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One Dose of Doxycycline for the Prevention of Lyme Disease: A Review of Clinical Effectiveness and Guidelines

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Abbreviations

CI	Confidence Interval
ILADS	International Lyme and Associated Diseases Society
NRS	Non-Randomized Study
RCT	Randomized Controlled Trial
SR	Systematic Review

Context and Policy Issues

Lyme disease affected 2025 Canadians in 2017,[1] making it the most common vector-borne infection in Canada.[2,3] Immature black-legged ticks – *Ixodes scapularis* in Eastern and Central Canada or *I. pacificus* in British Columbia – infected with the bacteria spirochete *Borrelia burgdorferi* are responsible for transmitting Lyme disease to humans in Canada.[2-4] Erythema migrans, fever, and arthralgia are the diagnostic triad for Lyme disease.[2-4]

In Canada, Lyme disease became a nationally reportable disease in 2009 with black-legged ticks confirmed in sections of British Columbia, Manitoba, Ontario, Quebec, New Brunswick and Nova Scotia.[2-4] However, half of reported Lyme disease cases in Canada were caused by infected ticks encountered during travel to the eastern United States and Europe.[3]

If an infected tick bite is not detected or is left untreated, Lyme disease can progress to neurological, joint, and cardiac involvement.[2-4] Lyme disease from an infected tick bite can be prevented if the tick is removed within 24 to 36 hours.[2-4] Prophylaxis might be considered within 72 hours of tick removal if the vector was identified as an immature black-legged tick which remained attached for more than 36 hours and the patient had visited a region where local rates of infection are greater than 20%.[2-5] If any of these criteria are unclear, clinician judgment and patient preference is used to determine if prophylaxis or watchful waiting is warranted.[6,7] If any of these criteria are not met, watchful waiting for 30 days has been recommended to monitor the appearance of fever, arthralgia, and rash symptoms.[3,4]

For adults, a single dose of doxycycline (200 mg) has been recommended for prophylaxis after tick attachment for prevention of Lyme disease.[2,4,5,7-11] For children eight years of age and older, a single dose of doxycycline (4 mg/kg up to the adult dosage).[6-8,11] Doxycycline is contraindicated in pregnant or lactating women as well as in young children due to the risk of possible effects on fetus bone formation and permanent tooth staining.[3]

Use of a single dose of doxycycline as prophylaxis for the prevention of Lyme disease after a tick bite is debated for several reasons: the low risk of infection transmission; the contraindication of doxycycline in children younger than eight years of age; and the uncertainty surrounding its clinical effectiveness. Since the risk of infection is low, even in endemic areas, and Lyme disease is readily treatable once symptoms develop, watchful waiting has been employed instead of prophylaxis, particularly in children.[5,8,10,12]

As a tetracycline, doxycycline is contraindicated in children younger than eight years of age due to the risk of permanent tooth staining or enamel hypoplasia.[3,12,13] However according to research into Rocky Mountain spotted fever, short courses of doxycycline did not cause permanent tooth staining in children younger than ten years of age.[13-15] Additionally, in a 2018 survey, 82% of parents would consent to a hypothetical trial of doxycycline for children with Lyme disease.[16] This research may make the case for permitting one dose of doxycycline in all age groups to prevent Lyme disease after tick attachment.[4,13,15,17]

The objective of this report is to summarize the evidence regarding the clinical effectiveness of one dose of doxycycline for the prevention of Lyme disease in patients with tick attachment as well as relevant evidence-based guidelines associated with the use of one dose of doxycycline for the prevention of Lyme disease in patients with tick attachment.

Research Questions

1. What is the clinical effectiveness of one dose of doxycycline for the prevention of Lyme disease in patients with tick attachment?
2. Are the evidence-based guidelines associated with the use of one dose of doxycycline for the prevention of Lyme disease in patients with tick attachment?

Key Findings

Based primarily on a very-low quality randomized controlled trial, one dose of doxycycline appears to be clinically effective for the prevention of Lyme disease in patients with tick attachment. The very-low quality of this evidence decreases confidence in these findings.

Evidence-based guidelines offer conflicting recommendations based on the same low-quality randomized controlled trial. Two guidelines recommend one dose of doxycycline for the prevention of Lyme disease in patients with tick attachment and two guidelines recommend against one dose of doxycycline for the prevention of Lyme disease in patients with tick attachment, citing high risk of bias in the randomized controlled trial, low infection rates, and proven clinical effectiveness of treatment for Lyme disease once signs and symptoms manifest.

Further high-quality studies are needed to confirm the results of this randomized controlled trial with appropriate enrollment and follow-up of a validated outcome in a generalizable setting. Ideally this research would be conducted in Canada to inform Canadian clinical decision-making and policy making.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and April 16, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Pediatric or adult patients who have had a tick attached
Intervention	One dose of doxycycline
Comparator	Question 1: No antibiotics; Watchful waiting for signs of Lyme disease (no treatment); Standard of care Question 2: No comparator
Outcomes	Question 1: Clinical effectiveness (e.g., prevention of Lyme disease, incidence/chances of Lyme disease) and safety (e.g., adverse effects from doxycycline use) Question 2: Guidelines
Study Designs	HTA/Systematic Reviews/Meta-Analyses, Randomized Controlled Trials, Non-Randomized Studies, Evidence-based Guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, were not published in English, or were published prior to 2009. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic review (SR)[18] was critically appraised by one reviewer using AMSTAR II,[19] the non-randomized study (NRSs)[20] was assessed using the ROBINS-I Tool,[21] and guidelines[12,22-24] were assessed with the AGREE II instrument.[25] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 211 citations were identified in the literature search. Following screening of titles and abstracts, 152 citations were excluded and 59 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 55 publications were excluded for various reasons, and six publications met the inclusion criteria and were included in this report. These comprised one systematic review,[18] one non-randomized study,[20] and four evidence-based guidelines.[12,22-24] Appendix 1 presents the PRISMA[26] flowchart of the study selection. Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

The systematic review with meta-analysis was published in 2010 as an update to a 1995 systematic review search. The original review searched 1983 to 1995 and the update searched from January 1st, 1995 to April 1st, 2009. One of the four included RCTs was relevant to this report and was the same RCT referred to in all of the guidelines.[18]

The non-randomized study was a prospective cohort study published in 2014.[20]

The four included guidelines were: the Sanchez et al. guideline published in 2016 for JAMA's Clinical Review and Education section;[22] Prescrire Editorial Staff guideline published in 2015;[12] the Cameron et al. guideline published in 2014 for International Lyme and Associated Diseases Society (ILADS);[23] and Wright et al. published in 2012.[24] All the guidelines conducted systematic searches of the relevant literature with the Sanchez et al. guideline using the American Heart Association scoring system and consensus for rating the quality and strength of evidence;[22] the Prescrire guideline verified evidence selection and analysis using unnamed quality controls and external review;[12] the ILADS guideline used Grading of Recommendations Assessment, Development and Evaluation (GRADE) for rating the quality and strength of evidence but method of agreement on recommendations is unclear;[23] and the Wright et al. guideline using the Strength of Recommendation Taxonomy (SORT) for rating the quality and strength of evidence but with unclear methods for agreement on recommendations.[24]

Country of Origin

The systematic review, non-randomized study and three of the guidelines were produced in or for the United States of America.[18,20,22-24] The Prescrire guideline was produced in France.[12]

Patient Population

The systematic review drew data from one RCT relevant to this report that enrolled 506 patients 12 years of age or older with no clinical evidence of Lyme disease at two hospitals within 72 hours following an *Ixodes* tick bite.[18]

The non-randomized study recruited eight patients presenting to a pharmacy in Rhode Island aged 18 years or older with an *Ixodes scapularis* tick attached for 36 hours or more and intervention administered within 72 hours of tick removal.[20]

Three guidelines targeted clinicians as their intended users.[12,22,24] The ILADS guideline was aimed at healthcare providers who evaluate and manage patients with Lyme disease.[23]

Interventions and Comparators

The intervention was described as a single 200 mg dose of doxycycline in all included literature.[12,18,20,22-24]

The comparators of interest varied across the included studies and guidelines and were described as:

- Placebo[12,18,22-24]
- 100 to 200 mg of doxycycline, twice daily for 20 days[23]
- 10 day course of amoxicillin[18]

- Tick removal within 24 to 36 hours[12,24]
- Lifestyle and daily methods to prevent a tick bite: Avoiding areas with ticks,[24] daily body checks for ticks,[12,22,24] bathing or showering within two hours of tick exposure,[22,24] tick repellents,[22,24] protective clothing,[22,24] placing clothes in a dryer for up to an hour,[22] landscape modifications[22,24]
- Watchful waiting[23]
- Patient education (prevention of future bites, as well as potential manifestations of Lyme disease and other tick-borne diseases).[23]

Outcomes

Outcomes were defined as:

- Erythema migrans prevention, used as an unvalidated surrogate outcome for Lyme disease prevention measured after six weeks[12,18,22-24]
- Any signs or symptoms of Lyme disease at any time within 30 days after intervention[20]
- Adverse events after intervention within six weeks[23] or within 30 days.[20]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Review with Meta-Analysis

The systematic review appropriately described the population, intervention, comparator group, outcome, and timeframe for follow-up in the research questions and inclusion criteria of the review. The review questions, search strategy, inclusion and exclusion criteria as well as meta-analysis plan and investigation of heterogeneity were all established prior to the conduct of the review and any deviations were justified. It is unclear whether the risk of bias assessment plan was established prior to the conduct of the review, however, an appropriate risk of bias assessment was used in the final publication and likely did not affect the quality of the review. No explanation was given for selecting only randomized controlled trials for inclusion, but this decision was determined prior to the conduct of the review and randomization was part of the inclusion criteria such that the lack of explanation likely did not affect the quality of the review. The search strategy included searching at least two databases and with appropriate justification of restrictions was provided and searches were conducted within a year of review publication. Trial registries and bibliographies of included trials were searched.[18] These review characteristics limit bias in: research questions and inclusion criteria; *a priori* protocol registration with explanation of deviations from this protocol; study design selection; search strategy, which therefore increase the confidence in the results of the systematic review.

The review is unclear regarding whether study selection was conducted in duplicate – if the reviewers did not conduct study selection in duplicate then this could introduce bias into the review, with reduced quality and confidence in its results. Grey literature was not searched and content experts were not consulted, which may have omitted relevant data and introduced publication bias. This omission is of particular importance since publication bias was not assessed. The sources of funding for each included trial were not discussed and

risk of bias from the selection of the reported result from multiple measurements or analyses was not assessed.[18] These review characteristics may increase bias in: study selection; search strategy; risk of bias assessments and their impact on the meta-analysis, interpretation of results, and discussion; sources of funding and conflicts of interest, which therefore decrease the confidence in the results of the systematic review.

Data extraction was conducted in duplicate. The exclusion of studies was justified with a list of excluded studies available on request. Included studies were described in detail and assessed for bias. The potential effect of risk of bias from included studies on the results was discussed. The review reported no conflicts of interest.[18] These review characteristics limit bias in: data extraction; description of inclusion and exclusion for each study; risk of bias assessments and their impact on the meta-analysis, interpretation of results, and discussion; sources of funding and conflicts of interest, which therefore increase the confidence in the results of the systematic review.

The review justified combining the data in a meta-analysis but weighting was not described. The statistical test for homogeneity found that all four included trials were homogenous, but the included trials differed in terms of antibiotic type and duration used as well as in trial population. These differences and their potential effect on the results were discussed and combining their results was justified.[18] These review characteristics limit bias in: meta-analysis; assessment of heterogeneity; and publication bias or small study bias, which therefore increase the confidence in the results of the meta-analysis.

Non-Randomized Study

The non-randomized study appropriately controlled, measured, and documented known confounders. Selection of participants into the study was not based on characteristics observed after the start of intervention and coincided with the start of follow-up. Intervention groups were clearly defined, were recorded at the start of intervention, and could not have been affected by knowledge of the outcome. The intervention was implemented successfully for all participants and all participants adhered to their assigned intervention regimen.[20] These study characteristics limit bias in: presence of confounding variables; selection of participants; and implementation of and adherence to intervention, which therefore increase confidence in the results of the study

Outcome data were available for all participants and no participants were excluded due to missing data. Selection of the reported results is not likely based on multiple outcome measurements, multiple analyses, or differing subgroups.[20] These study characteristics limit bias in: missing data; and selection of reported result, which therefore increase confidence in the results of the study.

Outcome measurement may have been influenced by knowledge of received intervention since the outcome assessors were aware of the intervention received by study participants and may therefore decrease confidence in the results of the study.[20]

Guidelines

The evidence-based guidelines clearly described their respective objectives, health questions, and populations to whom the guidelines were meant to apply.[12,22-24] Two guidelines clearly defined their target users.[22,23] All guidelines used systematic methods to search for evidence and explicitly linked recommendations to the supporting evidence.[12,22-24] The Sanchez et al. guideline clearly described methods for evidence selection and formulation of recommendations as well as the strengths and limitations of selected

evidence.[22] The Prescrire guideline considered side effects and risks as well as external review comments in formulating the guideline but was unclear on the methods of selecting evidence and formulating the recommendations as well as the strengths and limitations of the supporting evidence.[12] The ILADS guideline was unclear on the method of evidence selection, but clearly described the methods of formulating recommendations with consideration of external reviewer comments, the strengths and limitations of the evidence, as well as side effects and risks.[23] This guideline was also the only guideline to provide a procedure for updating in the future.[23] The Wright et al, guideline clearly described evidence selection and methods for recommendation formulation, including side effects and benefits but was unclear on the strengths and limitations of the supporting body of evidence.[24] These guideline characteristics limit bias in: scope and purpose; stakeholder involvement; and rigour of development, which therefore increase confidence in the recommendations of the guideline.

However, the role of all relevant professional groups in development of the guideline is unclear for all guidelines and the views and preferences of the target population were either not sought[22,24] or it is unclear whether they were sought.[12,23] Additionally, two guidelines did not clearly define their target users.[12,24] The Sanchez et al. guideline failed to consider side effects and risks in recommendation formulation and was not externally reviewed.[22] The Wright et al guideline was also not externally reviewed.[24] These guideline characteristics increase bias in: stakeholder involvement; and rigour of development, therefore decreasing confidence in the recommendations of the guideline.

All the guidelines wrote specific and unambiguous recommendations that presented different options for management of Lyme disease prevention and clearly identified key recommendations. These guidelines also described facilitators and barriers to application and advice on implementation as well as resource implications.[12,22-24] However, only the ILADS guideline presented monitoring criteria.[23] The views of the funding body did not influence guideline recommendations and the conflicts of interest of the guideline development groups were recorded and addressed.[12,22-24] These guideline characteristics limit bias in: clarity of presentation; applicability; and editorial independence, which therefore increase confidence in the recommendations of the guideline.

Summary of Findings

Appendix 4 presents tables of the main findings and authors' conclusions.

Clinical Effectiveness of One Dose of Doxycycline for the Prevention of Lyme Disease in Patients with Tick Attachment

In the systematic review, one RCT was relevant to this review which found that erythema migrans at site of tick bite is prevented by one dose of doxycycline instead of placebo (odds ratio [OR] = 0.13, 95% CI: 0.003 to 0.97; relative risk reduction [RRR] 87%) for non-allergic patients older than eight years of age who are not pregnant or lactating. However, this confidence interval is very wide which limits its clinical value and decreases confidence in the degree of benefit. This review recommends monitoring for signs and symptoms of Lyme disease after receiving one dose of doxycycline since prophylaxis was not 100% effective at preventing Lyme disease. Additionally, the review suggests that prophylaxis is unnecessary even in highly endemic areas because of the low risk of transmission.[18] Further comments on this RCT are available in the Limitations section. This review also proposes, based on a different systematic review, a 10-day course of amoxicillin for patients younger than eight

years of age or adults who are pregnant or lactating even though the exact benefit of amoxicillin as prophylaxis for Lyme disease has not been established.[18]

None of the eight patients 18 years or older from the non-randomized study who received one dose of doxycycline experienced any signs or symptoms of Lyme disease at any time within 30 days after intervention. Two of the patients experienced self-limiting fatigue, dizziness, flushing, and nausea within 24 hours of taking doxycycline. However, this study had low patient enrollment, which decreases our confidence in the applicability of its result.[20]

One dose of doxycycline appears to be clinically effective for the prevention of Lyme disease in patients with tick attachment based on one RCT from 2001 with wide confidence intervals[18] and one NRS from 2014 with low patient enrollment.[20]

Guidelines

Guidelines offer conflicting recommendations on the use of one dose of doxycycline for the prevention of Lyme disease in patients with tick attachment and are all referring to one RCT, the same RCT included in the systematic review included in this review. Additional comments on this RCT are available in the Limitations section.

Sanchez et al. and Wright et al. recommend one dose of doxycycline prophylaxis,[22,24] whereas Prescrire and ILADS do not recommend prophylaxis.[12,23] Sanchez et al. note that the confidence interval around the effect estimate in the RCT is wide[22] and Wright et al. rated their recommendation as inconsistent or limited-quality patient-oriented evidence.[24]

The Prescrire guideline advises against routine prophylaxis after a tick bite because of low risk of infection and the effectiveness of treatment for Lyme disease if it develops to avoid unnecessary treatment and adverse effects of doxycycline.[12]

The ILADS guideline recommends against routine prophylaxis after a tick bite on the basis of very low-quality evidence. The referenced RCT had several limitations including: the use of erythema migrans prevention as an unvalidated surrogate for prevention of Lyme disease; and insufficient follow-up of six weeks to measure the late stage manifestations of Lyme disease, thus biasing the results towards effectiveness of treatment. This RCT was imprecise and affected by few cases of erythema migrans, a wide confidence interval surrounding the relative treatment effectiveness, as well as the assumption that no patients lost to follow-up developed erythema migrans.[23] According to the RCT's Fragility Index, which is a measure of the robustness of a trial's results,[27] if one of the patients lost to follow-up developed erythema migrans, the treatment effectiveness would no longer be statistically significant and the conclusion of the RCT would no longer find doxycycline as effective for preventing erythema migrans.[23] In the RCT treatment group, 26 patients were lost to follow-up.[28] This RCT's effectiveness has not been replicated in other trials and is inconsistent with murine models.[23] The RCT is also indirect, because the results are only applicable to adults bitten by the *Ixodes scapularis* exposed only to Lyme disease to prevent erythema migrans – the results are not generalizable to patients bitten by other black-legged ticks, patients exposed to multiple tick-borne diseases, or manifestations of Lyme disease other than erythema migrans.[23]

The ILADS guideline recommends 100 to 200 mg of doxycycline, twice daily for 20 days for a known *Ixodes* bite regardless of degree of tick engorgement or local infection rates, however, this recommendation is based on very low-quality evidence.[23]

Three of the guidelines recommend lifestyle and daily methods to prevent a tick bite: daily body checks for ticks,[12,22,24] bathing or showering within two hours of tick exposure,[22,24] tick repellents,[22,24] protective clothing,[22,24] and placing clothes in a dryer for up to an hour,[22] as interventions with minimal risks and limited benefit.[22] Sanchez et al. do not recommend landscape modifications since they appear not to affect transmission risk of incidence of Lyme disease,[22] but Wright et al. do recommend landscape modifications, albeit on evidence rated as consensus, disease-oriented evidence, usual practice, expert opinion, or case series.[24]

The Prescrire guideline and Wright et al. recommend proper tick removal within 24 hours as a method to reduce risk of transmission[12] and prevent Lyme disease.[24]

The ILADS guideline also recommends patient education for prevention of future bites as well as other potential manifestations of Lyme disease and other tick-borne diseases. While this recommendation is based on very low-quality evidence, the authors feel that the benefits of education outweigh any potential risks of education in the context of shared medical decision-making to incorporate patient values and preferences.[23]

Limitations

One of the main limitations of the body of evidence is it rests on the results of a single RCT published in 2001. The effectiveness estimate in the RCT has a wide confidence interval,[22,23] and if one of the 26 patients lost to follow-up in the treatment group developed erythema migrans, effectiveness would no longer be statistically significant. The use of erythema migrans as a surrogate outcome for Lyme disease has not been validated. The length of follow-up was insufficient to detect late manifestations of Lyme disease. The trial is also ungeneralizable to patients bitten by other black-legged ticks, patients exposed to multiple tick-borne diseases, or manifestations of Lyme disease other than erythema migrans.[23,29] Additionally, a medical entomologist was used to identify the tick as *Ixodes scapularis*, which requires a certain level of expertise not generalizable to the medical community as a whole.[29]

The non-randomized study had a low enrollment of eight patients, which decreases confidence in the applicability of its findings.[20]

Furthermore, much of the research surrounding Lyme disease has been conducted in Europe or the United States of America – high quality Canadian-specific content is lacking. The USA shares the same black-legged tick populations as Canada (*Ixodes scapularis* on the east coast and *Ixodes pacificus* on the west coast) but have different vector host-animal density, whereas a different black-legged tick is seen in Europe (*Ixodes ricinus*).[5,30]

Conclusions and Implications for Decision or Policy Making

One systematic review,[18] one non-randomized study,[20] and four evidence-based guidelines[12,22-24] regarding one dose of doxycycline for the prevention of Lyme disease were included in this review.

Based on the systematic review one dose of doxycycline appears to be clinically effective for the prevention of Lyme disease in patients with tick attachment. However, this clinical effectiveness is based on one RCT from 2001 with wide confidence intervals,[18,22,23] a fragile conclusion, an unvalidated surrogate outcome, insufficient follow-up, and lack of generalizability.[23,29] None of the eight patients enrolled in the NRSnon-randomized study from 2014 experienced signs or symptoms of Lyme disease within 30 days of receiving doxycycline prophylaxis, though it is unclear if this was due to doxycycline use given the small number of participants and lack of control group.[20]

Evidence-based guidelines offer conflicting recommendations the use of one dose of doxycycline for the prevention of Lyme disease in patients with tick attachment based on that same RCT.[12,22-24] Two guidelines recommending prophylaxis mention the wide confidence interval[22] and rate their recommendation as based on inconsistent or limited-quality patient-oriented evidence.[24] Other guidelines recommend against prophylaxis based on the fragile conclusions of the RCT[23] as well as the low risk of infection and the effectiveness of treatment for Lyme disease if it does present.[12]

Guidelines recommending proper tick removal within 24 hours as a method to reduce risk of transmission[12] and prevent Lyme disease[24] as well as daily body checks for ticks,[12,22,24] bathing or showering within two hours of tick exposure,[22,24] tick repellents,[22,24] protective clothing,[22,24] and placing clothes in a dryer for up to an hour,[22] as interventions with minimal risks and limited benefit.[22]

The ILADS guideline advocates patient education for prevention of future bites as well as other potential manifestations of Lyme disease and other tick-borne diseases. While this recommendation is based on very low-quality evidence, the authors feel the benefits of education outweigh any potential risks in the context of shared medical decision-making to incorporate patient values and preferences.[23]

Further high-quality studies are needed to confirm the results of this RCT with appropriate enrollment and follow-up of a validated outcome in a generalizable setting. Ideally this research would be conducted in Canada to inform Canadian clinical decision-making and policy making.

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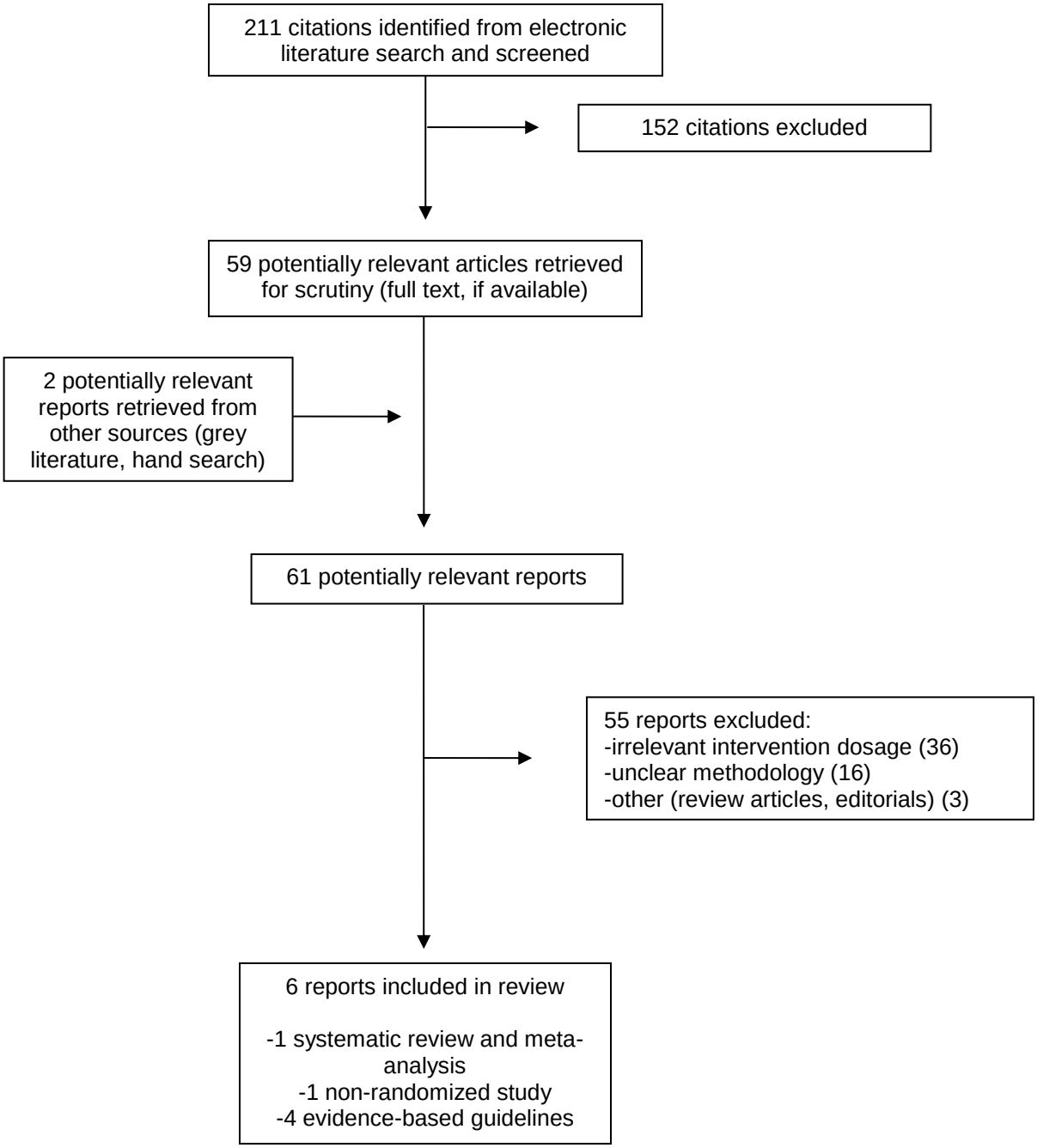
30. Gasmi S, Ogden NH, Leighton PA, et al. Practices of Lyme disease diagnosis and treatment by general practitioners in Quebec, 2008-2015. *BMC Fam Pract.* 2017;18(1):65.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review and Meta-Analysis

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Warshafsky 2010, United States of America[18]	Systematic Review and Meta-Analysis - 1 RCT (3 additional RCTs with irrelevant interventions for this rapid review)	Patients with no clinical evidence of Lyme disease at enrollment enrolled within 72 hours following an *Ixodes* tick bite - No restriction on antibiotics used, age of patients, length of follow-up, or observed outcomes	Intervention - Doxycycline (200 mg/day for 1 day) Comparators - Placebo - 10 day course of amoxicillin	Erythema migrans at site of tick bite, 1.5 months

RCT = Randomized Controlled Trial

Table 3: Characteristics of Included Primary Clinical Study

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Non-Randomized Study				
Jackson et al, 2014, United States of America[20]	Prospective Cohort Study	Patients presenting to a pharmacy in Rhode Island aged 18 years or older with an *Ixodes scapularis* tick attached for 36 hours or more and intervention was administered within 72 hours of tick removal.	Intervention: - Doxycycline (two 100 mg tablets taken as a single dose with food)	- Any signs or symptoms of Lyme disease at any time within 30 days after intervention. - Adverse effects within 30 days after intervention.

Table 4: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Sanchez et al, 2016[22]						
Clinicians	Interventions: - Single 200 mg dose of doxycycline - Daily body checks for ticks, bathing or showering within two hours of tick exposure, tick repellents, protective clothing, placing clothes in a dryer for up to an hour, landscape modifications	- Erythema migrans prevention	Systematic search of relevant literature using two databases, including one for grey literature. At least two reviewers assessed relevant literature for inclusion. All articles deemed relevant by at least one author were reviewed in detail.	At least two reviewers independently rated quality of evidence using the American Heart Association scoring system.	At least two reviewers independently rated strength of recommendations using the American Heart Association scoring system and then reviewed until consensus was reached by all authors through discussion or majority opinion.	Not validated.
Prescrire Editorial Staff, 2015[12]						
Clinicians	Interventions: - Antibiotics (including a single 200 mg dose of doxycycline) - Daily body checks for ticks	- Erythema migrans prevention	Systematic search of relevant literature using more than two databases, including grey literature. Exact methodology of selection is unclear, but includes some verification of chosen articles.	Exact methodology of quality assessment is unclear, but includes some verification of quality control.	Exact methodology of recommendation development is unclear, but includes some verification by all authors.	External review.
ILADS, 2014[23]						
Healthcare providers who evaluate and manage patients with Lyme disease	Interventions: - Single 200 mg dose of doxycycline - 100 to 200 mg of doxycycline, twice daily for 20 days - Watchful waiting - Patient education (prevention of future bites, potential manifestations of Lyme disease and other tick-borne diseases)	- Erythema migrans prevention - Adverse events	A panel systematically searched for relevant literature using clear search strategy but exact methodology of selection is unclear.	A panel rated quality of evidence using GRADE.	Exact methodology of recommendation development is unclear. A panel rated strength of recommendations using GRADE.	Outside reviewers reviewed and commented on a preliminary draft of the guidelines.

Table 4: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Wright et al, 2012[24]						
Clinicians	Interventions: - Single 200 mg dose of doxycycline - Avoiding areas with ticks, protective clothing, tick repellants daily body checks, bathing after outdoor activities, landscape modifications	- Lyme disease prevention	Systematic search of relevant literature using more than two databases, including grey literature. Exact methodology of selection is unclear, but includes some verification of chosen articles.	Exact methodology of quality assessment is unclear, but the SORT evidence rating system was used.	Exact methodology of recommendation development is unclear, but the SORT evidence rating system was used.	Not validated.

GRADE = Grading of Recommendations Assessment, Development and Evaluation, SORT = Strength of Recommendation Taxonomy

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Review and Meta-Analysis using AMSTAR II[19]

Item	Systematic Reviews and Meta-Analyses
	Warshafsky et al, 2010[18]
Domain 1: PICO	
1. Research questions and inclusion criteria include the population.	Yes
2. Research questions and inclusion criteria include the intervention.	Yes
3. Research questions and inclusion criteria include the comparator group.	Yes
4. Research questions and inclusion criteria include the outcome.	Yes
5. Research questions and inclusion criteria include the timeframe for follow-up.	Yes
Domain 2: Protocol	
6. Review question(s) were established prior to the conduct of the review.	Yes
7. Any significant deviations from the protocol regarding the review question(s) were justified.	Yes
8. A search strategy was established prior to the conduct of the review.	Yes
9. Any significant deviation from the protocol regarding the search strategy was justified.	Yes
10. Inclusion/exclusion criteria was established prior to the conduct of the review.	Yes
11. Any significant deviations from the protocol regarding the inclusion/exclusion criteria were justified.	Yes
12. A risk of bias assessment was established prior to the conduct of the review.	Unclear
13. Any significant deviation from the protocol regarding the risk of bias assessment was justified.	Unclear
14.If appropriate, a meta-analysis/synthesis plan was established prior to the conduct of the review.	Yes
15. If appropriate, any significant deviation from the protocol regarding the meta-analysis/synthesis plan was justified.	Yes
16.If appropriate, a plan for investigating causes of heterogeneity was established prior to the conduct of the review.	Yes
17. If appropriate, any significant deviation from the protocol regarding the plan for investigating causes of heterogeneity was justified.	Yes
Domain 3: Study Design Selection	
18. The review explained the selection of either: only RCTs; only NRSs; or RCTs and NRSs.	No

Item	Systematic Reviews and Meta-Analyses
	Warshafsky et al, 2010[18]
Domain 4: Search Strategy	
19. At least 2 databases (relevant to research question) were searched.	Yes
20. Key words and/or search strategy were provided.	Yes
21. Publication restrictions (e.g. language) were justified.	Yes
22. The reference lists / bibliographies of included studies were searched.	Yes
23. Trial/study registries were searched.	Yes
24. Content experts in the field were included or consulted.	No
25. Grey literature was searched.	No
26. The search was conducted within 24 months of completion of the review.	Yes
Domain 5: Duplication of Study Selection	
27. At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	Unclear
Domain 6: Duplication of Data Extraction	
28. At least two reviewers achieved consensus on which data to extract from included studies OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	Yes
Domain 7: Excluded Studies	
29. A list of all potentially relevant studies that were read in full-text form but excluded from the review was provided.	No (available on request)
30. The exclusion from the review of each potentially relevant study was justified.	Yes

Item	Systematic Reviews and Meta-Analyses
	Warshafsky et al, 2010[18]
Domain 8: Included Studies	
31. Population(s) of each included study were described in detail.	Yes
32. Intervention(s) of each included study were described in detail.	Yes
33. If applicable, dosage and timing of intervention(s) were described.	Yes
34. Comparator(s) of each included study were described in detail.	Yes
35. If applicable, dosage and timing of comparator(s) were described.	N/A
36. Outcomes of each included study were described in detail.	Yes
37. Timeframe for follow-up of each included study was described in detail.	Yes
38. Study setting(s) of each included study were described in detail.	Yes
39. Research design of each included study was described in detail.	Yes
Domain 9: Risk of Bias Assessment	
40. RCTs: Risk of bias from unconcealed allocation was assessed.	Yes
41. RCTs: Risk of bias from the lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality) was assessed.	Yes
42. RCTs: Risk of bias from an allocation sequence that was not truly random was assessed.	Yes
43. RCTs: Risk of bias from the selection of the reported result from among multiple measurements or analyses of a specified outcome was assessed.	No
44. NRSs: Risk of bias from confounding was assessed.	N/A
45. NRSs: Risk of bias from selection bias was assessed.	N/A
46. NRSs: Risk of bias from methods used to ascertain exposures and outcomes was assessed.	N/A
47. NRSs: Risk of bias from selection of the reported result from among multiple measurements or analyses of a specified outcome was assessed.	N/A
Domain 10: Sources of Funding	
48. If available, the sources of funding of each included study were reported.	No

Item	Systematic Reviews and Meta-Analyses
	Warshafsky et al, 2010[18]
Domain 11: Meta-Analysis (if applicable)	
49. RCTs: Combining the data in a meta-analysis was justified.	Yes
50. RCTs: An appropriate weighted technique to combine study results used.	No
51. RCTs: If applicable, heterogeneity was adjusted for.	N/A
52. RCTs: If applicable, the causes of any heterogeneity were investigated.	N/A
53. NRSs: Combining the data in a meta-analysis was justified.	N/A
54. NRSs: An appropriate weighted technique to combine study results used.	N/A
55. NRSs: If applicable, heterogeneity was adjusted for.	N/A
56. NRSs: Statistically combined effect estimates were adjusted for confounding, rather than combining raw data, or combining raw data when adjusted effect estimates were not available was justified.	N/A
57. Separate summary estimates for RCTs and NRSs were reported separately when both were included in the review.	N/A
Domain 12: Potential Impact from Risk of Bias on Meta-Analysis (if applicable)	
58. Only low risk of bias RCTs were included OR if the pooled estimate was based on RCTs and/or NRSs at variable risks of bias, the possible impact from risks of bias on summary estimates of effect were analyzed.	Yes
Domain 13: Potential Impact from Risk of Bias on Review Interpretation and Discussion of Results	
59. Only low risk of bias RCTs were included OR if RCTs with moderate or high risk of bias or NRSs were included the review, a discussion of the likely impact of risk of bias on the results was provided.	Yes
Domain 14: Heterogeneity (if applicable)	
60. No significant heterogeneity in the results was found OR if heterogeneity was found, sources of any heterogeneity in the results were investigated and the impact of this on the results of the review was discussed.	Yes
Domain 15: Publication Bias / Small Study Bias (if applicable)	
61. Graphical or statistical tests for publication bias were performed and the likelihood and magnitude of impact of publication bias was discussed.	No
Domain 16: Conflict of Interest	
62. No competing interests (including funding) were reported OR funding sources were reported and how potential conflicts of interest were managed was described.	Yes

RCT = randomized controlled trial, NRS = non-randomized study

Table 6: Strengths and Limitations of Non-Randomized Studies using the ROBINS-I Tool[21]

Item	Non-Randomized Study
	Jackson et al, 2014[20]
Domain 1: Confounding	
1. There is no potential for confounding of the effect of intervention in this study. The study can be considered to be at low risk of bias due to confounding. *No further items are assessed.*	No
2. The analysis was not based on splitting participants' follow up time according to intervention received. *Baseline confounding only assessed.*	Yes
3. Intervention discontinuations or switches were not likely to be related to factors that are prognostic for the outcome. *Baseline confounding only assessed.*	Yes
4. Baseline confounding: The authors used an appropriate analysis method that controlled for all the important confounding domains.	Yes
5. Baseline confounding: If applicable, confounding domains that were adjusted for were measured validly and reliably by the variables available in this study.	Yes
6. Baseline confounding: The authors controlled for any post-intervention variables that could have been affected by the intervention.	Yes
7. Baseline and time-varying confounding: The authors used an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding.	N/A
8. Baseline and time-varying confounding: If applicable, confounding domains that were adjusted for were measured validly and reliably by the variables available in this study.	N/A
Domain 2: Selection of participants into the study	
9. Selection of participants into the study (or into the analysis) was not based on participant characteristics observed after the start of intervention.	Yes
10. If applicable, the post-intervention variables that influenced selection were not likely to be associated with intervention.	N/A
11. If applicable, the post-intervention variables that influenced selection were not likely to be influenced by the outcome or a cause of the outcome.	N/A
12. Start of follow-up and start of intervention coincide for most participants.	Yes
13. If applicable, adjustment techniques were used that are likely to correct for the presence of selection biases.	N/A
Domain 3: Classification of Interventions	
14. Intervention groups were clearly defined.	Yes
15. The information used to define intervention groups was recorded at the start of the intervention.	Yes
16. Classification of intervention status could not have been affected by knowledge of the outcome or risk of the outcome.	Yes

Item	Non-Randomized Study
	Jackson et al, 2014[20]
Domain 4: Intended Interventions	
17. Assignment to intervention: There were no deviations from the intended intervention beyond what would be expected in usual practice.	N/A
18. Assignment to intervention: If applicable, these deviations from intended intervention were balanced between groups and unlikely to have affected the outcome.	N/A
19. Adherence to intervention: Important co-interventions were balanced across intervention groups.	N/A
20. Adherence to intervention: The intervention was implemented successfully for most participants.	Yes
21. Adherence to intervention: Study participants adhered to the assigned intervention regimen.	Yes
22. Adherence to intervention: If applicable, an appropriate analysis was used to estimate the effect of starting and adhering to the intervention.	N/A
Domain 5: Missing Data	
23. Outcome data were available for all, or nearly all, participants.	Yes
24. Participants were not excluded due to missing data on intervention status.	Yes
25. Participants were not excluded due to missing data on other variables needed for the analysis.	Yes
26. If applicable, the proportion of participants and reasons for missing are data similar across interventions.	N/A
27. If applicable, there is evidence that results were robust to the presence of missing data.	N/A
Domain 6: Measurement of Outcomes	
28. The outcome measure could not have been influenced by knowledge of the intervention received.	Probably No
29. Outcome assessors were not aware of the intervention received by study participants.	No
30. The methods of outcome assessment were comparable across intervention groups.	N/A
31. Any systematic errors in measurement of the outcome were not related to intervention received.	Probably No
Domain 7: Selection of the Reported Result	
32. The reported effect estimate is unlikely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain.	Yes
33. The reported effect estimate is unlikely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship.	Yes
34. The reported effect estimate is unlikely to be selected, on the basis of the results, from different subgroups.	Yes

Table 7: Strengths and Limitations of Guidelines using AGREE II[25]

Item	Guideline			
	Sanchez et al, 2016[22]	Prescrire Editorial Staff, 2015[12]	ILADS, 2014[23]	Wright et al, 2012[24]
Domain 1: Scope and Purpose				
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes	Yes
Domain 2: Stakeholder Involvement				
4. The guideline development group includes individuals from all relevant professional groups.	Unclear	Unclear	Unclear	Unclear
5. The views and preferences of the target population (patients, public, etc.) have been sought.	No	Unclear	Unclear	No
6. The target users of the guideline are clearly defined.	Yes	No	Yes	No
Domain 3: Rigour of Development				
7. Systematic methods were used to search for evidence.	Yes	Yes	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	Unclear	Unclear	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Unclear	Yes	Unclear
10. The methods for formulating the recommendations are clearly described.	Yes	Unclear	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	No	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	No	Yes	Yes	No
14. A procedure for updating the guideline is provided.	No	No	Yes	No

Item	Guideline			
	Sanchez et al, 2016[22]	Prescrire Editorial Staff, 2015[12]	ILADS, 2014[23]	Wright et al, 2012[24]
Domain 4: Clarity of Presentation				
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes
Domain 5: Applicability				
18. The guideline describes facilitators and barriers to its application.	Yes	Yes	Yes	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	Yes	Yes	Yes
20. The potential resource implications of applying the recommendations have been considered.	Yes	Yes	Yes	Yes
21. The guideline presents monitoring and/or auditing criteria.	No	No	Yes	No
Domain 6: Editorial Independence				
22. The views of the funding body have not influenced the content of the guideline.	Yes	Yes	Yes	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes	Yes	Yes

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings Included Systematic Review and Meta-Analysis

Main Study Findings	Authors' Conclusion
Warshafsky et al, 2010[18]	
Erythema migrans at site of tick bite is prevented by one dose of doxycycline over (OR = 0.13, 95% CI: 0.003 to 0.97) Nadelman RB, Nowakowski J, Fish D et al. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an Ixodes scapularis tick bite. *N Engl J Med* 2001; 345: 79–84.	"*[O]ne 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.*" (p.1143) "*The Nadelman et al. study … 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.*" (p.1141) "*In the Nadelman et al. study, of the 448 ticks for which engorgement status was available, 223 (49.8%) were partially engorged. …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.*" (p.1142) "*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 amoxicillin and 15 cases of nausea would occur following a 200 mg dose of doxycycline.*" (p.1142)

OR = Odds Ratio, CI = Confidence Interval, RRR = Relative Risk Reduction, NNT = Number Needed to Treat

Table 9: Summary of Findings of Included Non-Randomized Study

Main Study Findings	Authors' Conclusion
Jackson et al, 2014[20]	
Doxycycline (two 100 mg tablets taken as a single dose with food) - Eight enrolled patients ○ One excluded due to tick attachment greater than 72 hours ○ Two experienced adverse effects (fatigue, dizziness, flushing, and nausea) from doxycycline within 24 hours of taking doxycycline (28.6%) ○ None developed any signs or symptoms of Lyme disease at any time during the 30-day follow-up.	"*Under a collaborative practice agreement, trained pharmacists at an independent pharmacy in Rhode Island identified patients eligible for postexposure antibiotic prophylaxis following attachment and removal of an Ixodes scapularis tick (commonly known as a deer tick) and dispensed doxycycline to the patients. The results indicated a high level of patient satisfaction with the pharmacy services provided and no reports of subsequent development of Lyme disease symptoms or major adverse events.*" (p.70)

Table 10: Summary of Recommendations of Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Sanchez et al, 2016[22]	
"*A single 200-mg prophylactic dose of doxycycline following a tick bite was 87% effective in preventing the development of erythema migrans at the bite site, but the confidence interval surrounding this efficacy rate was wide. Prophylaxis is only recommended when an Ixodes tick from a Lyme disease–endemic area has been attached for 36 hours or longer and prophylaxis can be started within 72 hours.*" (p.1174) - One RCT Nadelman RB, Nowakowski J, Fish D, et al. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an Ixodes scapularis tick bite. *N Engl J Med*. 2001;345(2):79-84	Not reported.
Daily body checks for ticks, bathing or showering within 2 hours of tick exposure, tick repellents, protective clothing, placing clothes in a dryer for up to an hour - "*These interventions have minimal potential risks, so although they may have limited benefit, they can be recommended.*" (p.1174)	Not reported.
"*Modifications of the home environment have not clearly been shown to affect transmission risk. Spraying pesticides around the home effectively reduces tick populations but is not associated with the incidence of Lyme disease. … Altering landscape characteristics by removing leaf litter or having a barrier to adjacent wooded areas has not consistently reduced the incidence of Lyme disease.*" (p.1774)	Not reported.
Prescrire Editorial Staff, 2015[12]	
"*Routine antibiotic prophylaxis is not justified after a tick bite, even in an endemic area, as the risk of infection is low. It is best to monitor the skin around the bite and to prescribe an antibiotic only if erythema migrans develops, thus avoiding unnecessary treatment and adverse effects.*" (p.247)	Not reported.
"*The risk of transmission appears to be very low when the tick remains attached for less than 24 hours. It then increases with longer attachment time... After possible exposure, the risk of infection can be markedly reduced by closely inspecting the entire body … and removing any ticks, if necessary with a dedicated tick remover.*" (p.249)	Not reported.
"*Antibiotic prophylaxis generally not justified*." (p.249) - One systematic review Warshafsky et al, 2010[18] ○ Erythema migrans development 2.2% in placebo group versus 0.2% in antibiotic group (p=0.004) ○ ~50 patients with tick bites needed to treat with antibiotics instead of placebo to prevent one case of erythema migrans	Not reported.

Table 10: Summary of Recommendations of Included Guidelines

Recommendations	Strength of Evidence and Recommendations
"*French and U.S. guidelines agree that antibiotic prophylaxis should not be given routinely after a tick bite, but only on a case-by-case basis, when the risk of infection is considered high, for example in case of multiple bites in a highly endemic area with an attachment time of more than 36 to 48 hours. In these high-risk situations, a single 200-mg dose of doxycycline appears to be the antibiotic of choice for a non-pregnant adult.*" (p.249)	Not reported.
"*In practice. Antibiotics appear to prevent the onset of erythema migrans associated with Lyme disease. However, even in endemic areas, there is a very low risk of being bitten by an infected tick and developing Lyme disease. It is often best to monitor the patient for erythema migrans and other manifestations, as antibiotic treatment is usually effective in preventing disease progression. The available data do not support routine antibiotic treatment following a tick bit, even in endemic areas.*" (p.249)	Not reported.
ILADS, 2014[23]	
"*Clinicians should not use a single 200 mg dose of doxycycline for Lyme disease prophylaxis.*" (p.1106 and 1112) - One RCT Nadelman RB, Nowakowski J, Fish D, et al. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an Ixodes scapularis tick bite. *N Engl J Med*. 2001;345(2):79-84 ○ Erythema migrans prevention 87% (95% CI: 3.2 to 99.7%). - Two murine studies Zeidner NS, Brandt KS, Dadey E, et al. Sustained-release formulation of doxycycline hyclate for prophylaxis of tick bite infection in a murine model of Lyme borreliosis. *Antimicrob Agents Chemother*. 2004;48(7): 2697-9 ○ Lyme disease prevention 43% Zeidner NS, Massung RF, Dolan MC, et al. A sustained-release formulation of doxycycline hyclate (Atridox) prevents simultaneous infection of Anaplasma phagocytophilum and Borrelia burgdorferi transmitted by tick bite. *J Med Microbiol*. 2008;57(Pt 4):463-8 ○ Lyme disease prevention 20%	Recommendation, very low-quality evidence - "*Limitations* - *Inappropriate surrogate (erythema migrans prevention)* - *Insufficient duration of observation* - *Insufficient reporting of negative treatment-associated outcomes* - *Imprecision* - *Few events* - *Wide CI* - *Unsupported assumption regarding outcomes in dropouts* - *Inconsistency* - *Non-replicated in humans* - *Inconsistent with animal model* - *Indirectness* - *Not applicable to patients bitten by species other than Ixodes scapularis* - *Not applicable to patients exposed to multiple tick-borne diseases* - *Efficacy not applicable to other antibiotics* - *Effectiveness findings applicable to prevention of erythema migrans only and not other, non-erythema migrans presentations*" (p.1111)
100 to 200 mg of doxycycline, twice daily for 20 days (or other treatment options) - Known *Ixodes* tick bite - Regardless of degree of tick engorgement or local infection rates	Recommendation, very low-quality evidence
Patient education (prevention of future bites as well as	Recommendation, very low-quality evidence

Table 10: Summary of Recommendations of Included Guidelines

Recommendations	Strength of Evidence and Recommendations
potential manifestations of Lyme disease and other tick-borne diseases)	
Wright et al, 2012[24]	
"*Antimicrobial prophylaxis with a single 200-mg dose of doxycycline is recommended for adults with exposure to Ixodes scapularis if prophylaxis can be given within 72 hours of tick removal and there is at least a 20 percent rate of tick infection with Borrelia burgdorferi in the area. Children eight years or older may also be given a single 4-mg-per-kg dose of doxycycline (maximal dose of 200 mg) for prophylaxis.*" (p.1087) - Two SRs Bratton RL, Whiteside JW, Hovan MJ, Engle RL, Edwards FD. Diagnosis and treatment of Lyme disease. *Mayo Clin Proc*. 2008;83(5):566-571. Murray TS, Shapiro ED. Lyme disease. *Clin Lab Med*. 2010;30(1):311-328. - One clinical practice guideline Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2006;43(9):1089-1134. - One RCT Nadelman RB, Nowakowski J, Fish D, et al.; Tick Bite Study Group. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an Ixodes scapularis tick bite. *N Engl J Med.* 2001;345(2):79-84.	B (inconsistent or limited-quality patient-oriented evidence)
"*Removal of ticks within 24 hours of attachment can usually prevent acquisition of Lyme disease*." (p.1088 and 1092)	Not reported.
"*Recommended measures to prevent Lyme disease include avoiding areas with high tick burdens, wearing protective clothing, using tick repellants (e.g., diethyltoluamide [DEET]), performing frequent body checks for ticks and bathing following outdoor activities, and instituting environmental landscape modifications (e.g., grass mowing, deer exclusion fencing, removing leaf litters and woodpiles) to reduce the tick burden.*" (p.1087)	C (consensus, disease-oriented evidence, usual practice, expert opinion, or case series)

RCT = Randomized Controlled Trial, CI = Confidence Interval

Appendix 5: Overlap between Included Systematic Reviews

Table 11: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation				
	Sanchez et al, 2016[22]	Prescrire Editorial Staff, 2015[12]	ILADS, 2014[23]	Wright et al, 2012[24]	Warshafsky et al, 2010[18]
Agre and Schwartz, 1993					X
Bratton et al, 2008				X	
Costello et al, 1989					X
Institut de veille sanitaire, 2014		X			
Murray and Shapiro, 2010				X	
Nadelman et al, 2001	X	(indirect, through Warshafsky)	X	X	X
PHAC, 2014		X			
Prescrire Rédaction, 2006		X			
Shapiro et al, 1992					X
Société de pathologie de langue française, 2006		X			
Warshafsky et al, 2010		X			
Wormser et al, 2006	X	X		X	
Zeidner et al, 2004			X		
Zeidner et al, 2008			X		

Appendix 6: Additional References of Potential Interest

Outside search date range

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