple time points, the time point closest to 6 months was given preference. There was no restriction of language, study location, or study setting.

Data Extraction and Quality Assessment

Two independent reviewers (JH and MO) extracted the name of first author, year of publication, the generic name, dosage, frequency and duration of the experimental and comparator interventions. Also extracted were patient characteristics (e.g. mean age, percent female, number of erythema migrans), study size, duration of follow-up, details on the outcomes of interest, and type and source of financial support from each study. We used data from intention-to-treat populations, if possible. There was one study that had three arms, two of which were given cefuroxime in different dosages (20 mg/kg/d or 30 mg/kg/d divided every 12 hours for 20 days (8)). We only used data from the higher dose

group (30mg/kg/d), as this is the same dose used by another study and the same dose recommended by the current Lyme guidelines (9, 10).

The Cochrane risk of bias tool (11) was used by two independent reviewers (JH and MO) to assess the risk of bias in each study. The seven domains of risk of bias tool (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other biases) were evaluated and rated as low risk, high risk, or unclear for each domain. Disagreements between the two reviewers were resolved by discussion. To assess publication bias, we examined the funnel plot of standard errors as a function of log odds ratios of having acute treatment response centered at comparison-specific pooled effect.

Data Synthesis and Analysis

Given the limited number of RCTs for individual antibiotics, we categorized treatments by therapeutic class: cephalosporins (cefuroxime), macrolides (azithromycin, clarithromycin, and erythromycin), penicillins (amoxicillin, amoxicillin with probenecid, and phenoxymethylpenicillin) and tetracyclines (doxycycline, minocycline, and tetracycline) for our primary analysis. We calculated the odds ratios (ORs) and 95% confidence intervals (95% CI) of having the outcomes from the individual studies. Traditional meta-analyses were conducted to calculate the pooled OR and 95% CI of having outcomes in each pairwise comparison that included more than two non-double-zero studies (double zero studies are studies that have no event in both treatment arms; odds ratios cannot be calculated from double-zero studies).

For each outcome, we performed a Bayesian hierarchical random effects model network meta-analysis using a Markov Chain Monte Carlo simulation technique. We used random effects models to adjust for any differences in study and patient characteristics that may have occurred due to chance. Non-informative priors (=vague prior) were used for the effect parameters, as we wanted to synthesize evidence based on the available data, so that the posterior distribution would be similar to that of likelihood and the effect estimates would be unbiased. We ran 50,000 iterations of the Markov Chains Monte Carlo simulation with 4 chains. The simulated samples prior to convergence (burn-in samples) were discarded. The effect estimates were presented as odds ratios (ORs) along with their corresponding 95% credibility intervals (95% CrI). A credibility interval is the probability that the true value of a parameter falls within the credible region. The network plots of each study outcome were generated.

To test the robustness of these findings, we synthesized evidence for each outcome by each antimicrobial agent and repeated the analyses described above using network meta-analyses as sensitivity analyses. In addition, several sensitivity analyses by network meta-analyses, traditional meta-analyses, and meta-regression were performed to determine whether there were differences in treatment and toxic effects of different antimicrobial classes between adults and children and between patients in the US and patients in the EU. Resolution of erythema migrans, time to resolution of erythema migrans and time to resolution of signs and symptoms of Lyme disease were also compared using traditional meta-analyses. The detailed methods are explained in Appendix Section 4.2.

Heterogeneity was assessed using the I^2 statistics within each pairwise comparison, which reports the percentage of variation across the studies that is due to heterogeneity (rather than chance) (12, 13) . I^2 values of less than 25%, between 25% and 75%, and greater than 75% were considered as low, moderate, and high heterogeneity, respectively. We checked for consistency by comparing the direct and indirect evidence in each closed loop (inconsistency factors) and by comparing the direct and indirect evidence from the entire model that was split at each pair of treatments (node-splitting methods) (14). If the 95% confidence interval of the inconsistency factor values is truncated at zero or if the difference between direct effect and indirect effect by node-splitting method is not statistically significant, then the inconsistency is considered to be non-significant (15).

All network meta-analyses were performed by using Markov chain Monte Carlo simulation implemented through OpenBUGS software (Version 3.2.3). We modified codes available in *NICE DSU Technical Support Document 1 – 7* (available from: http://www.nicedsu.org.uk) and used them for our analysis (16-22).

Results

Literature Search

The search of relevant databases identified a total of 20,001 citations, 19,552 of which were excluded during title and abstract screening. Of 449 full texts, 17 studies met our eligibility criteria and were considered for data-extraction. However, we could not

obtain the full text of one study that was published in a Croatian journal, even after multiple attempts to contact the authors. We, therefore, included 16 studies for the network meta-analyses. (Figure 2.1)

Patient/Study Characteristics

Patient and treatment characteristics of the included studies are shown in Table 4.3. A total of 1,659 patients aged between 6 months and 83 years were randomized to receive oral antibiotics. The proportion of females ranged from 38% to 69%. All patients enrolled in the included studies had early Lyme disease with erythema migrans, with exception of two patients. They had flu-like symptoms with serologic evidence of infection with *B. Burgdorferi* (a four-fold change in antibody titer) and were used in our analysis (23). Seven studies enrolled patients with multiple erythema migrans (ranged from 9.4% to 17.9%). The proportion of patients with signs and symptoms of Lyme disease other than erythema migrans at baseline ranged from 40.7% to 82.9%, excluding two studies that did not report the outcome. The average duration of erythema migrans prior to enrollment ranged from 3.3 days to 32.5 days.

Seven studies were conducted in the United States, and nine were conducted in Europe. Studies were published between 1983 and 2012. Most studies did not provide detailed diagnostic criteria for erythema migrans, except for 4 studies where the modified Centers for Disease Control and Prevention diagnostic criteria were used (9, 23-25). The size of the trials ranged from 43 patients to 246 patients, and the number of patients randomized to each treatment arm ranged from 13 to 124. Treatment duration varied

between 5 days and 21 days, and follow-up duration ranged from 6 months to 24 months. Acute treatment response was reported in 7 trials (890 patients; two were three arm studies), dissemination of Lyme disease was reported in 14 trials (1,286 patients; two were three arm studies), and treatment-related adverse events were reported in 16 trials (978 patients; Table 4.4).

Most of the included studies had high risk of bias (Table 4.5). A total of four studies were funded by pharmaceutical companies, and two were supported by government agencies. Ten studies did not report the source of funding. Nine of the 16 studies used intention-to-treat analysis.

Acute treatment response

Overall, 73.7% of 890 patients achieved acute treatment response. The network of trials that measured acute treatment response in patients with early Lyme disease associated with erythema migrans is shown in Figure 2.2.1. Of six possible comparisons, outcome data were available for only four comparisons. Compared with penicillins, macrolides and tetracyclines were significantly less effective in achieving acute treatment response (OR: 0.37 [95% CrI: 0.15, 0.88] and 0.28 [95% CrI: 0.09, 0.94], respectively; Table 2.1). Cephalosporins were less effective in achieving acute treatment response compared with penicillins, but the difference was not statistically significant (OR: 0.29 [95% CrI: 0.07, 1.55]). Tetracyclines were comparable with cephalosporins and macrolides.

In traditional meta-analyses, patients taking macrolides were less likely to achieve acute treatment response, compared to those who took penicillins (Odds ratio: 0.37 [95% Confidence interval: 0.22, 0.66]; Figure 4.1). Pair-wise comparisons also showed that tetracyclines were comparable to penicillins, cephalosporins, and macrolides in achieving acute treatment response.

Dissemination of Lyme disease

Only 3.8% of 1,286 patients showed objective findings of dissemination of Lyme disease. The network of trials that compared dissemination of Lyme disease shows five direct comparisons of six possible comparisons (Figure 2.2.2). When compared with each other, none of the therapeutic classes was statistically significantly different with regard to the proportion of patients reporting objective findings of dissemination of Lyme disease (Table 2.1). The effect estimates from traditional meta-analyses were similar to the effect estimates from the network meta-analysis (Figure 4.2).

Treatment-related Adverse Events

Fifteen studies reported data on treatment-related adverse events (Table 4.6). Eight studies reported the total number of patients who experienced at least one treatment-related adverse event. Overall, 25.8% of 978 patients experienced at least one treatment related adverse event. Five of six possible comparisons had direct evidences that compared treatment-related adverse events (Figure 2.2.3). Network meta-analysis showed that a greater proportion of patients experienced adverse events from cephalosporins and tetracyclines compared with penicillins (OR: 4.41 [95% CrI: 1.50, 17,76] and 6.54 [95%

CrI: 2.31, 24.15], respectively; Table 2.1); and more patients experienced adverse events from tetracyclines compared with macrolides (OR: 4.00 [95% CrI: 1.19, 14.75]).

In pairwise comparisons, there was no significant difference found in the proportion of patients who experienced treatment-related adverse events between macrolides and penicillins and between cephalosporins and tetracyclines. Patients who took macrolides were more likely to experience gastrointestinal adverse events than those who took penicillins (OR: 2.76 [95% CI: 1.14, 6.17]), but were less likely to experience gastrointestinal adverse events compared with those who took tetracyclines (OR: 0.40 [95%CI: 0.21, 0.75]). More patients taking tetracyclines reported allergic reactions compared with those who received cephalosporins and macrolides (OR: 0.17 [95% CI:0.06, 0.51] and 0.12 [0.03, 0.57], respectively). We found no differences in the frequency of serious adverse events or withdrawals due to adverse events in available treatment comparisons. (Figure 4.3)

Quality of Evidences

Most studies had high risk of bias (Table 4.5). There was no evidence of publication bias (Figure 4.4). We observed low to moderate heterogeneity within each comparison for each outcome (I^2 ranged from 0 to 52%; Table 4.7). There was no evidence of inconsistency within each network when we compared direct estimates with indirect estimates within a closed loop by loop-based analysis (Table 4.8). However, node-splitting analysis showed a difference between the direct and the indirect estimates in the comparison between cephalosporins and tetracyclines for dissemination of Lyme (p=0.04).

Sensitivity Analysis

Network meta-analyses by each antimicrobial agent showed similar results: penicillin V was more efficacious in achieving acute treatment response than azithromycin, cefuroxime and doxycycline (Table 4.10). Patients who took penicillin V were less likely to experience treatment-related adverse events compared with those who took cefuroxime, doxycycline, and minocycline (Table 4.11).

Our network excluding children only studies showed that patients who took penicillins were less likely to experience treatment-related adverse events compared with those who took tetracyclines, however there was no longer statistical difference between cephalosporins and penicillins (Table 4.11). When studies conducted in the EU were excluded, there were no differences in the rate of achieving acute treatment response among all oral antibiotic classes (Table 4.12). The results from the rest of sensitivity analyses are shown in Appendix Section 4.2 and Figure 4.5-4.8.

Discussion

Our findings suggest that penicillins have better efficacy and toxicity profiles compared with other antimicrobial classes. Network meta-analyses showed that penicillins were more efficacious than tetracyclines and macrolides in achieving acute treatment response. In preventing dissemination of Lyme disease, all therapeutic classes were comparable in terms of the proportion of patients who reported objective findings. However, fewer people experienced treatment-related adverse events from penicillins,

compared with those who received cephalosporins. A greater proportion of patients experienced treatment-related adverse events from tetracyclines compared with macrolides and penicillins.

In contrast to our observations concluding that penicillins are the drugs of choice for early Lyme with erythema migrans, the current IDSA guidelines recommend amoxicillin, cefuroxime, and doxycycline as first-line therapies (2). The difference in their conclusions might be due to i) their exclusion of the studies conducted in the EU and ii) the scarcity of RCTs, which hindered traditional meta-analysis to compare all treatment options to each other. As expected, their recommendations are similar to our results from traditional meta-analyses excluding the EU studies: in achieving acute treatment response, macrolides were less efficacious compared to penicillins (OR: 0.37 [95%CI: 0.21, 0.64]) and tetracyclines were comparable with cephalosporins, macrolides and penicillins in the studies conducted in US. However, for dissemination of Lyme, when the EU studies were excluded, there were not enough trials remaining to synthesize data for the majority of our proposed treatment comparison, due to the scarcity of non-double zero studies.

Unlike traditional meta-analysis, network meta-analysis allows comparison of treatments that have never been examined in a single trial by combining both direct and indirect evidence. As described above, the data available from direct evidence were insufficient to draw conclusions on which antimicrobial agent works the best for patients among available antibiotics. However, our network meta-analyses provided effect estimates for all treatment comparisons for acute treatment response, dissemination of

Lyme disease, and treatment-related adverse events, concluding that penicillins have preferable efficacy and toxicity profiles compared with other therapeutic classes.

The majority of patients (73.4%) achieved acute treatment response at the end of treatment. Our network meta-analysis showed that penicillins were more efficacious compared to macrolides and tetracyclines in achieving acute treatment response. Our sensitivity analysis showed similar trends. Amoxicillin was more effective than azithromycin, cefuroxime, doxycycline, and erythromycin, and penicillin V was more effective than azithromycin, cefuroxime, doxycycline, and erythromycin. However, statistical differences were found only in the comparisons between penicillin V and azithromycin, between penicillin V and cefuroxime, and between penicillin V and doxycycline.

Interestingly, when only US studies were included, all of the therapeutic classes were not different from each other with respect to achieving acute treatment response. This might be due to different Borrelia species affecting the US and the EU: *B. burgdoferi* is predominant in the US, whereas *B. afzelii*, *B. garinii*, and *B burgdoferi* are found in the EU. However, *in vitro* studies have demonstrated no difference in the minimal inhibitory concentrations (the minimal antibiotic concentration needed to inhibit the growth of microbial organism) of cephalosporins, macrolides, penicillins, and tetracyclines against these three *Borrelia* species (26, 27). Furthermore, because most patients with early Lyme were treated without serologic testing confirming which strain patients were infected with, it is difficult to conclude whether different species responded to different oral

antimicrobials differently *in vivo* or whether Lyme disease in the EU is different from Lyme disease in the US.

Only a small proportion of patients (4%) reported objective findings of dissemination of Lyme disease and all therapeutic classes were not significantly different from each other in preventing dissemination of Lyme disease. However, these findings should be interpreted with caution. First, dissemination of Lyme disease was evaluated in only 78% (1,224 of 1,568) of patients in the studies that reported the outcome, because some studies evaluated dissemination of Lyme disease only in patients who achieved acute treatment response. In addition, we identified four double-zero studies and included them in our analysis. However, depending on whether there is a true treatment effect (in our case, the difference in the rate of dissemination of Lyme between two treatment groups), adding double zero studies can affect pooled estimates differentially. If a true treatment effect exists, adding double zero studies would bias the magnitude of the pooled estimate, resulting in underestimation of the effect estimate. However, if a true treatment effect does not exist, the inclusion of double zero studies would only narrow down the confidence interval for effect estimates. The reasons described above could have resulted in underestimation of the proportion of patients who developed dissemination of Lyme disease, and therefore could have biased our effect estimates.

Our findings showed that tetracyclines, which have wide acceptance as a standard of care for treatment for Lyme disease, were poorly tolerated compared with other antimicrobial classes. Patients who were treated with tetracyclines were more likely to

experience gastrointestinal adverse events compared with those who were treated with macrolides. Allergic reactions, such as rash or drug eruptions, were more common with tetracyclines compared with cephalosporins and macrolides. On the other hand, penicillins showed better tolerability than cephalosporins and tetracyclines, which provides further support that penicillins are the drugs of choice for early Lyme disease with erythema migrans in light of their better effectiveness. This is particularly relevant for patients who have experienced substantial toxicities during previous treatment with tetracyclines for other infections.

We synthesized our study outcomes by therapeutic class. Therefore, clinicians should be careful in applying our findings to clinical practice and should not extrapolate the findings to other antibiotics that were not studied and included in our analysis. For example, cephalexin, a first generation cephalosporin, has been shown ineffective in treating early Lyme disease and should not be considered as a therapeutic option when selecting antibiotics (28).

To our knowledge, this is the first network meta-analysis comparing the effectiveness and toxicity of different oral antimicrobials for early Lyme disease with erythema migrans. We also performed traditional meta-analyses to compare the results with those from network meta-analyses. Finally, extensive sensitivity analyses were conducted to examine whether there was a difference between Lyme disease in EU and Lyme disease in US. However, our study has some limitations. First, the number and size of included studies were small. Secondly, most of the studies had high risk of bias, due to

the lack of (or unreported) randomization sequence generation, allocation concealment, and/or blinding. Lastly, none of the studies included in our network meta-analysis of treatment-related adverse events had a placebo comparator due to ethical challenges; therefore, we do not know whether the toxicity profiles of those studied antibiotics are well tolerated compared with placebo.

This systematic review and network meta-analysis compared the relative effectiveness and safety of oral antibiotics for early Lyme disease with erythema migrans, concluding that penicillins are the drug of choice for the management of this condition. Our results showed that penicillins demonstrated a significant benefit over macrolides and tetracyclines with regard to acute treatment response and a more favorable safety profile than cephalosporins and tetracyclines in patients with early Lyme disease. We found that all therapeutic classes of oral antibiotics were similarly effective in preventing dissemination of Lyme disease. Our findings should be of use for clinicians in balancing the risks and benefits when selecting oral antibiotics for patients who present with early Lyme disease associated with erythema migrans.

Figure 2.1. Summary of evidence search and selections

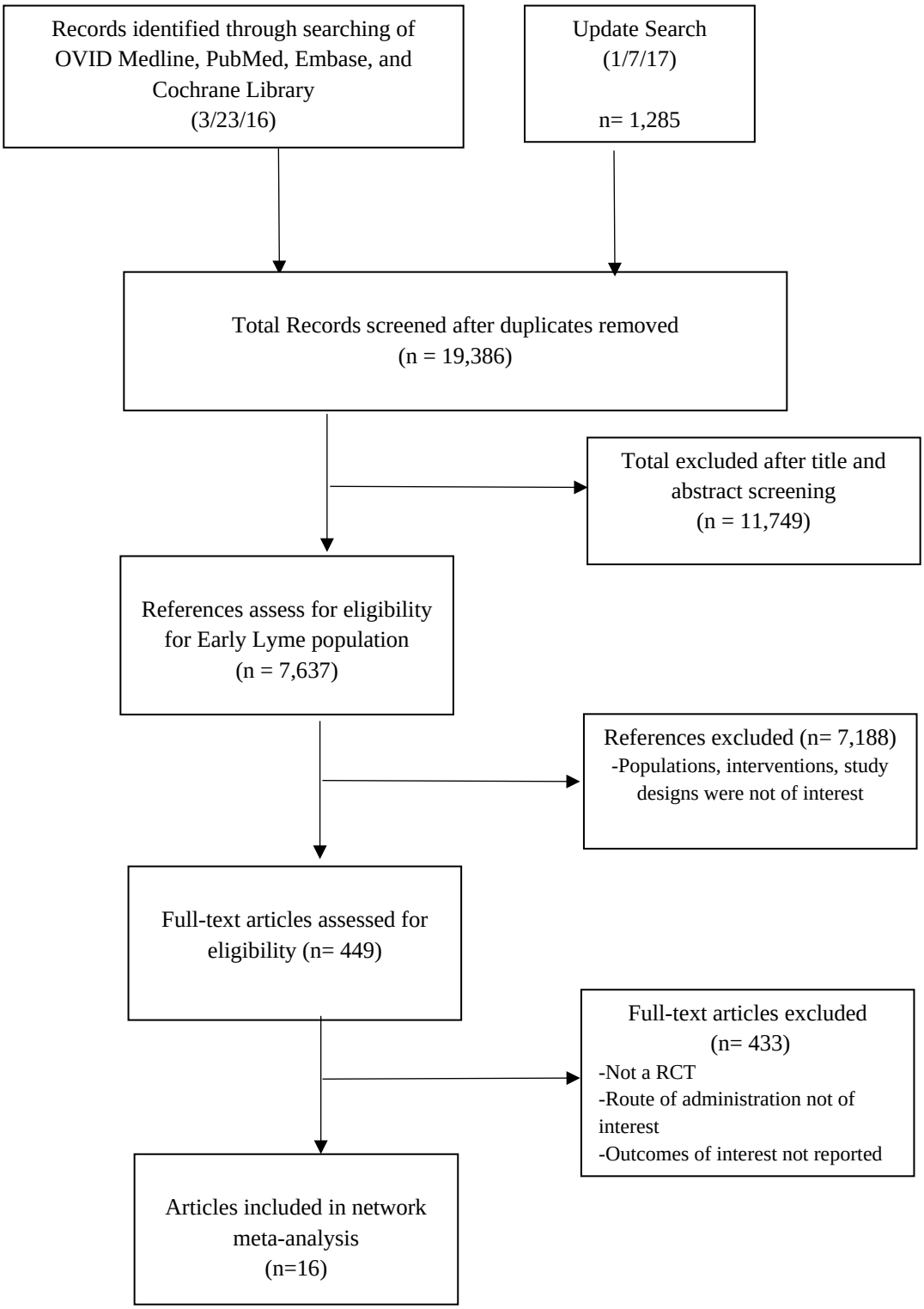
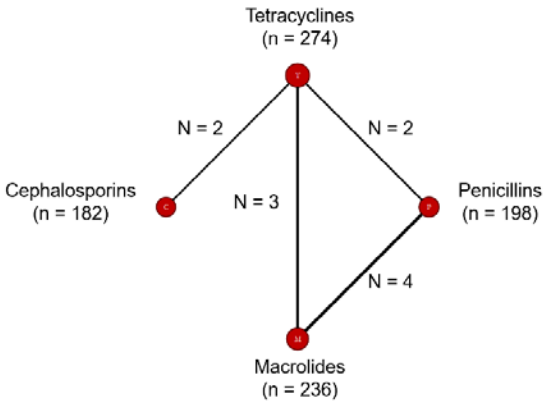
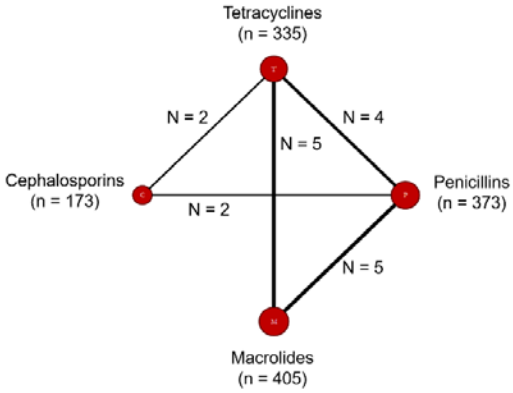


Figure 2.2. Network plots of treatment comparisons for acute treatment response, dissemination of Lyme disease, and treatment-related adverse event

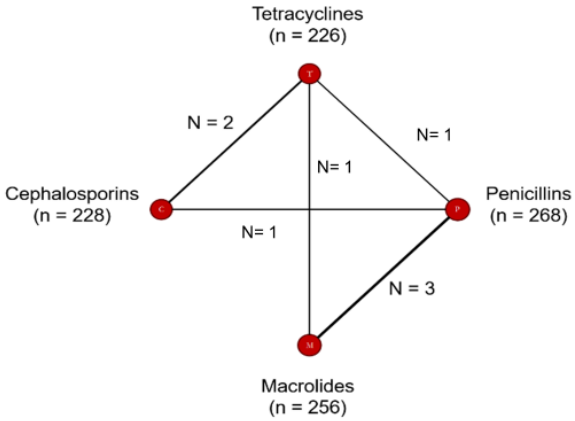
1. Acute treatment response [a]



2. Dissemination of Lyme disease [a]



3. Treatment-related adverse event



[a] There are 2 three-arm studies.

Circle size reflects the number of participants that were randomized to receive the drug in the circle and were evaluated for each outcome. Line width reflects number of direct comparisons available. No connecting line between two circles indicates that there was no direct comparison between the two treatments.

Cephalosporins include cefuroxime, macroldies include azithromycin, erythromycin, and clarithromycin, penicillins include amoxicillin, amoxicillin with probenecid, and phenoxymethylpenicillin, and tetracyclines include doxycycline, minocycline, and tetracycline

Table 2.1. Effect estimates of acute treatment response, dissemination of Lyme disease, and treatment related adverse events.

	Odds ratios (95% credibility intervals)			
	Penicillins	**Cephalosporins**	**Macrolides**	**Tetracyclines**
	Acute Treatment Response			
Penicillins		0.29 (0.07, 1.55)	**0.37 (0.15, 0.88)**	**0.28 (0.09, 0.94)**
Cephalosporins			1.27 (0.26, 5.03)	0.95 (0.33, 2.60)
Macrolides				0.75 (0.29, 2.19)
Tetracyclines				
	Dissemination of Lyme			
Penicillins		4.34 (0.14, 262.95)	0.48 (0.07, 2.58)	0.75 (0.08, 5.85)
Cephalosporins			0.11 (0.00, 4.00)	0.17 (0.00, 6.01)
Macrolides				1.58 (0.08, 5.85)
Tetracyclines				
	Treatment-related Adverse Events			
Penicillins		**4.41 (1.50, 17.76)**	1.64 (0.78, 4.08)	**6.54 (2.31, 24.15)**
Cephalosporins			0.37 (0.09, 1.38)	1.48 (0.58, 3.65)
Macrolides				**4.00 (1.19, 14.75)**
Tetracyclines				

For achievement of acute treatment response, an odds ratio greater than 1 favors the therapeutic class in the column header row (dark blue). For dissemination of Lyme disease and treatment-related adverse events, an odds ratio less than 1 favors the therapeutic class in the column header row (dark blue).

Cephalosporins include cefuroxime, macroldies include azithromycin, erythromycin, and clarithromycin, penicillins include amoxicillin, amoxicillin with probenecid, and phenoxymethylpenicillin), and tetracyclines include doxycycline, minocycline, and tetracycline

Chapter 3. Discussion

3.1. Summary of Study Findings

Our findings suggest that penicillins have better efficacy and toxicity profiles compared with other antimicrobial classes. Network meta-analyses showed that penicillins were more efficacious than tetracyclines and macrolides in achieving acute treatment response. In preventing dissemination of Lyme disease, all therapeutic classes were comparable in terms of the proportion of patients who reported objective findings. However, fewer people experienced treatment-related adverse events from penicillins, compared with those who received cephalosporins. A greater proportion of patients experienced treatment-related adverse events from tetracyclines compared with macrolides and penicillins.

3.2. Comparison with the current recommendations

In contrast to our observations concluding that penicillins are the drugs of choice for early Lyme with erythema migrans, the current IDSA guidelines recommend amoxicillin, cefuroxime, and doxycycline as first-line therapies (2). The difference in their conclusions might be due to i) their exclusion of the studies conducted in the EU and ii) the scarcity of RCTs, which hindered traditional meta-analysis to compare all treatment options to each other. As expected, their recommendations are similar to our results from traditional meta-analyses excluding the EU studies: in achieving acute treatment response, macrolides were less efficacious compared to penicillins and tetracyclines were comparable with cephalosporins, macrolides and penicillins in the studies conducted in US.

However, for dissemination of Lyme, when the EU studies were excluded, there were not enough trials remaining to synthesize data for the majority of our proposed treatment comparison, due to the scarcity of non-double zero studies.

Interestingly, when only US studies were included, all of the therapeutic classes were not different from each other with respect to achieving acute treatment response. This might be due to different Borrelia species affecting the US and the EU: *B. burgdoferi* is predominant in the US, whereas *B. afzelii*, *B. garinii*, and *B burgdoferi* are found in the EU. However, *in vitro* studies have demonstrated no difference in the minimal inhibitory concentrations (the minimal antibiotic concentration needed to inhibit the growth of microbial organism) of cephalosporins, macrolides, penicillins, and tetracyclines against these three *Borrelia* species (26, 27). Furthermore, because most patients with early Lyme were treated without serologic testing confirming which strain patients were infected with, it is difficult to conclude whether different species responded to different oral antimicrobials differently *in vivo* or whether Lyme disease in the EU is different from Lyme disease in the US.

3.3. Strengths and Limitations

The clear advantage of this study is its use of network meta-analysis. Unlike traditional meta-analysis, network meta-analysis allows comparison of treatments that have never been examined in a single trial by combining both direct and indirect evidence. As described above, the data available from direct evidence were insufficient to draw conclusions on which one works the best for patients among available antibiotics.

However, our network meta-analyses provided effect estimates for all treatment comparisons for acute treatment response, dissemination of Lyme disease at 6 months and beyond, and treatment-related adverse events, concluding that penicillins have preferable efficacy and toxicity profiles compared with other therapeutic classes.

To our knowledge, this is the first network meta-analysis comparing the effectiveness and toxicity of different oral antimicrobials for early Lyme disease with erythema migrans. We also performed traditional meta-analyses to compare the results with those from network meta-analyses. Finally, extensive sensitivity analyses were conducted to examine whether there was a difference between Lyme disease in EU and Lyme disease in US. However, our study has some limitations. First, the number and size of included studies were small. Secondly, most of the studies had high risk of bias, due to the lack of (or unreported) randomization sequence generation, allocation concealment, and/or blinding. Lastly, none of the studies included in our network meta-analysis of treatment-related adverse events had a placebo comparator due to ethical challenges; therefore, we do not know whether the toxicity profiles of those studied antibiotics are well tolerated compared with placebo.

3.4. Implications of the findings

This systematic review and network meta-analysis showed that tetracyclines, which have wide acceptance as a standard of care for treatment for Lyme disease, were poorly tolerated compared with other antimicrobial classes. Patients who were treated with tetracyclines were more likely to experience gastrointestinal adverse events compared with

those who were treated with macrolides. Allergic reactions, such as rash or drug eruptions, were more common with tetracyclines compared with cephalosporins and macrolides. On the other hand, penicillins showed better tolerability than cephalosporins and tetracyclines, which provides further support that penicillins are the drugs of choice for early Lyme disease with erythema migrans in light of their better effectiveness. This is particularly relevant for patients who have experienced substantial toxicities during previous treatment with tetracyclines for other infections.

This systematic review and network meta-analysis compared the relative effectiveness and safety of oral antibiotics for early Lyme disease with erythema migrans, concluding that penicillins are the drug of choice for the management of this condition. Our results showed that penicillins demonstrated a significant benefit over macrolides and tetracyclines with regard to acute treatment response and a more favorable safety profile than cephalosporins and tetracyclines in patients with early Lyme disease. We found that all therapeutic classes of oral antibiotics were similarly effective in preventing dissemination of Lyme disease. Our findings should be of use for clinicians in balancing the risks and benefits when selecting oral antibiotics for patients who present with early Lyme disease associated with erythema migrans.

Chapter 4. Appendix

4.1.Rationales for specific inclusion criteria

Inclusion of children and adolescents

Clinical presentations of early Lyme disease and the clinical course of Lyme disease in children are similar to those in adults (1-6). Therefore, all of the antibiotics used for adults are used in pediatric populations, except for tetracyclines (6, 7). Tetracyclines are contraindicated in patients who are younger than 8 years due to teeth discoloration (8). Because pediatric patients would respond to antibiotics the same way, except for tetracyclines, we included pediatric studies that enrolled patients with early Lyme with erythema migrans. In addition, inclusion of these population will lead our study to have more power and its findings to be more generalizable.

Inclusion of participants with erythema migrans without positive serologic testing

Confirmation with positive serological testings would be impractical, also suggested by the IDSA guidelines (6), given the amount of time to take for patients to develop immune response and have increased antibody levels to become detectable and the prevalence of persistence of antibodies from previous infection even after the eradication of B. burgdorferi (9). Because clinicians would treat early Lyme disease as soon as possible to prevent any dissemination of Lyme, therefore we did not include the confirmation with serological testing prior to initiation of therapy in our study eligibility criteria.

Exclusion of non-randomized controlled trials

There are several concerns with including non-randomized controlled studies (non-RCTs), such as a prospective cohort or an open-labelled study, in network meta-analysis, even if these observational studies can add valuable information with regards to real-life effectiveness and toxicity in a general population. Including non-RCTs could introduce the biases that are unknown or unmeasured. Therefore, there would be a high risk of violating the homogeneity assumption of network meta-analysis, when non-RCTs are included. In addition, the analysis of network meta-analysis that include both RCTs and non-RCTs is less understood than network meta-analysis that only includes RCTs. There are various approaches proposed to combine RCTs and non-RCTs in network meta-analysis, but there is currently a lack of consensus on which of these approaches is the most suitable (10).

4.2.**Sensitivity Analysis**

Methods

We performed network meta-analyses excluding the studies that enrolled children only and excluding the studies conducted in the European countries. The network excluding studies that enrolled adult only did not have enough data to generate a well-connected network, therefore, is not presented. In addition, we conducted additional traditional meta-analyses stratified by study region, whether studies enrolled children, and whether studies enrolled adults for the comparisons between macrolides and penicillins and between macrolides and tetracyclines. Furthermore, we performed meta-regression to assess the effect of adults-only enrollment, children-only enrollment, and study region (the EU vs. the US) on these comparisons. Meta-regression is a regression-based method used in traditional meta-analysis to examine potential effect modifiers on effect estimates.

As some studies examined the resolution of erythema migrans, the time to resolution of erythema migrans, and time to resolution of signs and symptoms of Lyme as measures of acute treatment response, we conducted traditional meta-analyses to compare these outcomes. Time to resolution of erythema migrans was defined as the time, in days, from the initiation of antimicrobial until the complete resolution of erythema migrans (duration of erythema migrans after the initiation of antimicrobials). Time to resolution of signs and symptoms of Lyme was defined as the time, in days, from the initiation of antimicrobial until the complete resolution of signs and symptoms (the duration of signs and symptoms of Lyme disease after the initiation of antimicrobials).

Results

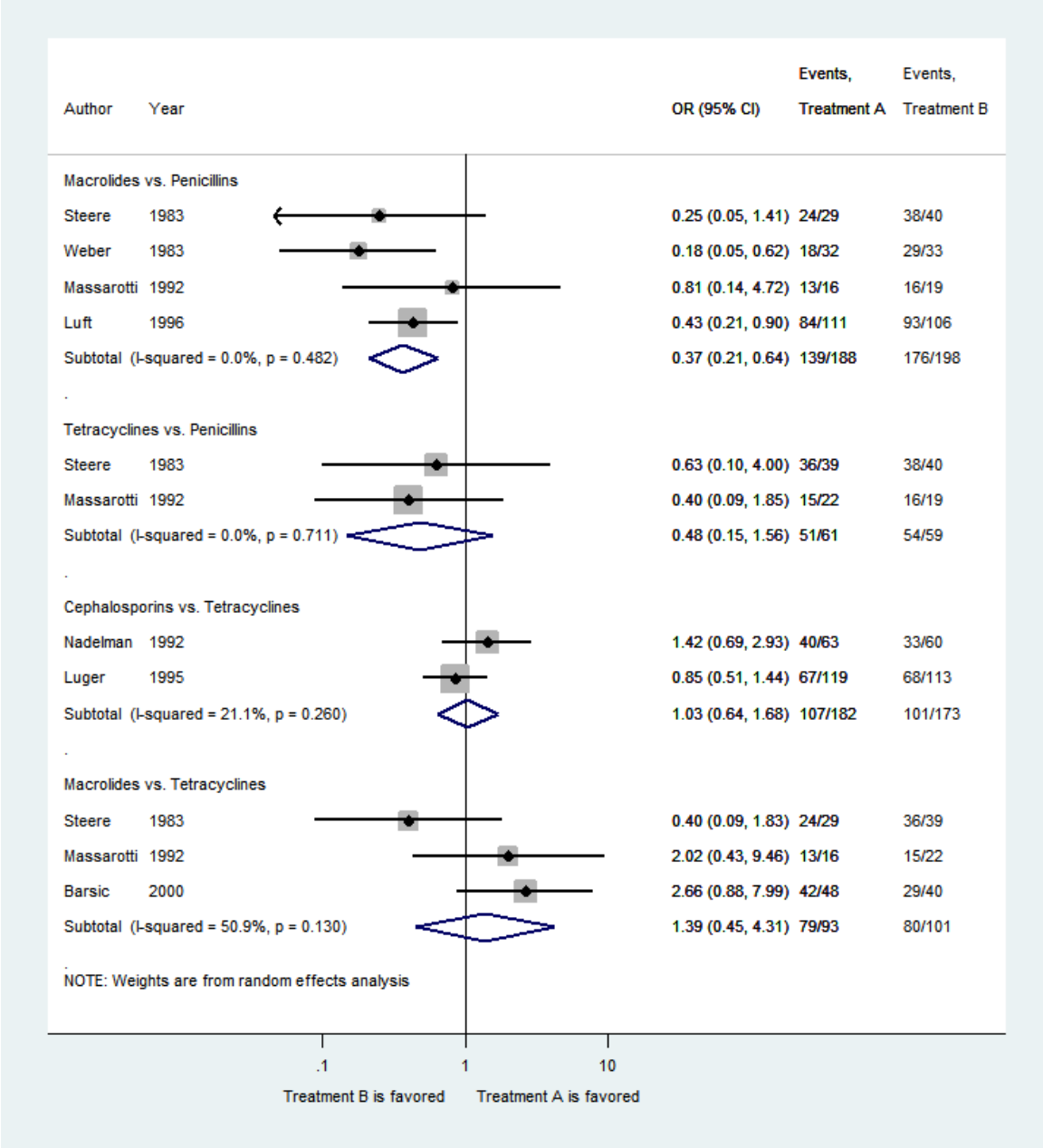
All studies which compared acute treatment response enrolled at least one adult with early Lyme disease with erythema migrans. Our network excluding studies that enrolled children only showed that patients who took penicillins were less likely to experience treatment-related adverse events compared with those who took tetracyclines (OR: 7.57 [95% CrI: 1.59, 38.31]; Table 4.11). When studies conducted in the EU were excluded, there were no differences in the rate of achieving acute treatment response among all oral antibiotic classes (Table 4.12). The estimates from the networks comparing dissemination of Lyme excluding adults-only studies, children-only studies, EU studies were very large and unstable, therefore are not presented.

We observed no effect of study region, child only enrollment, adult only enrollment on dissemination of Lyme disease in the comparison between macrolides and penicillins by subgroup analyses (Figure 4.5). There were no effect of study region and adult-only enrollment on dissemination of Lyme in the comparison between macrolides and tetracyclines. Meta-regression of dissemination of Lyme in the comparisons between macrolides and tetracyclines and between macrolides and tetracyclines showed a difference in the pooled log odds ratios between studies conducted in EU and US: EU studies favored macrolides, whereas US studies favored tetracyclines and penicillins in each treatment comparison (both $p<0.05$; Figure 4.6-4.7). We found no effect of children only enrollment or adults only enrollment on dissemination of Lyme by meta-regression.

In traditional meta-analyses, more patients had erythema migrans resolved at the end of treatment with penicillins compared to macrolides. However, there was no difference in the time to resolution of erythema migrans and the time to resolution of signs and symptoms of Lyme disease after initiation of therapy in available treatment comparisons. (Figure 4.8)

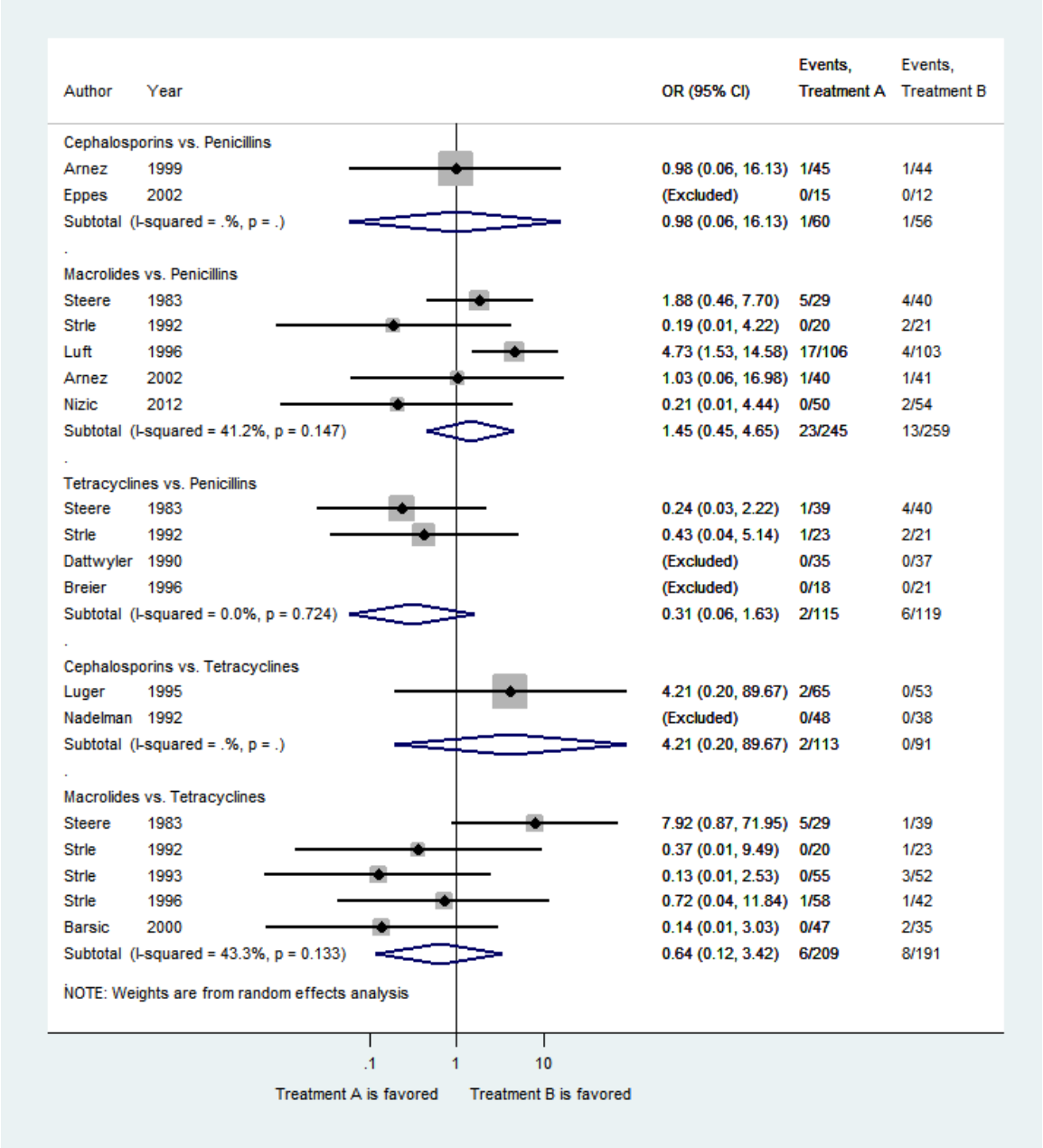
4.3.Supplement Figures and Tables

Figure 4.1. Acute treatment response at the end of treatment based on direct evidence: Treatment A vs. Treatment B



OR: odds ratio; 95% CI: 95% confidence interval
I-squared values less than 25%, between 25 and 75%, and greater than 75% are considered as low, moderate, and high heterogeneity
A p-value less than < 0.5 is considered as significant heterogeneity ($\chi 2$ test of heterogeneity)

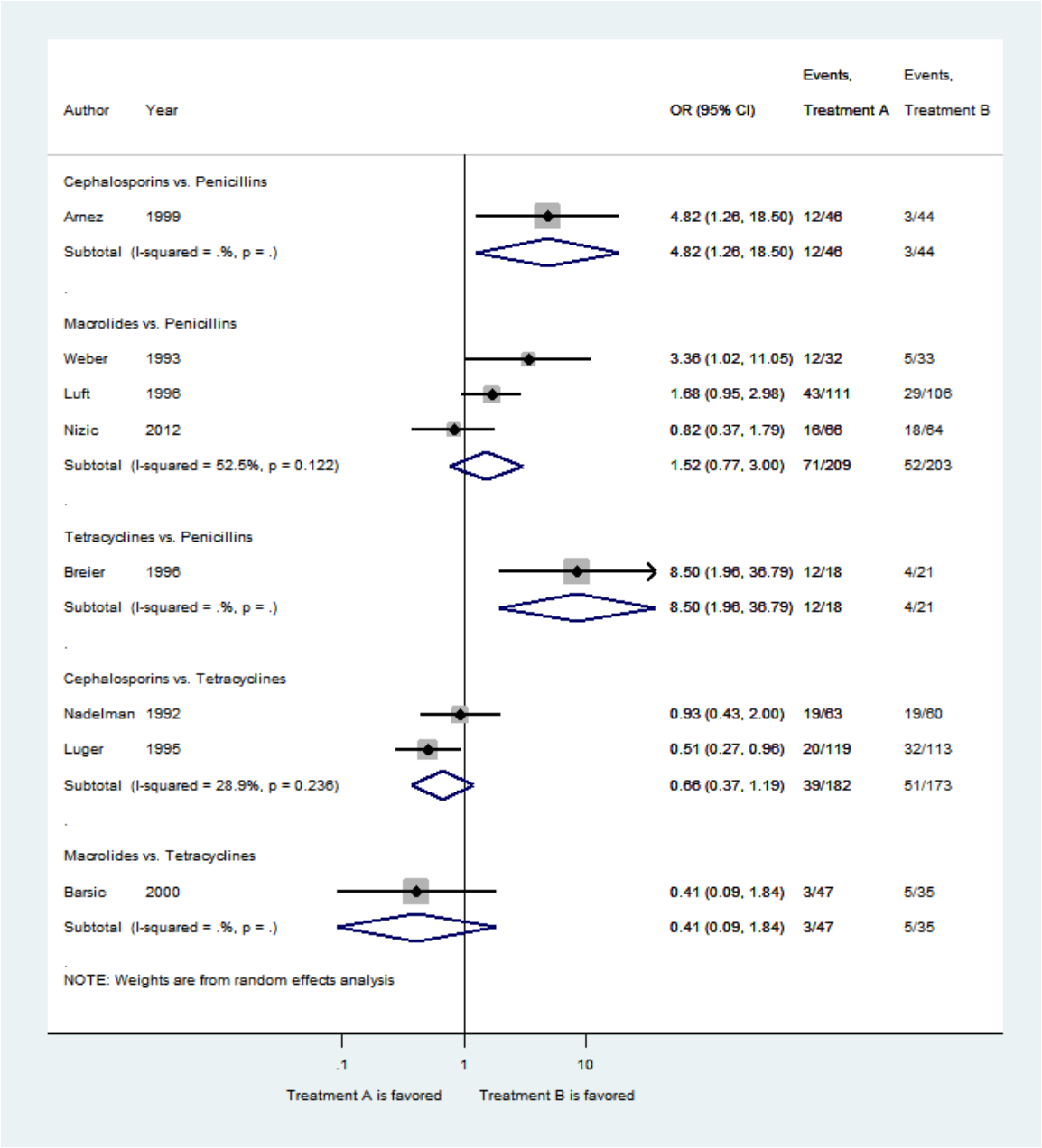
Figure 4.2. Dissemination of Lyme disease based on direct evidence: Treatment A vs. Treatment B



OR: odds ratio; 95% CI: 95% confidence interval
I-squared values less than 25%, between 25 and 75%, and greater than 75% are considered as low, moderate, and high heterogeneity
A p-value less than < 0.5 is considered as significant heterogeneity ($\chi 2$ test of heterogeneity)

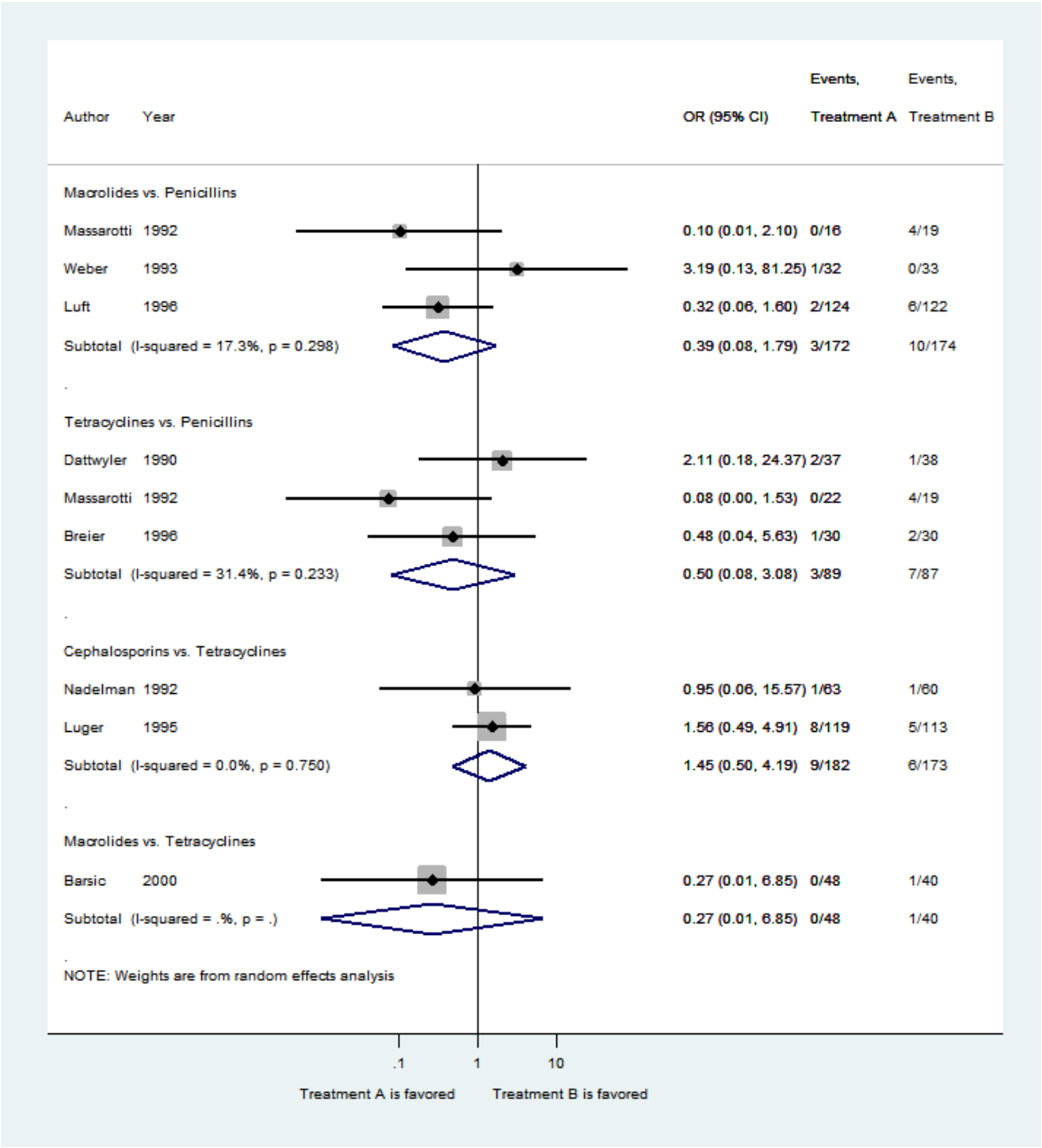
Figure 4.3. Treatment-related adverse events based on direct evidence

1. Treatment-related adverse events: Treatment A vs. Treatment B



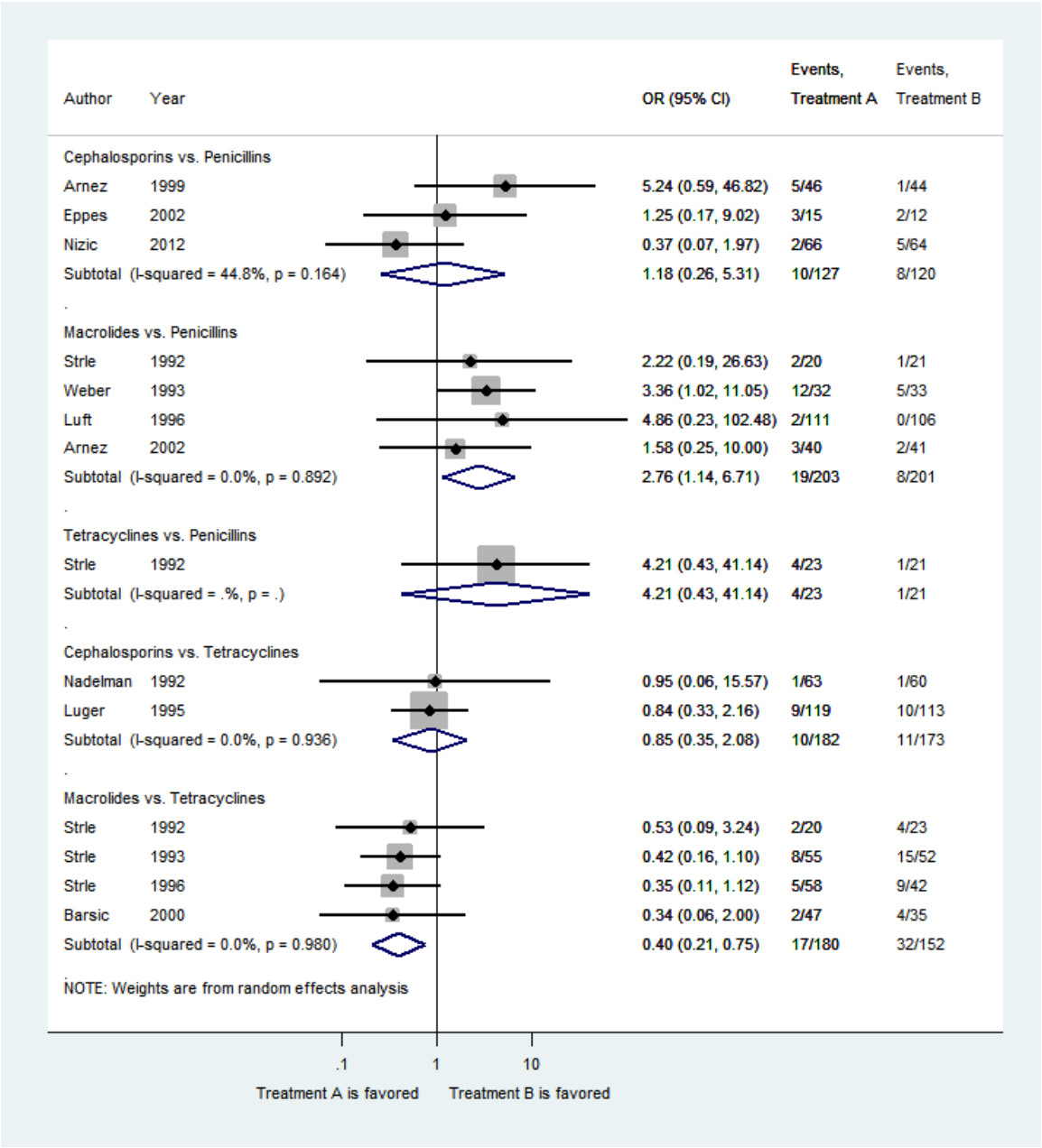
OR: odds ratio; 95% CI: 95% confidence interval
I-squared values less than 25%, between 25 and 75%, and greater than 75% are considered as low, moderate, and high heterogeneity
A p-value less than < 0.5 is considered as significant heterogeneity ($\chi 2$ test of heterogeneity)

2. Withdrawals due to adverse events



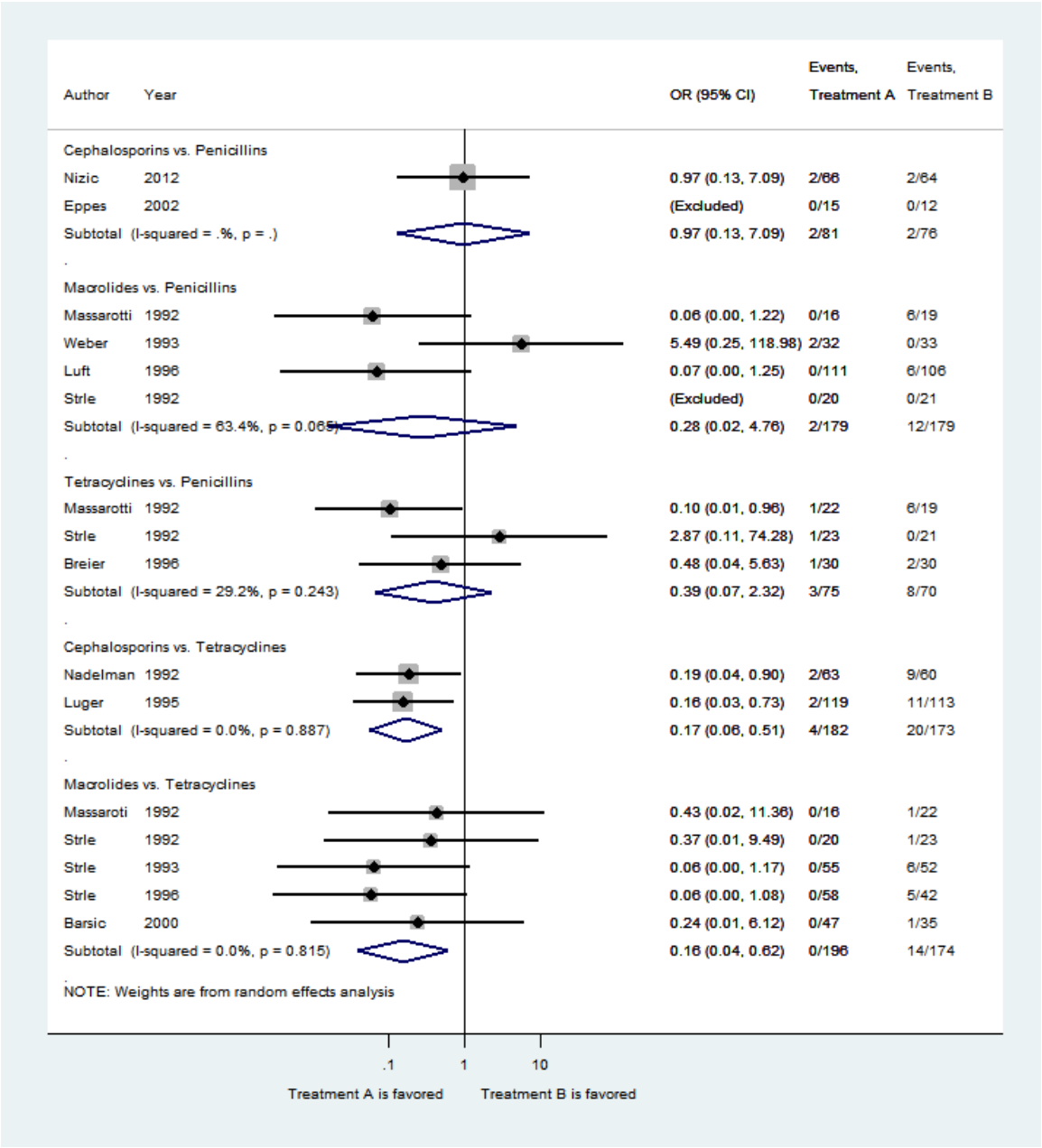
OR: odds ratio; 95% CI: 95% confidence interval
I-squared values less than 25%, between 25 and 75%, and greater than 75% are considered as low, moderate, and high heterogeneity
A p-value less than < 0.5 is considered as significant heterogeneity ($\chi 2$ test of heterogeneity)

3. Gastrointestinal adverse events: Treatment A vs. Treatment B



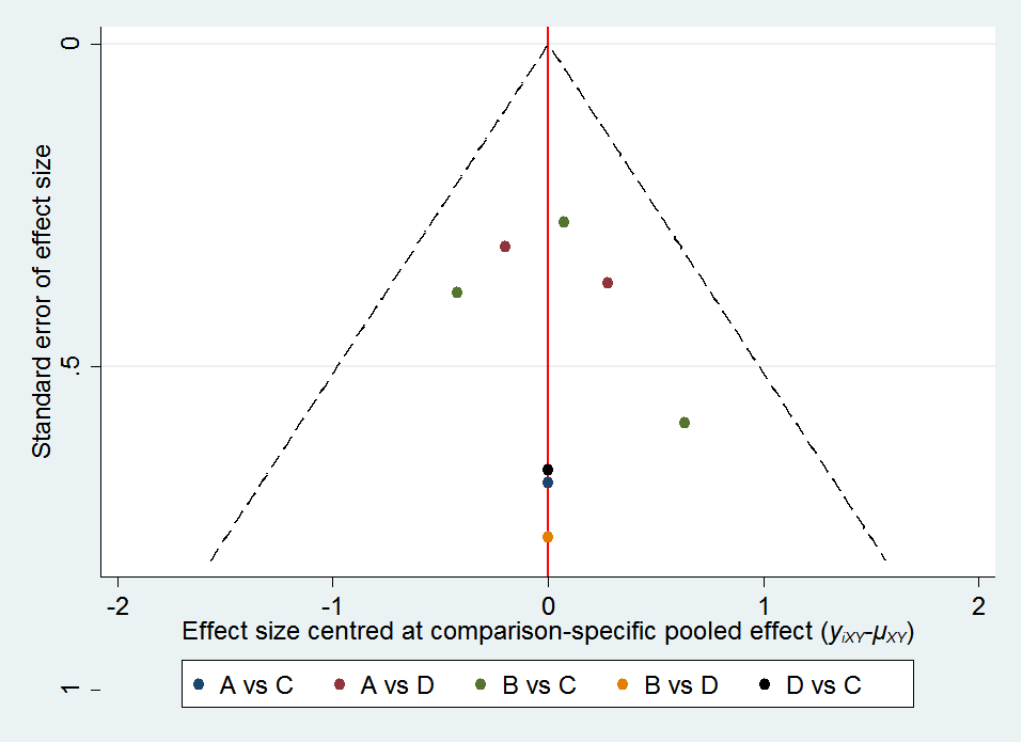
OR: odds ratio; 95% CI: 95% confidence interval
I-squared values less than 25%, between 25 and 75%, and greater than 75% are considered as low, moderate, and high heterogeneity
A p-value less than < 0.5 is considered as significant heterogeneity ($\chi 2$ test of heterogeneity)

4. Allergic reactions: Treatment A vs. Treatment B



OR: odds ratio; 95% CI: 95% confidence interval
I-squared values less than 25%, between 25 and 75%, and greater than 75% are considered as low, moderate, and high heterogeneity
A p-value less than < 0.5 is considered as significant heterogeneity ($\chi 2$ test of heterogeneity)

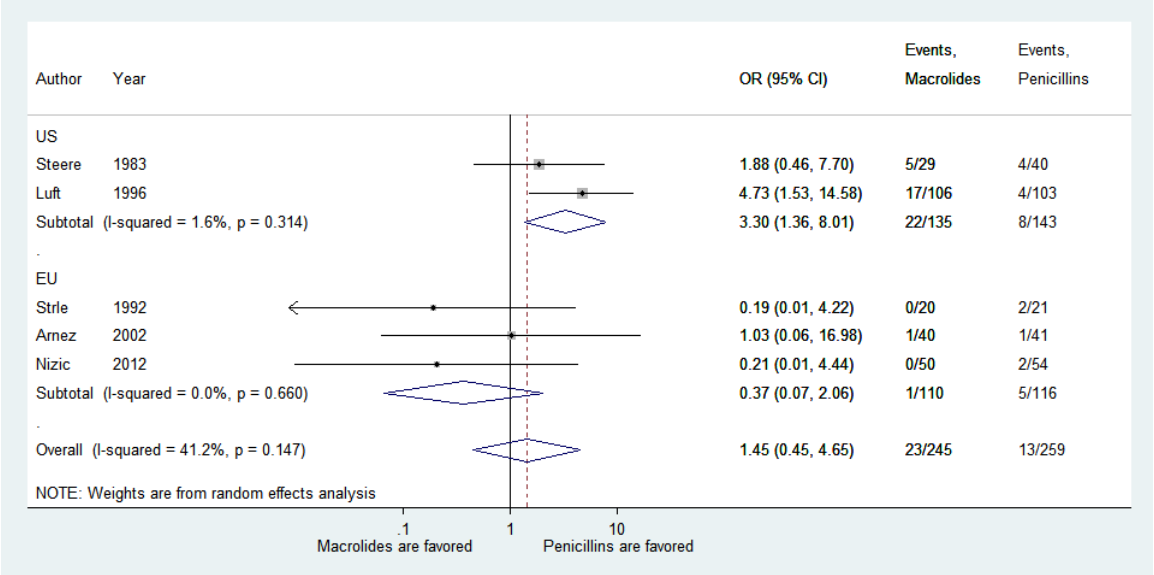
3. Treatment-related adverse events



Funnel plots of standard errors as a function of log odds ratios of having outcomes centered at comparison-specific pooled effect are shown above. The logarithms of pooled odds ratio from each comparison are centered (red line). The two diagonal lines represent the 95% confidence intervals. A total of 7 studies (2 were 3 arm studies) reported acute treatment response, 16 studies (2 were 3 arm studies) reported dissemination of Lyme disease, and 8 studies reported treatment-related adverse events. Note that 2 studies were 3 arm studies. A: cephalosporins; B: macrolides; C: penicillins; D: tetracyclines

Figure 4.5. The effect of study region, adult-only enrollment, and children-only enrollment on dissemination of Lyme: Treatment A vs. Treatment B

1. Dissemination of Lyme by study region: macrolides vs. penicillins



2. Dissemination of Lyme by adult-only enrollment: macrolides vs. penicillins

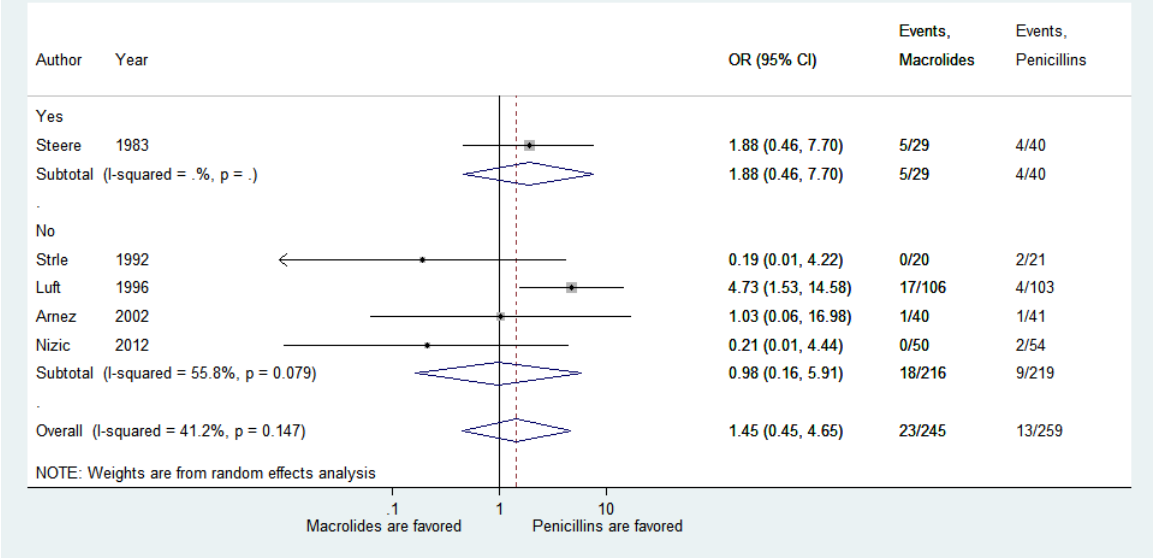
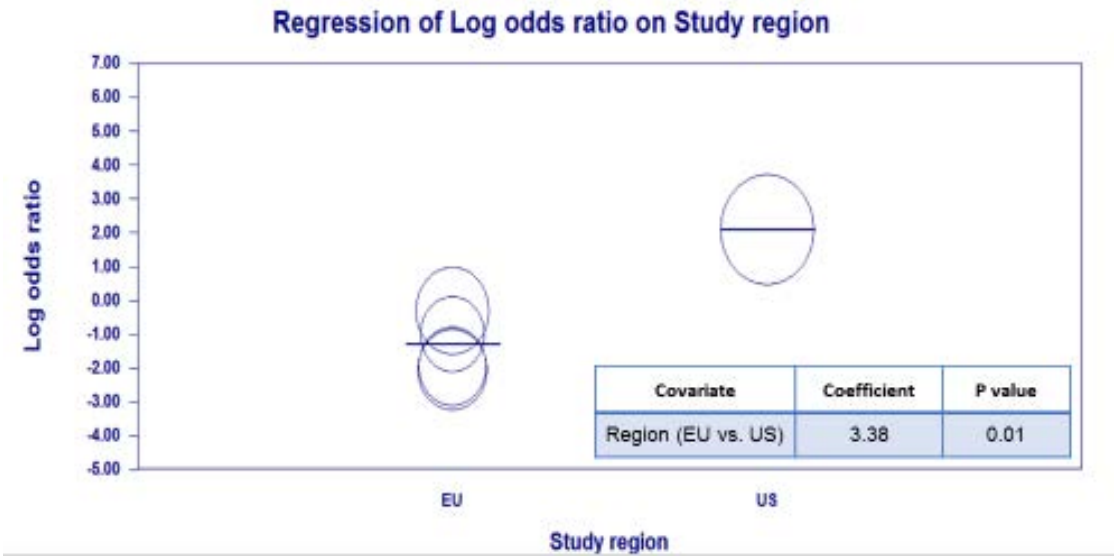
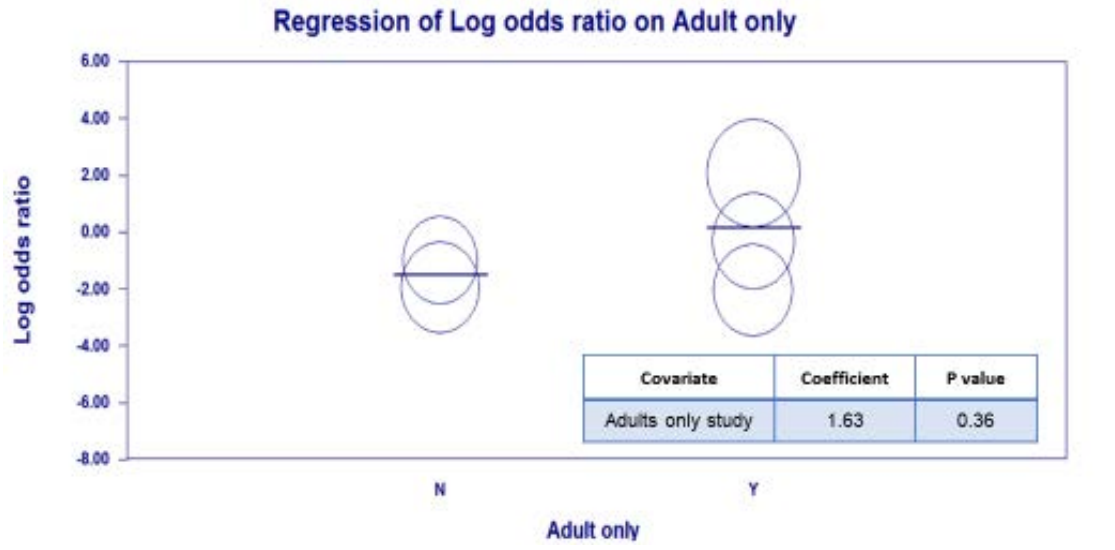


Figure 4.7. The effect of study region (US vs. EU) and adult-only enrollment on dissemination of Lyme disease: Macrolides vs. Tetracyclines

1. Study region (EU vs. US)



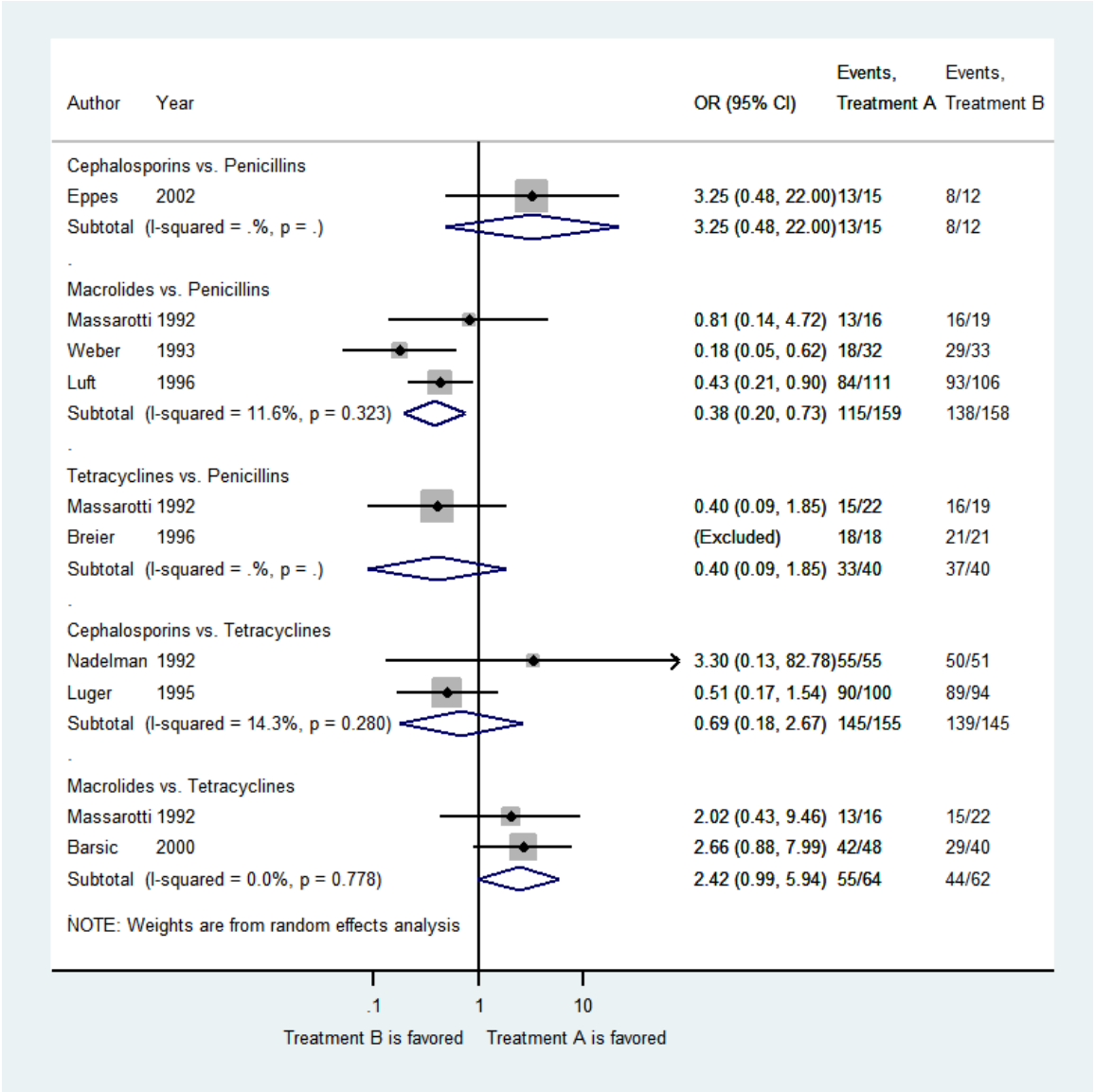
2. Adult only studies vs. the rest of studies



Meta-regression plots of log odds ratio of dissemination of Lyme disease evaluating the effect of study region (Figure 4.7.1) and adult-only enrollment (Figure 4.7.2) by random effects model. None of studies in macrolides vs. tetracyclines treatment comparisons were children-only studies. Therefore, we were unable to perform meta-regression with child only enrollment as a covariate. A log odds ratio less than 0 favors macrolides. Lines represent the pooled log odds ratio. Circles represent studies included in the analysis and the size of circle represents each study's weight.
Figure 4.7.2-- Y: Studies enrolled adults only; N: Studies enrolled both children and adults or children only

Figure 4.8. Sensitivity analysis: acute treatment response by resolution of erythema migrans at the end of treatment, time to resolution of erythema migrans, and time to resolution of signs and symptoms of Lyme disease

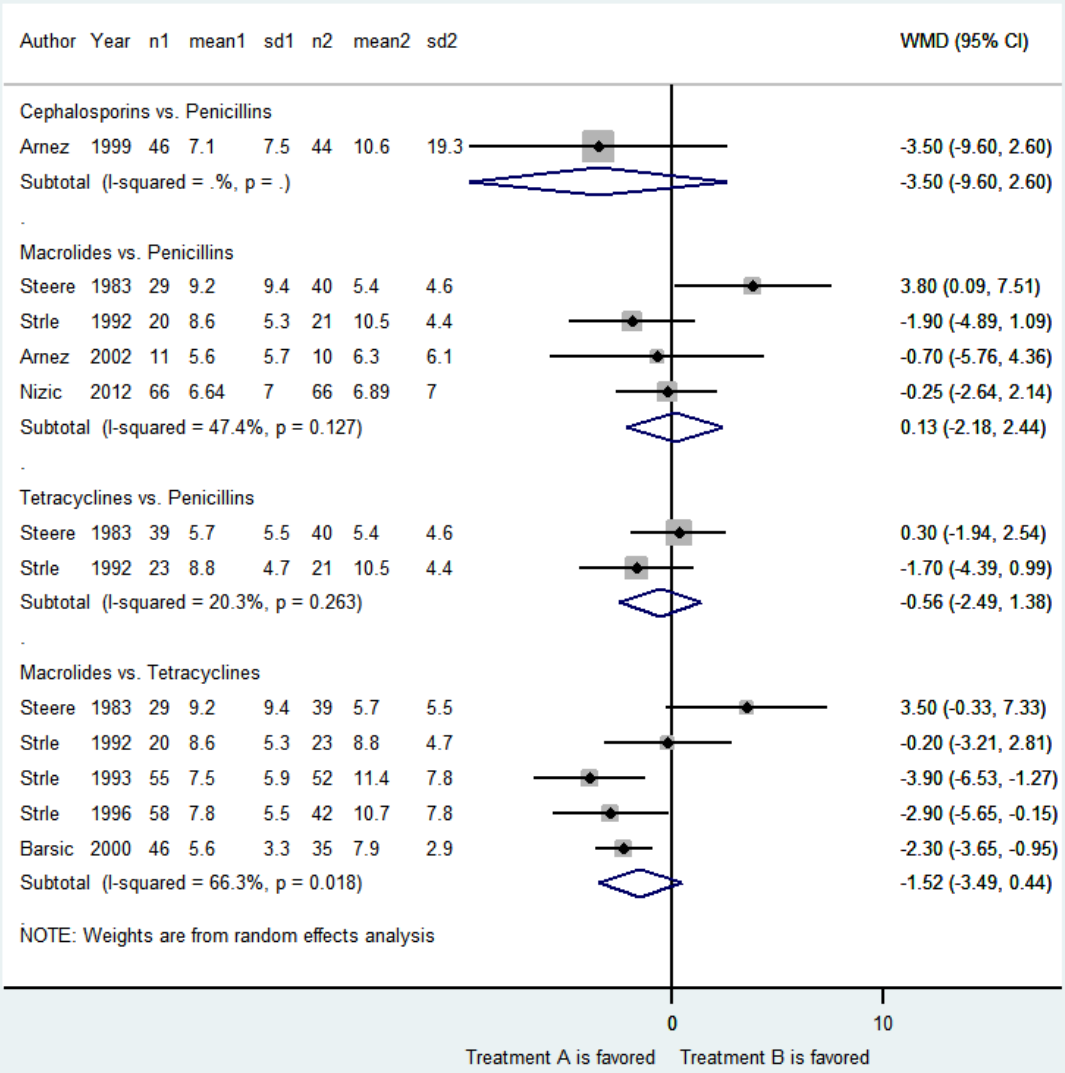
1. Resolution of erythema migrans at the end of treatment: Treatment A vs. Treatment B



OR: odds ratio; 95% CI: 95% confidence interval

I-squared values less than 25%, between 25 and 75%, and greater than 75% are considered as low, moderate, and high heterogeneity
A p-value less than < 0.5 is considered as significant heterogeneity ($\chi 2$ test of heterogeneity)

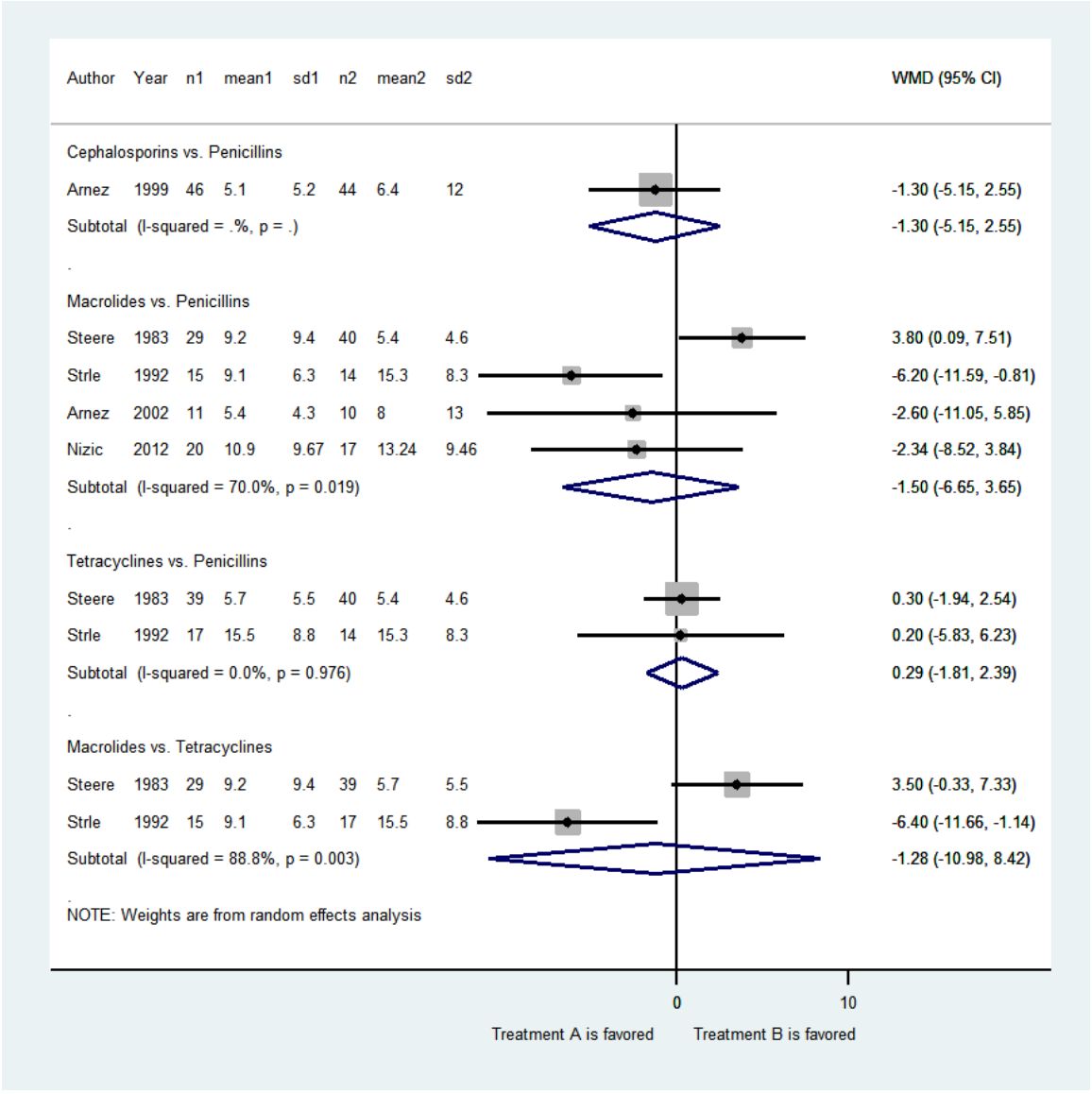
2. Time to resolution of erythema migrans (in days): Treatment A vs. Treatment B



n1: the number of patients in treatment A; mean1: the mean time to the resolution of erythema migrans in treatment A, in days; sd1: the standard deviation for the time to the resolution of erythema migrans in treatment A; n2: number of patients in treatment B; mean2: the mean time to the resolution of erythema migrans in treatment B, in days; sd2: the standard deviation for the time to the resolution of erythema migrans in treatment B; WMD: weighted mean difference

I-squared values less than 25%, between 25 and 75%, and greater than 75% are considered as low, moderate, and high heterogeneity
A p-value less than < 0.5 is considered as significant heterogeneity ($\chi 2$ test of heterogeneity)

3. Time to resolution of signs and symptoms of Lyme disease (in days): Treatment A vs. Treatment B



n1: the number of patients in treatment A; mean1: the mean time to the resolution of erythema migrans and signs and symptoms of Lyme in treatment A, in days; sd1: the standard deviation for the time to the resolution of erythema migrans and signs and symptoms of Lyme in treatment A; n2: number of patients in treatment B; mean2: the mean time to the resolution of erythema migrans and signs and symptoms of Lyme in treatment B, in days; sd2: the standard deviation for the time to the resolution of erythema migrans and signs and symptoms of Lyme in treatment B; WMD: weighted mean difference

I-squared values less than 25%, between 25 and 75%, and greater than 75% are considered as low, moderate, and high heterogeneity

A p-value less than < 0.5 is considered as significant heterogeneity ($\chi 2$ test of heterogeneity)

Table 4.1. Search strategies

EMBASE search: 1974 to March 22, 2016 (3.23.16)		
	Searches	**Results**
1	borrelial lymphocytoma$.mp.	82
2	acrodermatitis chronicum atrophicans.mp.	5
3	STARI.mp.	255
4	southern tick-associated rash illness.mp.	48
5	exp Borrelia Infections/	15052
6	post lyme disease syndrome.mp.	45
7	erythema migrans.mp.	1311
8	exp Borrelia/	11541
9	borrel$.mp.	15552
10	lyme disease$.mp.	14215
11	neuroborreliosis.mp.	1361
12	neuro$.mp.	2326313
13	acrodermatitis.mp.	3125
14	exp Acrodermatitis/	2527
15	carditis.mp.	3327
16	arthrit$.mp.	283042
17	meningitis.mp.	81079
18	exp Meningitis/	79337
19	radiculoneuropath$.mp.	110

20	cranial neuropath$.mp.	3791
21	exp Cranial Nerve Diseases/	106645
22	lyme.mp.	14930
23	(11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21) and 22	5368
24	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 23	20777
25	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 22 or 23	20876
26	limit 25 to humans	14168
27	limit 25 to animals	3932
28	26 or 27	18100
29	25 not 28	2776
30	26 or 29	16944

Table 4.2. Interventions and comparators

Drug	Dosage and frequency		Duration
	Adults	Children	
Doxycycline	100mg BID to TID	1 - 4 mg/kg divided BID (max.100 mg/dose) [a]	10-21 days
Minocycline	100 mg BID	2 mg/kg BID (max.200 mg/d) [a]	14-21 days
Tetracycline	250 - 500 mg QID	25 to 50 mg/kg/day divided QID [a]	10-21 days
Cefuroxime axetil	500mg BID	30 mg/kg/d divided BID (max. 500 mg/dose)	14-21 days
Azithromycin	250 - 500 mg QD	10 - 20 mg/kg/day (max. 500 mg/day)	5–20 days
Clarithromycin	500 mg BID	7.5 mg/kg BID (max. 500 mg/dose)	14-21 days
Erythromycin	250 - 500 mg QID	12.5 mg/kg/d divided QID (max. 500 mg/dose).	14-21 days
Penicillin V potassium/ phenoxymethylpenicillin	250mg - 1000 mg (200,000 to 1,500,000 IU units) TID to QID	12 ≥ years:125 – 250mg TID to QID; 12<years: 25-50 mg/kg/day divided TID to QID (max 3g daily)	14-21 days
Amoxicillin	500mg TID with or without 500 mg of probenecid TID	50 mg/kg/d divided TID (max. 500 mg/dose)	10-21 days

QD: once daily; BID: twice daily; TID: three times daily; QID: four times daily; IU: international unit;

[a] For patients older than 8 years only

Table 4.3. Patient and treatment characteristics of included studies

Study ID/ region	Dosage and duration of treatments; n	Age, mean (years)	Female, %	Pt with EM, %	Erythema migrans diagnostic criteria	Other signs and symptoms of Lyme disease	EM duration, mean (days)
Cephalosporins vs. Penicillins (N=2)							
Arnez 1999(9) Slovenia	Cefuroxime axetil 30 mg/kg/day (max. 1g/day) divided BID for 14 days; n= 46 Phenoxymethyl penicillin 100,000 IU/kg/day (max. 3 M. IU/day) divided TID for 14 days; n=44	7.0	52	100	CDC diagnostic criteria (1990) OR EM less than 5 cm, if patients recall tick bite at the site of EM, had a symptom-free interval between the bite and the onset of EM, and reported an expanding skin lesion prior to diagnosis	70% had mild (EM + 0-1 symptom), 29% had moderate (EM + 2-5 symptoms) and 1 % had severe (EM + ≥ 6 symptoms) initial symptoms	7.8
Eppes 2002(8) United States	Cefuroxime axetil 30 mg/kg/d (max. 1g/d) divided BID for 20 days; n= 15 Amoxicillin 50 mg/kg/d (max. 1.5 g /d) divided TID for 20 days; n= 13 Cefuroxime axetil 20 mg/kg/d (max.750 mg/d) divided BID for 20 days; n=15	6.7	44	100	Patients with physician-diagnosed EM	Multiple EM presented in 14.0%	3.3
Macrolides vs. Penicillins (N=7)							
Steere 1983(29) United States	Erythromycin 250 mg QID for 10 days; n=29 Phenoxymethlypenicillin 250 mg QID for 10 days; n=40 Tetracycline 250mg QID for 10 days; n=39	36.7	50	100	Patients with EM	NA	9.6

Massarotti 1992(23) United States	Azithromycin 500 mg QD on day 1, then 250 mg QD for 4 days; n=16 Amoxicillin 500 mg and probenecid 500 mg TID for 10 days; n=19 Doxycycline 100 mg BID for 10 days; n=22	45.5	47	87 [b]	Patients with EM (≥5 cm) and/or flu-like symptoms with a fourfold change in antibody titer between acute and convalescent sera 4 weeks later	28% had symptoms suggestive of local infection; 28% symptoms suggestive of dissemination to non-neurological sites; 44% had symptoms suggestive of dissemination to neurological sites	7.0
Strle 1992(30) Slovenia	Azithromycin 250 mg BID for 2 days, then 250 mg QD for 8 days; n=20 Phenoxymethylpenicillin 1 M. IU TID for 14 days; n=21 Doxycycline 100 mg BID for 14 days; n=23	38.5	58	100	Patients with typical EM	9.4% had multiple EM; 71.9% had local and/or systematic symptoms of Lyme disease	32.5
Weber 1993(31) Germany	Azithromycin 500 mg QD for 10 days; n=32 Penicillin V 1 M. IU TID for 10 days; n=33	46 (19-74) [c]	57	100	Patients with EM	61.5% had signs and symptoms of Lyme disease	4 (1-34) [c]
Luft 1996(32) United States	Azithromycin 500 mg QD for 7 days and placebo BID for 20 days; n=124 Amoxicillin 500 mg TID for 20 days; n= 122	42.7	38	100	Patients who had had EM (≥5 cm) diagnosed by a physician	31.3% presented with flu-like illness; 15.4% had multiple EM; 56% had no signs of Lyme disease at baseline	NA
Arnez 2002(24) Slovenia	Azithromycin 20 mg/kg/day (max.1g/day) on day 1, followed by 10 mg/kg/day (max. 0.5 g/day) for 4 days; n=42 Penicillin V 100,000 IU/kg/day (max. 3 M. IU/day) divided TID for 14 days; n=42	6.5	52	100	Patients with untreated solitary EM; CDC diagnostic criteria (1990) + Criteria used by Arnez *et al* (9)	58.3% had symptoms of Lyme disease other than EM	5.7
Nizic 2012(25)	Clarithromycin 15 mg/kg/day divided BID	6.7	50	100	CDC criteria+ Criteria used by Arnez *et al* (9)	40.7% had symptoms other than EM	7.2

Slovenia	(max. 500 mg/12 h) for 14 days; n=66 Amoxicillin 50 mg/kg/day divided TID (max. 500 mg/8 h) for 14 days; n=69						
Tetracyclines vs. Penicillins (N=5)							
Steere 1983(29) United States	Tetracycline 250 mg QID for 10 days; n=39 Phenoxymethlypenicillin 250 mg QID for 10 days; n=40 Erythromycin 250 mg QID for 10 days; n=29	36.7	50	100	Patients with EM	NA	9.6
Dattwyler 1990(33) United States	Doxycycline 100 mg BID for 21 days; n= 37 Amoxycillin 500 mg and probenecid 500 mg TID for 21 days; n= 38	37.5	46	100	Patients with EM	15% had multiple EM; 43% had systemic signs or symptoms of Lyme disease	NA
Massarotti 1992(23) United States	Doxycycline 100 mg BID for 10 days; n=22 Amoxicillin 500 mg and probenecid 500 mg TID for 10 days; n= 19 Azithromycin 500 mg on day 1, then 250 mg QD for 4 days; n=16	45.5	47	87 [b]	Patients with EM (≥5 cm) and/or flu-like symptoms with a fourfold change in antibody titer between acute and convalescent sera 4 weeks later	28% had symptoms suggestive of local infection; 28% symptoms suggestive of dissemination to non-neurological sites; 44% had symptoms suggestive of dissemination to neurological sites	7
Strle 1992(30) Slovenia	Doxycycline 100 mg BID for 14 days; n=23 Phenoxymethylpenicillin 1 M. IU TID for 14 days; n=21	38.5	58	100	Patients with typical EM	9.4% had multiple EM; 71.9% had local and/or systematic symptoms of Lyme disease	32.5

	Azithromycin 250 mg BID for 2 days, then 250 mg QD for 8 days; n=20						
Breier 1996(34) Austria	Minocycline 100 mg BID for 21 days; n=18 Phenoxymethylpenicillin 1.5 M. IU TID for 21 days; n=21	43	69	100	Patients with typical EM	NA	NA
Cephalosporins vs. Tetracyclines (N=2)							
Nadelman 1992(35) United States	Cefuroxime axetil 500 mg BID for 20 days (+ sunblock); n=63 Doxycycline 100 mg TID for 20 days (+sunblock); n=60	44.8	44	100	Early Lyme with physician-documented EM (with or without systemic manifestations of infection)	17.9% had multiple EM; systematic manifestation in 82.9% (presence of Lyme disease signs and symptoms in addition to EM)	6.0
Luger 1995(36) United States	Cefuroxime axetil 500 mg BID for 20 days (+sunblock); n=119 Doxycycline 100 mg TID for 20 days (+sunblock); n=113	46	38	99 [a]	Diagnosed with early Lyme disease confirmed by the presence of physician documented EM (with or without systemic manifestations of infection)	76.7% had systemic manifestations (presence of signs and symptoms in addition to EM)	6.5
Macrolides vs. Tetracyclines (N=6)							
Steere 1983(29) United States	Erythromycin 250 mg QID for 10 days; n=29 Tetracycline 250 mg QID for 10 days; n=39 Phenoxymethlypenicillin 250 mg QID for 10 days; n=40	36.7	50	100	Patients with EM	NA	9.6
Massarotti 1992(23) United States	Azithromycin 500 mg on day 1, then 250 mg QD for 4 days; n=16 Doxycycline 100 mg BID for 10 days; n=22	45.5	47	87 [b]	Patients with EM (≥5 cm) and/or flu-like symptoms with a fourfold change in antibody titer between acute and convalescent sera 4 weeks later	28% had symptoms suggestive of local infection; 28% symptoms suggestive of dissemination to non-neurological sites; 44% had	7

	Amoxicillin 500 mg and probenecid 500 mg TID for 10 days; n=19					symptoms suggestive of dissemination to neurological sites	
Strle 1992(30) Slovenia	Azithromycin 250 mg BID for 2 days, then 250 mg QD for 8 days; n=20 Doxycycline 100 mg BID for 14 days; n=23 Phenoxymethylpenicillin 1 M. IU TID for 14 days; n=21	38.5	58	100	Patients with typical EM	9.4% had multiple EM; 71.9% had local and/or systematic symptoms of Lyme disease	32.5
Strle 1993(37) Slovenia	Azithromycin 500 mg BID on day 1, then 500 mg QD for 4 days;n=55 Doxycycline 100 mg BID for 14 days; n=52	43.7	47	100	Patients with typical EM	10.3% had multiple EM; 57.9% had local symptoms; 45.8% had systematic symptoms	17.1
Strle 1996(38) Slovenia	Azithromycin 500 mg BID on day 1, then 500 mg QD for 4 days;n=58 Doxycycline 100 mg BID for 14 days; n=42	48.6	52	100	Patients with typical solitary EM	56% had local symptoms; 51% had systematic symptoms	19.7
Barsic 2000(39) Croatia	Azithromycin 500 mg BID on day 1, then 500 mg QD for 4 days;n=48 Doxycycline 100 mg BID for 14 days; n=40 Minocycline 100 mg BID for 21 days; n=18	44.8	56	100	Patients with early Lyme disease confirmed by the presence of physician-documented EM (>5cm) with or without systemic manifestations of infection	11.4% had multiple EM; 44.3% had systemic symptoms	23.7

NA=Not available; EM= erythema migrans; M.=million; IU=international unit; QD: once daily; BID: twice daily; TID: three times daily; QID: four times daily

[A] 2 in ceftriaxone group had misdiagnosed skin lesion- one with ringworm and the other with herpes lesion

[B] 55 out of 57 patients had EM. 2 patients only had flu-like symptoms with serologic evidence of infection with *B. Burgdorferi*

[C] Presented as median (range)

Table 4.4. Outcomes reported in included studies that are relevant to our study

Study ID	Acute Treatment Response	Dissemination of Lyme Disease at 6 months and beyond	Adverse events	Follow up (month)
Nizic 2012(25)	Duration of EM; duration of local and systemic symptoms	Development of major and minor manifestations of Lyme disease	Patients with 1≥ TAE; GI AE; serious AE; withdrawal due to AE	12
Arnez 2002(24)	Time to resolution of EM; duration of local and systematic symptoms	Development of major and/or minor manifestations of Lyme disease	Patients with 1≥ TAE; GI AE; serious AE; withdrawal due to AE	12
Eppes 2002(8)	Resolution of EM; resolution of Lyme disease symptoms	Development of any late-occurring complications	Serious AE; allergic reaction; diarrhea; withdrawal due to AE	12
Barsic 2000(39)	Resolution of EM and other clinical signs and symptoms of Lyme disease	Persistence or new appearance of minor and major symptoms	Patients with 1≥ TAE; serious AE; GI AE; diarrhea; allergic reaction; withdrawal due to AE	12
Arnez 1999(9)	Duration of EM; Duration of local and systematic symptoms	Development of major and/or minor manifestations of Lyme disease	Patients with 1≥ TAE; GI AE; serious AE; withdrawal due to AE	12
Breier 1996(34)	Resolution of EM	Minor extracutaneous symptoms; signs and symptoms of late Lyme disease	Patients with 1≥ TAE; Serious AE; GI AE; diarrhea; allergic reaction (skin eruption); withdrawal due to AE	12
Luft 1996(32)	Resolution of EM and all objective signs of Lyme disease	11 key subjective symptoms on VAS score	Patients with 1≥ TAE; diarrhea; allergic reaction (rash); withdrawal due to AE	6
Strle 1996(38)	Duration of EM	Major and minor manifestations of Lyme disease	GI AE, serious AE; allergic reaction (photosensitivity); withdrawal due to AE	12

Luger 1995(36)	Resolution of EM and other clinical signs and symptoms	Signs and symptoms of late Lyme (arthralgia, fatigue, arthritis, carditis, neurologic disease)	Patients with 1≥ TAE; GI AE; diarrhea; allergic reactions (rash/drug eruption, photosensitivity); withdrawal due to AE	12
Strle 1993(37)	Duration of EM	Major and minor manifestations of Lyme disease	GI AE; serious AE; diarrhea, allergic reaction (photosensitivity rash); withdrawal due to AE	12
Weber 1993(31)	Resolution of EM and signs and symptoms of Lyme disease; Duration of EM	Development of manifestations (meningitis, meningo-encephalitis, carditis or arthritis)	Patients with 1≥ TAE; Serious AE; diarrhea; allergic reaction (skin eruption); GI AE; withdrawal due to AE	6
Massarotti 1992(23)	Resolution of Lyme disease symptoms including EM	Symptoms suggestive of disseminated infection	allergic rash (drug eruption, photosensitivity rash); diarrhea; withdrawal due to AE	6
Nadelman 1992(35)	Resolution of EM and other clinical signs and symptoms	Signs and symptoms of late Lyme (arthralgia, fatigue, arthritis, carditis, neurologic disease)	Patients with 1≥ TAE; serious AE; GI AE; diarrhea; allergic reaction (photosensitivity); withdrawal due to AE	12
Strle 1992(30)	Duration of EM; duration of signs and symptoms	Major and minor manifestations of Lyme disease	GI AE; allergic reaction (photosensitivity); serious AE	24
Dattwyler 1990(33)	Resolution of EM	Major and minor late features of Lyme disease	GI AE; allergic reaction (photodermatitis and rash); withdrawal due to AE	6
Steere 1983(29)	Resolution of EM and associated symptoms; duration of EM	Major and minor manifestations of Lyme disease	NA	>12

EM: erythema migrans; TAE: treatment-related adverse event; AE: adverse event; GI AE: gastrointestinal adverse event; NA: not available

Duration of EM was measured from the initiation of therapy to the resolution. Duration of local and systematic symptoms was measured from the initiation of therapy to the resolution

Table 4.5. Risk of bias in included studies

Study ID	Random Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Outcome Assessor	Incomplete Outcome Data	Selective Reporting	Other Bias	Intention-to-treat analysis	Industrial funding
Steere 1983(29)	Low[a]	Unclear[a]	Unclear	Unclear	Unclear[a]	Low[a]	Unclear	Yes	No
Dattwyler 1990(33)	Unclear	Unclear	Unclear	Unclear	Low	Low	High	No	No
Massarotti 1992(23)	Low	Low[a]	Unclear	Unclear	High	Low	High	Yes	Unclear
Nadelman 1992(35)	Low	Unclear	High	Unclear[a]	Unclear	Low	Unclear	Yes	Unclear
Strle 1992(30)	High	High	Unclear	Unclear	Low	Low	High	Yes	Unclear
Strle 1993(37)	High	High	Unclear	Unclear	Low	Low	High	Yes	Unclear
Weber 1993(31)	Unclear	Unclear	Unclear	Unclear	Low	Low	High	Yes	Unclear
Luger 1995(36)	Low	Unclear	High[a]	Unclear[a]	High	Unclear	Unclear	Yes	Yes
Breier 1996(34)	Low	Unclear[a]	High[a]	High[a]	High[a]	Low	Unclear	Yes	Unclear
Luft 1996(32)	Low[a]	Unclear[a]	Low	Low	Low[a]	Low	Unclear	No	Yes
Strle 1996(38)	High	High	Unclear	Unclear	Unclear	Unclear	High	Yes	Unclear
Arnez 1999(9)	High	High	Unclear	Unclear	Low	Low	High[a]	No	Unclear
Barsic 2000(39)	Low	Unclear	High	High	Low	Low	Unclear	No	Yes[b]
Arnez 2002(24)	High	High	Unclear	Unclear	Low	Low	High	No	Unclear
Eppes 2002(8)	Unclear	Unclear	High[a]	High[a]	Low	Low	Unclear	No	Yes
Nizic 2012(25)	High	High	Unclear	Unclear	High	Low	High	No	No[c]

[a] There were disagreements in the ratings between two independent reviewers, and these were resolved by discussion.

[b] One of the author was an employee of Pliva Pharmaceuticals, Zagreb, Croatia; However, it is not clear whether the company supported the study.

[c] The authors declared no conflict of interest

Table 4.6. Adverse events reported in included studies

AE and Study ID	Treatment Group	Patients With ≥1 Event, *n*	Total Patients, *n*
Treatment-related adverse event	Overall: 25.8%		
Nadelman 1992(35)	Cefuroxime axetil	19	63
	Doxycycline	19	60
Weber 1993(31)	Azithromycin	12	32
	Penicillin V	5	33
Luger 1995(36)	Cefuroxime axetil	20	119
	Doxycycline	32	113
Breier 1996(34)	Phenoxymethylpenicillin	12	18
	Minocycline	4	21
Luft 1996(32)	Azithromycin	43	111
	Amoxicillin	29	106
Arnez 1999(9)	Cefuroxime axetil	12	46
	Phenoxymethyl penicillin	3	44
Barsic 2000(39)	Azithromycin	3	47
	Doxycycline	5	35
Nizic 2012(25)	Clarithromycin	16	66
	Amoxicillin	18	64
Withdrawal due to adverse events	Overall: 2.4%		
Dattwyler 1990(33)	Doxycycline	2	37
	Amoxycillin	1	38
Massarotti 1992(23)	Azithromycin	0	16
	Doxycycline	0	22
	Amoxicillin	4	19
Nadelman 1992(35)	Cefuroxime axetil	1	63
	Doxycycline	1	60
Strle 1993(37)	Azithromycin	0	55
	Doxycycline	0	52
Weber 1993(31)	Azithromycin	1	32
	Penicillin V	0	33
Luger 1995(36)	Cefuroxime axetil	8	119
	Doxycycline	5	113
Strle 1996(38)	Azithromycin	0	58
	Doxycycline	0	42
Luft 1996(32)	Azithromycin	2	124
	Amoxicillin	6	122
	Phenoxymethylpenicillin	2	30

Breier 1996(34)	Minocycline	1	30
Arnez 1999(9)	Cefuroxime axetil	0	46
	Phenoxymethyl penicillin	0	44
Barsic 2000(39)	Azithromycin	0	48
	Doxycycline	1	40
Arnez 2002(24)	Azithromycin	0	42
	Penicillin V	0	42
Eppes 2002(8)	Cefuroxime axetil	0	15
	Amoxicillin	0	12
Nizic 2012(25)	Clarithromycin	0	66
	Amoxicillin	0	68
Any gastrointestinal adverse events	Overall: 2.4%		
Strle 1992(30)	Azithromycin	2	20
	Doxycycline	4	23
	Phenoxymethylpenicillin	1	21
Nadelman 1992(35)	Cefuroxime axetil	14	63
	Doxycycline	6	60
Weber 1993(31)	Azithromycin	12	32
	Penicillin V	5	33
Strle 1993(37)	Azithromycin	8	55
	Doxycycline	15	52
Luger 1995(36)	Cefuroxime axetil	9	119
	Doxycycline	10	113
Luft 1996(32)	Azithromycin	2	111
	Amoxicillin	0	106
Strle 1996(38)	Azithromycin	5	58
	Doxycycline	9	42
Arnez 1999(9)	Cefuroxime axetil	5	46
	Phenoxymethyl penicillin	1	44
Barsic 2000(39)	Azithromycin	2	47
	Doxycycline	4	35
Arnez 2002(24)	Azithromycin	3	40
	Penicillin V	2	41
Eppes 2002(8)	Cefuroxime axetil	3	15
	Amoxicillin	2	12
Nizic 2012(25)	Clarithromycin	2	66
	Amoxicillin	5	64
Allergic Reaction	Overall: 4.7%		
	Azithromycin	0	20

Strle 1992(30)	Doxycycline	1	23
	Phenoxymethylpenicillin	0	21
Massarotti 1992(23)	Azithromycin	0	16
	Amoxicillin	6	19
	Doxycycline	1	22
Nadelman 1992(35)	Cefuroxime axetil	2	63
	Doxycycline	9	60
Weber 1993(31)	Azithromycin	2	32
	Penicillin V	0	33
Strle 1993(37)	Azithromycin	0	55
	Doxycycline	6	52
Luger 1995(36)	Cefuroxime axetil	2	119
	Doxycycline	11	113
Luft 1996(32)	Azithromycin	0	111
	Amoxicillin	6	106
Strle 1996(38)	Azithromycin	0	58
	Doxycycline	5	42
Breier 1996(34)	Phenoxymethylpenicillin	2	30
	Minocycline	1	30
Barsic 2000(39)	Azithromycin	0	47
	Doxycycline	1	35
Eppes 2002(8)	Cefuroxime axetil	0	15
	Amoxicillin	0	12
Nizic 2012(25)	Clarithromycin	2	66
	Amoxicillin	2	64
Serious adverse events	Overall: 0.2%		
Strle 1992(30)	Doxycycline	1	23
	Phenoxymethylpenicillin	0	21
Strle 1993(37)	Azithromycin	0	55
	Doxycycline	0	52
Weber 1993(31)	Azithromycin	0	32
	Penicillin V	0	33
Strle 1996(38)	Azithromycin	0	58
	Doxycycline	0	42
Barsic 2000(39)	Azithromycin	0	47
	Doxycycline	0	35
Arnez 2002(24)	Azithromycin	0	40
	Penicillin V	0	41
Eppes 2002(8)	Cefuroxime axetil	0	15
	Amoxicillin	0	12
Diarrhea	Overall: 5.6%		

Massarotti 1992(23)	Azithromycin	3	16
	Doxycycline	1	22
	Azithromycin	2	19
Nadelman 1992(35)	Cefuroxime axetil	13	63
	Doxycycline	4	60
Weber 1993(31)	Azithromycin	4	32
	Penicillin V	3	33
Luger 1995(36)	Cefuroxime axetil	5	100
	Doxycycline	0	94
Luft 1996(32)	Azithromycin	2	111
	Amoxicillin	0	106
Barsic 2000(39)	Azithromycin	0	47
	Doxycycline	1	35
Eppes 2002(8)	Cefuroxime axetil	3	15
	Amoxicillin	2	12

Table 4.7. Heterogeneity within each comparison for each outcome

Comparison	RCTs, n	I^2	Included Studies
Acute Treatment Response			
Cephalosporins vs. Penicillins	0	NA[a]	NA
Macrolides vs. Penicillins	4	0	Steere 1983(29), Massarotti 1992(23), and Weber 1993(31), Luft 1996(32)
Tetracyclines vs. Penicillins	2	0	Steere 1983(29), Massarotti 1992(23)
Cephalosporins vs. Macrolides	0	NA[a]	NA
Cephalosporins vs. Tetracyclines	2	21	Nadelman 1992(35), Luger 1995(36)
Macrolides vs. Tetracyclines	3	51	Steere 1983(29), Massarotti 1992(23), and Barsic 2000(39)
Dissemination of Lyme disease			
Cephalosporins vs. Penicillins	2	NA[a]	Arnez 1999(9), and Eppes 2002(8)[b]
Macrolides vs. Penicillins	5	41	Steere 1983(29), Strle 1992(30), Luft 1996(32), Arnez 2002(24), Nizic 2012(25)
Tetracyclines vs. Penicillins	4	0	Steere 1983(29), Dattwyler 1990(33)[b], Strle 1992(30), Breier 1996(34)[b]
Cephalosporins vs. Macrolides	0	NA[a]	NA
Cephalosporins vs. Tetracyclines	2	NA[a]	Nadelman 1992(35)[b], Luger 1995(36)
Macrolides vs. Tetracyclines	5	43	Steere 1983(29), Strle 1992(30), Strle 1993(37), Strle 1996(38), Barsic 2000(39)
Treatment-related adverse events			
Cephalosporins vs. Penicillins	1	NA[a]	Arnez 1999(9)
Macrolides vs. Penicillins	3	52	Weber 1993(31), Luft 1996(32), Nizic 2012(25)
Tetracyclines vs. Penicillins	1	NA[a]	Breier 1996(34)
Cephalosporins vs. Penicillins	0	NA[a]	NA
Cephalosporins vs. Tetracyclines	2	29	Nadelman 1992(35), Luger 1995(36)

Macrolides vs. Tetracyclines	1	NA[a]	Barsic 2000(39)

I^2 values less than 25%, between 25 and 75, and greater than 75% are considered as low, moderate, and high heterogeneity.

NA: Not available

[a] Heterogeneity could not be calculated in comparisons that contained fewer than two non-double-zero study

[b] Double-zero studies (studies that had zero events in both treatment arms) could not be used to calculate heterogeneity

Table 4.8. Assessment of inconsistency in networks of treatment comparisons for all outcomes

1. Acute treatment response

Inconsistency factor (IF)

Cycle	Median (95% CrI)
Macrolides, penicillins, tetracyclines	0.58 (-0.52, 2.22)

Node-splitting method

Name	Direct effect	Indirect effect	Overall	P-value
Penicillins, tetracyclines	-0.83 (-2.18, 0.57)	-2.05 (-3.95, -0.27)	-1.28 (-2.41, -0.06)	0.2

2. Dissemination of Lyme

Inconsistency factor (IF)

Cycle	Median (95% CrI)
Cephalosporins, macrolides, penicillins, tetracyclines	0.19 (-1.73, 3.13)
Macrolides, penicillins, tetracyclines	-0.03 (-2.70, 2.46)

Node-splitting method

Name	Direct effect	Indirect effect	Overall	P-value
Cephalosporins, penicillins	-0.05 (-4.76, 4.90)	-9.65 (-29.86, 0.66)	-1.47 (-5.57, 1.94)	0.12
Cephalosporins, tetracyclines	-19.47 (-78.95, -0.84)	0.14 (-5.12, 5.43)	-1.75 (-5.99, 1.79)	0.04
Macrolides, penicillins	0.21 (-1.49, 2.13)	5.37 (-2.53, 19.61)	0.73 (-0.95, 2.70)	0.24
Macrolides, tetracyclines	0.77 (-1.06, 2.94)	-17.89 (-54.75, 0.56)	0.46 (-1.40, 2.42)	0.05
Penicillins, tetracyclines	-1.36 (-4.35, 1.31)	1.38 (-1.67, 4.68)	-0.29 (-2.50, 1.77)	0.16

3. Treatment-related adverse events

Inconsistency factor (IF)

Cycle	Median (95% CrI)
Cephalosporins, macrolides,penicillins, tetracyclines	-0.06 (-1.73, 1.24)
Macrolides, penicillins, tetracyclines	0.07 (-1.13, 1.74)

Node-splitting method

Name	Direct effect	Indirect effect	Overall	P-value
Cephalosporins, penicillins	-1.66 (-3.87, 0.30)	-1.44 (-3.56, 0.43)	-1.48 (-2.88, -0.41)	0.83
Cephalosporins, tetracyclines	0.42 (-0.77, 1.53)	0.25 (-2.41, 2.67)	0.39 (-0.54, 1.30)	0.9
Macrolides, penicillins	-0.45 (-1.42, 0.48)	-1.22 (-3.77, 1.53)	-0.49 (-1.41, 0.25)	0.57
Macrolides, tetracyclines	0.99 (-1.04, 3.16)	1.74 (-0.10, 3.54)	1.39 (0.17, 2.69)	0.57
Penicillins, tetracyclines	2.29 (0.28, 4.93)	1.74 (0.14, 3.44)	1.88 (0.84, 3.18)	0.69

Table 4.9. Effect estimates for acute treatment response by each antimicrobial agent

	Amoxicillin	**Azithromycin**	**Cefuroxime**	**Doxycycline**	**Erythromycin**	**PCN V**	**Tetracycline**
Amoxicillin		0.56 (0.17, 1.80)	0.27 (0.05, 1.55)	0.27 (0.06, 1.03)	0.94 (0.02, 17.12)	3.99 (0.43, 30.45)	2.21 (0.05, 48.01)
Azithromycin			0.51 (0.10, 2.42)	0.43 (0.13, 1.49)	1.72 (0.05, 26.40)	**7.35 (1.11, 39.75)**	3.08 (0.12, 68.08)
Cefuroxime				0.91 (0.33, 2.53)	3.45 (0.09, 77.02)	**15.52 (1.33, 139.69)**	6.35 (0.23, 203.68)
Doxycycline					3.90 (0.11, 67.67)	**16.45 (1.74, 134.83)**	6.91 (0.26, 191.78)
Erythromycin						4.56 (0.53, 56.97)	2.45 (0.38, 20.14)
PCN V							0.51 (0.04, 5.93)
Tetracycline							

An odds ratio greater than 1 favors the therapeutic class in the column header row
PCN V: penicillin V/phenoxymethylpenicillin

Table 4.10. Effect estimates for treatment-related adverse events by each antimicrobial agent

	Amoxicillin	**Azithromycin**	**Cefuroxime**	**Clarithromycin**	**Doxycycline**	**Minocycline**	**PCN V**
Amoxicillin		1.68 (0.35, 8.08)	2.80 (0.24, 30.16)	0.83 (0.15, 4.43)	3.81 (0.40, 42.25)	3.43 (0.25, 110.25)	0.43 (0.06, 4.49)
Azithromycin			1.60 (0.27, 9.68)	0.56 (0.05, 4.73)	2.12 (0.46, 13.60)	1.93 (0.25, 42.61)	0.26 (0.06, 1.37)
Cefuroxime				0.31 (0.02, 4.90)	1.41 (0.50, 4.40)	1.47 (0.14, 25.70)	**0.14 (0.04, 0.89)**
Clarithromycin					4.25 (0.31, 80.27)	3.84 (0.19, 178.26)	0.49 (0.04, 8.94)
Doxycycline						1.07 (0.10, 20.14)	**0.11 (0.02, 0.67)**
Minocycline							**0.10 (0.01, 0.68)**
PCN V							

An odds ratio less than 1 favors the therapeutic class in the column header row
PCN V: penicillin V/phenoxymethylpenicillin

Table 4.11. Effect estimates for treatment-related adverse events excluding pediatric studies

	Odds ratios (95% credibility intervals)			
	Penicillins	**Cephalosporins**	**Macrolides**	**Tetracyclines**
	Treatment-related adverse events			
Penicillins		4.92 (0.74, 40.46)	2.22 (0.81, 7.63)	**7.57 (1.59, 38.31)**
Cephalosporins			0.45 (0.07, 3.19)	1.53 (0.46, 4.92)
Macrolides				3.43 (0.71, 16.47)
Tetracyclines				

An odds ratio less than 1 favors the therapeutic class in the column header row

Table 4.12. Effect estimates for acute treatment response including US studies only
An odds ratio less than 1 favors the therapeutic class in the column header row

	Odds ratios (95% credibility intervals)			
	Penicillins	**Cephalosporins**	**Macrolides**	**Tetracyclines**
	Acute Treatment Response			
Penicillins		0.51 (0.11, 2.33)	0.43 (0.16, 1.09)	0.47 (0.14, 1.67)
Cephalosporins			0.87 (0.19, 3.62)	0.96 (0.37, 2.31)
Macrolides				1.09 (0.33, 3.72)
Tetracyclines				

An odds ratio greater than 1 favors the therapeutic class in the column header row

Chapter 5. Bibliography

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