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Post-tick bite antibiotic prophylaxis to prevent Lyme disease

Report in support of knowledge transfer tools, Quebec's provincial medical protocol and the collective prescription template

A production of the Institut national d'excellence en santé et en services sociaux (INESSS)

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Post-tick bite antibiotic prophylaxis to prevent Lyme disease

Report in support of knowledge transfer tools, Quebec's provincial medical protocol and the collective prescription template

Written by
Gaëlle Gernigon

Scientific coordination
Mélanie Tardif

Under the direction of
Sylvie Bouchard

This publication was written and edited by INESSS.

Project team members

Primary author of this report

Gaëlle Gernigon, Pharm.D., M.Sc.

Internal partners

Christiane Beaulieu
Jean-Marc Daigle, B.Sc., M.Sc.
Adriana Freitas, Ph.D.
Hélène Guay, Ph.D.
Fatiha Karam, Ph.D.
Sébastien Landry, intern
Geneviève Morrow, Ph.D.
José Pérez, M.Sc.
Éric Tremblay, B.Pharm., M.Sc.

Scientific coordinator

Mélanie Tardif, Ph.D.

Director

Sylvie Bouchard, B.Pharm., DPH, M.Sc. MBA

Scientific information retrieval

Caroline Dion, MLIS, professional librarian
Mathieu Plamondon, MSI
Flavie Jouandon, library technician

Administrative support

Ginette Petit

Editorial team	Coordination	In collaboration with
Patricia Labelle Denis Santerre Hélène St-Hilaire	Renée Latulippe, M.A.	Littera Plus, proofreading Mark A. Wickens, translation

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Advisory committee on Lyme disease

Dr. Cybèle Bergeron, FRCPC, microbiologist / infectious diseases specialist and pediatric infectious diseases specialist, Centre hospitalier universitaire de Sherbrooke (CHUS), CIUSSS de l'Estrie

Alexandre Chagnon, pharmacist, CIUSSS de l'Estrie – CHUS, Hôpital de Granby

Dr. Gaëlle Chédeville, FRCPC, pediatric rheumatologist, Montreal Children's Hospital, McGill University Health Centre (MUHC), CIUSSS de l'Ouest-de-l'île-de-Montréal, associate professor, McGill University, Department of Pediatrics, Division of Rheumatology

Claude Cartier, patient partner, Estrie

Dr. Isabelle Deschênes, FRCPC, rheumatologist, Centre Médi-Soleil, Saint-Jean-sur-Richelieu

Dr. Dominique Friedmann, FRCPC, dermatologist, Clinique médicale Pierre-Boucher, Longueuil

Dr. Josée Héroux, FRCPC, dermatologist, Hôpital de Granby, CIUSSS de l'Estrie – CHUS

Dr. Christos Karatzios, FRCPC, pediatric infectious diseases specialist, Montreal Children's Hospital (MUHC), CIUSSS de l'Ouest-de-l'île-de-Montréal, fellow, Department of Pediatrics, CHU Sainte-Justine

Dr. Mirabelle Kelly, FRCPC, microbiologist / infectious diseases specialist, Hôpital de Granby, CIUSSS de l'Estrie

Dr. Guillaume Lafortune, FRCPC, neurologist, Hôpital de Granby, CIUSSS de l'Estrie – CHUS

Dr. Louise Lambert, family physician, Direction de santé publique, CISSS de la Montérégie-Centre

Dr. Marc Lebel, FRCPC, pediatric infectious diseases specialist, Centre hospitalier universitaire (CHU) Sainte-Justine, associate clinical professor, Department of Pediatrics, Faculty of Medicine, Université de Montréal

Dr. Nancy Nadeau, FCFPC, family physician, GMF-U St-Hubert, clinical lecturer, Université de Montréal

Valérie Nolin-Rolland, RN Ph.D., primary care nurse practitioner, M.Sc., Centre local de services communautaires (CLSC) de Henryville

Ariane Quintal, patient partner, Montérégie

Dr. François Reeves, FRCPC, cardiologist, CHU Montréal and Cité-de-la-santé de Laval, associate professor of medicine affiliated with the Université de Montréal school of public health

Karine Thivierge, Ph.D., Head of Parasitology Laboratory, Laboratoire de santé publique du Québec (LSPQ), Institut national de santé publique du Québec (INSPQ)

Dr. Amélie Thuot, FRCPC, microbiologist / infectious diseases specialist, head of the microbiology department, Hôpital du Haut-Richelieu, CISSS de la Montérégie Centre

Dr. Anne Vibien, FRCPC, microbiologist / infectious diseases specialist, head of the infectious diseases department, CISSS de la Montégérie-Est

Dr. Matthieu Vincent, FRCPC, specialist in emergency medicine and pediatric emergency medicine, emergency physician, emergency department, Hôpital Charles-Le Moyne, pediatric emergency physician, emergency department, CHU Ste-Justine, assistant clinical professor, Université de Sherbrooke, assistant professor, Department of Pediatrics, McGill University

Advisory subcommittee on the provincial medical protocol for Lyme disease post-exposure prophylaxis

Dr. Geneviève Baron, FRCPC, M.Sc., consulting physician, Direction de santé publique du CIUSSS de l'Estrie – CHUS, full professor, Faculty of Medicine and Health Sciences, Université de Sherbrooke

Lyne Bérard, B.Sc. Inf., GMF Centre médical AJC, CIUSSS de la Mauricie-Centre-du-Québec

Alexandre Chagnon, pharmacist, Hôpital de Granby, CIUSSS de l'Estrie

Julie Coderre, pharmacist, Jean Coutu, Cowansville

Dr. Christos Karatzios, FRCPC, pediatric infectious disease specialist, Montreal Children's Hospital (MUHC), CIUSSS de l'Ouest-de-l'île-de-Montréal, fellow, Department of Pediatrics, CHU Sainte-Justine

Dr. Mirabelle Kelly, FRCPC, microbiologist / infectious diseases specialist, CIUSSS de l'Estrie, Hôpital de Granby

Dr. Alejandra Irace-Cima, FRCPC, consulting physician, INSPQ

Dr. Louise Lambert, family physician, Direction de santé publique, CISSS de la Montérégie-Centre

Nancy Wade, B.Sc. Inf., senior advisor on nursing care, CISSS de l'Outaouais

Monitoring committee

Lise Bertrand, representative from Info-Santé 8-1-1, Ministère de la Santé et des Services sociaux (MSSS)

Dr. Josée Bourgault, representative from the Collège des médecins du Québec (CMQ) (for the February 2019 meeting)

Michel Caron, representative from the Ordre des pharmaciens du Québec (OPQ)

Julie Gélinas, representative from the Ordre des infirmières et des infirmiers du Québec (OIIQ)

Dr. J. Marc Girard, representative from the Fédération des médecins spécialistes du Québec (FMSQ)

Dr. Claude Guimond, representative from the Fédération des médecins omnipraticiens du Québec (FMOQ)

Dr. Yves Robert, representative from the CMQ (for the March and November 2018 meetings)

Dr. Patricia Hudson, representative from the Institut national de santé publique du Québec (INSPQ) (for the February 2019 meeting)

Dr. Alejandra Irace-Cima, representative from the INSPQ (for the March and November 2018 meetings)

Francois Sanschagrin, representative from the DBBM, MSSS

Dr. Louise Valiquette, representative from the DGAPSP, MSSS

External reviewers

Dr. Catherine Besner, FCFPC, family physician**,** CLSC de Hull, Gatineau

Dr. Alex Carignan, FRCPC, microbiologist / infectious diseases specialist, CIUSSS de l'Estrie – CHUS, associate professor, Faculty of Medicine and Health Sciences, Université de Sherbrooke

Sylvie Carle, pharmacist, MUHC, CIUSSS de l'Ouest-de-l'île-de-Montréal, lecturer, Faculty of Pharmacy, Université de Montréal

Patient associations

The mission of the Association québécoise de la maladie de Lyme (AQML) is to raise awareness of Lyme disease and tick-borne co-infections and to lobby medical, governmental, public and private authorities to provide adequate services to prevent, detect, diagnose, treat and support all stages and aspects of these diseases. The AQML has on multiple occasions publicly criticized various aspects of how Lyme disease is handled in Quebec.

The following AQML representatives contributed experiential knowledge for this report, but did not participate in the formulation of recommendations:

Chantal Barabé
Catherine Breton
Robert Huneault
Sophie Legault
Annie Roussy

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Denis Henri
Raymond Lord
Elsie Salter
Yves Thérien

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Clinical Excellence Committee – Optimal medication use

Dr. Pierre Ernst (chair), FRCPC, pulmonologist, McGill University

Georges-Émile Bourgault, pharmacist, CIUSSS de la Capitale-Nationale

Dr. Maryse Cayouette, FRCPC, microbiologist / infectious diseases specialist, CISSS de Lanaudière, Direction de santé publique

Benoît Cossette, pharmacist, CIUSSS de l'Estrie – CHUS

Dr. Lucie Deshaies, FCFPC, family physician, Centre de santé et de services sociaux de la Vieille-Capitale

Dr. Mathieu Forster, FCFPC, family physician, CISSS Côte-Nord

Jean-Simon Fortin, ethics advisor, doctoral student (bioethics), Université de Montréal

Karina Gauthier, pharmacist, CISSS de Laval

Frédéric Grondin, senior clinical advisor, CIUSSS de l'Estrie – CHUS

Dr. Maxime Lamarre-Cliche, FRCPC, internist, Montreal Clinical Research Institute (IRCM)
Dr. Howard Margolese, FRCPC, psychiatrist, McGill University**,** MUHC, CIUSSS de l'Ouest-de-l'île-de-Montréal

Jean-François Proteau, member of the public

Governance committee

Dominic Bélanger, interim director, Direction des affaires pharmaceutiques et du médicament (DAPM), MSSS

Luc Boileau, president and executive director, INESSS

Sylvie Bouchard, director of medication, INESSS

Manon Lambert, executive director, OPQ

Dr. Lucy Opatrny, assistant deputy minister, Direction générale des services hospitaliers, de la médecine spécialisée et universitaire (DGSHMSU), MSSS

Lucie Poitras, assistant deputy minister, DGSHMSU, MSSS

Dr. Yves Robert, secretary and executive director, CMQ

Marco Thibault, president and executive director, Régie de l'assurance maladie du Québec (RAMQ)

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Christophe Augé, M.Sc., Ph.D., FOPQ, pharmacist, assistant editor and head of columns for the publication *Québec Pharmacie*

Dr. Denis Boucher, family physician, Centre médical Saint-Jean, Lévis

Dr. Marie Dominic Breault, emergency department physician, Hôpital de Chandler, CISSS de la Gaspésie

Amy-Lee Champagne, M.Sc., primary care nurse practitioner, CISSS de la Montérégie-Est

Jacques Gendron, community pharmacist, Pharmacie Jacques Gendron, Îles des Soeurs

Dr. Alexandre Faguy, FRCPC, emergency medicine specialist, Hôpital Pierre-Boucher, Longueuil, CISSS de la Montérégie-Est

Marie-Ève Jacques, primary care nurse practitioner, CLSC des Sources – Asbestos, CIUSSS de l'Estrie

Dr. Pierre La Rochelle, M.Sc., emergency department physician, Hôpital Notre-Dame-de-Fatima, La Pocatière, CISSS du Bas-St-Laurent

Simon Dumont Laviolette, B.Pharm, DESS in management, pharmacist, Farmer, Dupuis et Bergeron pharmacy, Joliette

Isabelle Levasseur, primary care nurse practitioner, CISSS de Laval

Valérie Paquet, pharmacist, GMF Jacques-Cartier, CIUSSS de l'Estrie

Estelle Rancourt, primary care nurse practitioner, GMF-U des Etchemins, Ste-Justine

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Responsibility

INESSS assumes full responsibility for the final form and content of this document. The conclusions and recommendations do not necessarily reflect the opinions of the external reviewers or other individuals consulted during its creation.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SUMMARY

Introduction

In Québec, asymptomatic individuals bitten by a tick in certain areas of the Eastern Townships, the Montérégie or Outaouais may receive single-dose doxycycline post-exposure prophylaxis (PEP) to prevent Lyme disease. However, several criteria, established by the Institut national de santé publique du Québec (INSPQ), must first be met. Children under 8 years of age and pregnant and nursing women are currently excluded from the PEP eligibility criteria because the use of doxycycline is generally not recommended in these populations. In 2018, to permit better access to this prophylaxis in the Eastern Townships and the Montérégie, collective prescriptions were put in place. However, people who meet the criteria but who seek medical attention outside these regions do not have this facilitated access. It was against this background that the Ministère de la Santé et des Services sociaux (MSSS) asked INESSS to review all the available scientific data on PEP and to develop a Québec's national medical protocol, together with a collective prescription template. This task is part of the larger project on Lyme disease given to INESSS, which includes developing recommendations and knowledge transfer tools for diagnosing and treating patients with the localized or disseminated stage of this disease.

Methodology

To carry out the task concerning PEP, INESSS conducted systematic reviews of the scientific literature on 1) the efficacy and safety of the antibiotics studied for use as PEP for preventing Lyme disease; 2) the safety of doxycycline in children under 8 years of age and in pregnant and nursing women, regardless of the indication for use; and 3) the best practice recommendations concerning PEP from clinical practice guidelines (CPGs) on Lyme disease. The information obtained from these systematic reviews was enriched with experiential knowledge from clinicians, patients and patient association representatives, and with contextual data specific to Québec.

The scientific data and the best clinical practice recommendations were found through a systematic search in several databases and a registry of ongoing clinical studies. Different specialized publications and databases on the use of medications during pregnancy and breastfeeding were consulted. A manual search was performed for (CPGs) or other relevant documents, specifically, by consulting the websites of health technology assessment agencies and those of recognized agencies, organizations, institutions and learned societies in the field of microbiology/infectious diseases or public health. The official product monographs for antibiotics approved by Health Canada or the Food and Drug Administration (FDA) were consulted as well. The bibliographies of the selected publications were examined for other relevant documents.

With regard to contextual data, the Google search engine was used to find documents prepared by professional bodies and associations. The respective websites of the MSSS, the INSPQ and the regional public health departments in the Eastern Townships and the Montérégie were consulted. A search was conducted for collective prescriptions published in Québec in 2018. In addition, the stakeholders consulted were invited to share information or documents that would help answer the assessment questions. Lastly, a cross-sectional study was carried out to document the use of single-dose doxycycline for the indication of PEP for preventing Lyme disease in persons covered by Québec's public prescription drug insurance plan (PPDIP) from 2014 to 2018.

To gather experiential knowledge, INESSS created an advisory committee consisting of clinicians, including specialists in different disciplines, an expert in parasitology and two patient partners who had been diagnosed with Lyme disease. In addition, an advisory subcommittee was formed to support INESSS in creating both a Québec's national medical protocol and a collective prescription template for PEP. Consultations with representatives from the Association

québécoise de la maladie de Lyme (AQML) and interviews with eight patients who had contracted or still had the disease rounded out the gathering of experiential knowledge.

Results

INESSS's systematic reviews concerning antibiotic PEP for the prevention of Lyme disease following a recent tick bite showed that the use of single-dose doxycycline for this indication is based on data considered overall to be of a low level of evidence. Indeed, although the authors of a double-blind randomized controlled trial (RCT) reported single-dose doxycycline to have had a statistically significant effect in preventing the appearance of erythema migrans (EM) at the bite site relative to placebo in subjects aged 12 years and over, limitations that compromise the internal validity of this trial were noted. Furthermore, the generalizability of the results of this trial to the Québec context does not seem guaranteed. As well, given the uncertainties regarding the actual safety and efficacy of single-dose doxycycline PEP and the contradictory recommendations from North American learned societies concerning the use of this prophylaxis, INESSS's work shows that the decision whether to the use single-dose doxycycline to prevent Lyme disease following a tick bite should be made within the context of a shared decision-making process between the clinician and the patient or his/her family, as the case may be. The different management options should be presented (PEP + symptom monitoring vs. symptom monitoring alone), and the benefits and risks of each option should be discussed, together with information on the risk of Lyme disease transmission.

In light of the results of the systematic review of the use of doxycycline in children under 8 years of age and the new recommendations from the American Academy of Pediatrics, it is proposed that single-dose doxycycline PEP be made available for this population when the PEP eligibility criteria are met. Indeed, the available data, although they are of a low level of evidence, are reassuring in terms of the risk of dental effects. However, the shared decision-making process seems even more important for this population, since there is no data on the efficacy and safety of single-dose doxycycline for the indication of PEP to prevent Lyme disease in under-8-year-olds. The use of single-dose doxycycline may also be considered in nursing women, since tetracyclines are found in low concentrations in breast milk and since the available data indicate that there is no detectable trace of drug in the serum of exposed infants. Furthermore, according to several specialized databases and reference publications, the short-term use of tetracyclines is compatible with breastfeeding. On the other hand, the available scientific data on the use of doxycycline during pregnancy are considered insufficient to freely recommend PEP in pregnant women who meet the eligibility criteria.

Lastly, INESSS's work served to identify the absolute and relative contraindications that need to be taken into consideration before prescribing single-dose doxycycline. As well, this work proposes modifying the recommended dosage in children weighing less than 45 kg. To promote the optimal use of single-dose doxycycline PEP and to approach the experimental conditions in which this intervention was studied, our work has led us to propose two changes to the PEP eligibility criteria: 1) the specimen from the bite site should be documented as being a tick; and 2) the maximum of 72 hours should apply from tick removal, not from the medical visit, to the intended time that doxycycline is to be taken.

Conclusion

The publication of the Québec's national medical protocol, the collective prescription template and the knowledge transfer tools developed by INESSS for single-dose doxycycline PEP for the prevention of Lyme disease should help better equip Québec health professionals manage patients who present with a tick bite and establish the indication of PEP, while at the same time involving these patients in making the final decision. Furthermore, the regional public health departments will be able to decide on the relevance of instituting a collective prescription in their region based on the Québec's national medical protocol and of identifying authorized professionals, which will promote access to PEP when it is indicated and in accordance with a practice harmonized across the province.

RÉSUMÉ

Prophylaxie post-exposition à une piqûre de tique par antibiotique pour prévenir la maladie de Lyme

Rapport en soutien aux outils de transfert des connaissances, au protocole médical national et au modèle d'ordonnance collective

Introduction

Au Québec, les personnes asymptomatiques piquées par une tique dans certains secteurs des régions de l'Estrie, de la Montérégie, et de l'Outaouais peuvent recevoir une prophylaxie post-exposition (PPE) par doxycycline en dose unique dans le but de prévenir la maladie de Lyme. Plusieurs critères, définis par l'Institut national de santé publique du Québec (INSPQ), doivent toutefois être réunis au préalable. Les enfants de moins de 8 ans, les femmes enceintes et celles qui allaitent sont actuellement exclues des critères d'accès de la PPE, car l'usage de la doxycycline n'est généralement pas conseillé chez ces populations. Pour permettre un accès plus rapide à cette PPE, des ordonnances collectives ont été mises en place en Estrie et en Montérégie en 2018. Cependant, les personnes qui réunissent les critères, mais qui consultent en dehors de ces régions ne bénéficient pas de cet accès facilité. C'est dans ce contexte que le ministère de la Santé et des Services sociaux (MSSS) a confié à l'INESSS le mandat de revoir l'ensemble des données scientifiques disponibles relatives à la PPE et d'élaborer un protocole médical national assorti d'un modèle d'ordonnance collective. Ces travaux s'inscrivent dans le cadre du mandat plus large confié à l'INESSS sur la maladie de Lyme, et qui comprend l'élaboration de recommandations et d'outils de transfert de connaissances concernant la pose du diagnostic et le traitement des patients atteints de cette maladie au stade localisé ou disséminé.

Méthodologie

Pour réaliser le mandat relatif à la PPE, l'INESSS a réalisé des revues systématiques de la littérature scientifique concernant 1) l'efficacité et l'innocuité des antibiotiques étudiés pour la PPE en prévention de la maladie de Lyme; 2) l'innocuité de la doxycycline chez l'enfant de moins de 8 ans, la femme enceinte ou qui allaite, quelle que soit l'indication d'usage; 3) les recommandations de bonne pratique relatives à la PPE issues des GPC sur la maladie de Lyme. Les informations ainsi recueillies ont été bonifiées par les savoirs expérientiels issus de cliniciens, de patients et de représentants d'association de patients, et par des données contextuelles propres au Québec.

Les informations scientifiques et les recommandations de bonne pratique clinique ont été repérées grâce à une recherche systématique effectuée dans plusieurs banques de données et dans un registre d'études cliniques en cours. Différents ouvrages et banques de données spécialisés sur l'usage des médicaments lors de la grossesse et de l'allaitement ont été consultés. Une recherche manuelle a été effectuée pour repérer des guides de pratique clinique (GPC) ou autres documents pertinents en consultant les sites internet des agences d'évaluation des technologies de santé, et ceux des agences, des organisations, des institutions et des sociétés savantes reconnues dans le domaine de la microbiologie-infectiologie ou de la santé publique notamment. Les monographies officielles des antibiotiques homologués par Santé Canada ou par la Food and Drug Administration (FDA) ont également été consultées. Les bibliographies des publications sélectionnées ont été consultées afin de répertorier d'autres documents pertinents.

Concernant les données contextuelles, le moteur de recherche Google a été utilisé afin de repérer des documents rédigés par des associations ou des ordres professionnels. Les sites internet respectifs du MSSS, de l'INSPQ, et des directions régionales de santé publique de l'Estrie et la

Montérégie ont été consultés. Une recherche des ordonnances collectives publiées au Québec en 2018 a été effectuée. Les parties prenantes consultées ont par ailleurs été invitées à partager les informations ou documents permettant de répondre aux questions d'évaluation. Enfin, une étude transversale a été menée pour documenter l'usage de la doxycycline en dose unique dans l'indication présumée de la PPE en prévention de la maladie de Lyme chez les personnes couvertes par le régime public d'assurance médicament (RPAM) du Québec de 2014 à 2018.

Pour recueillir des savoirs expérientiels, l'INESSS a mis en place un comité consultatif formé de cliniciens dont des médecins spécialistes dans différentes disciplines, d'un expert en parasitologie, et de deux patients partenaires atteints du stade disséminé de la maladie de Lyme. De plus, un sous-comité consultatif a été constitué pour accompagner l'INESSS dans la réalisation du protocole médical national et du modèle d'ordonnance collective relatifs à la PPE. Des consultations avec des représentants de l'Association québécoise de la maladie de Lyme (AQML) puis des entrevues avec huit patients ayant eu ou étant encore atteints de la maladie de Lyme ont complété le recueil des savoirs expérientiels.

Résultats

Les revues systématiques réalisées par l'INESSS concernant la PPE par antibiotique pour prévenir la maladie de Lyme à la suite d'une piqûre de tique récente ont révélé que l'usage de la doxycycline en dose unique dans cette indication repose sur des données jugées globalement de faible niveau de preuve. En effet, bien que les auteurs d'un essai comparatif à répartition aléatoire (ECRA) réalisé en double insu aient rapporté un effet statistiquement significatif de la doxycycline en dose unique pour prévenir l'apparition d'un érythème migrant (EM) au site de la piqûre, par rapport au placébo, chez des personnes âgées de 12 ans et plus, des limites affectant la validité interne de cet essai ont été constatées. De plus, la généralisabilité des résultats de cet essai au contexte québécois ne semble pas garantie. Aussi, considérant les incertitudes relatives à l'efficacité et à l'innocuité réelles de la PPE par doxycycline en dose unique, ainsi que les recommandations contradictoires des sociétés savantes nord-américaines et les avis divergents des patients consultés quant à l'utilité de cette PPE, il ressort des travaux de l'INESSS que la décision relative à la prise de la doxycycline en dose unique pour prévenir la maladie de Lyme à la suite d'une piqûre de tique devrait se faire dans le cadre d'un processus de prise de décision partagée entre le clinicien et la personne ou sa famille le cas échéant. Les différentes options de prise en charge devraient être présentées (PPE + surveillance des symptômes vs surveillance seule des symptômes), et les bénéfices et les risques de chaque option devraient être discutés, en intégrant à la discussion les informations sur le risque de transmission de la maladie de Lyme.

Considérant les résultats de la revue systématique concernant l'usage de la doxycycline chez l'enfant de moins de 8 ans, et les nouvelles recommandations de l'*American Academy of Pediatrics*, il est proposé d'ouvrir l'usage de la PPE par doxycycline en dose unique dans cette population, lorsque les critères pour recevoir la PPE sont réunis. En effet, les données disponibles, bien qu'elles soient de faible niveau de preuve, sont rassurantes par rapport aux craintes d'effets dentaires. Cependant, le processus de prise de décision partagée apparaît encore plus important pour cette population puisqu'il n'existe aucune donnée relative à l'efficacité et l'innocuité de la doxycycline en dose unique dans l'indication de la PPE en prévention de la maladie de Lyme chez les moins de 8 ans. L'usage de la doxycycline en dose unique peut également être considéré chez la femme qui allaite, car les tétracyclines se retrouvent en faibles concentrations dans le lait maternel, et les données disponibles indiquent qu'aucune trace de médicament n'est décelable dans le sérum des enfants exposés. De plus, selon plusieurs bases données et ouvrages de référence spécialisés, l'usage à court terme des tétracyclines est compatible avec l'allaitement. En revanche, les données scientifiques disponibles sur l'usage de la doxycycline lors de la grossesse ont été jugées insuffisantes pour recommander d'emblée la PPE chez les femmes enceintes qui réunissent les critères.

Enfin, les travaux de l'INESSS ont permis de préciser les contre-indications absolues et relatives à considérer avant de prescrire la doxycycline en dose unique. Ils amènent par ailleurs à modifier la posologie recommandée chez l'enfant pesant moins de 45 kg. Pour favoriser l'usage optimal de la PPE par doxycycline en dose unique et s'approcher des conditions expérimentales dans lesquelles cette intervention a été étudiée, les travaux menés conduisent à proposer deux modifications des critères d'accès à la PPE : 1) le spécimen à l'origine de la piqûre devrait être objectivé comme étant une tique; 2) le délai maximal de 72 heures qui court à compter du retrait de la tique et non celui de la consultation devrait s'appliquer jusqu'au moment présumé de la prise de la doxycycline.

Conclusion

La publication du protocole médical national, du modèle d'ordonnance collective, et des outils de transfert des connaissances de l'INESSS sur la PPE par doxycycline en dose unique dans la maladie de Lyme devrait permettre de mieux outiller les professionnels de la santé québécois à prendre en charge les personnes qui se présentent pour une piqûre de tique et à poser l'indication de la PPE, tout en impliquant les personnes piquées dans la décision finale. De plus, les directions régionales de santé publique pourront décider de la pertinence de déployer une ordonnance collective dans leur région à partir du protocole médical national et d'identifier les professionnels autorisés, ce qui favorisera un accès facilité à la PPE, lorsque celle-ci est indiquée, et selon une pratique harmonisée à l'échelle provinciale.

ACRONYMS AND ABBREVIATIONS

AAP	American Academy of Pediatrics
AGREE	Appraisal of Guidelines for Research and Evaluation
AQML	Association québécoise de la maladie de Lyme
AR	Absolute risk
ARR	Absolute risk reduction
CASP	Critical Appraisal Skills Programme
CDC	Centers for Disease Control and Prevention
CEC-UOM	Clinical Excellence Committee on Optimal Medication Use
CEPPP	Centre of Excellence on Partnership with Patients and the Public
CHEO	Children's Hospital of Eastern Ontario
CHU	University hospital centre
CHUS	Centre hospitalier universitaire de Sherbrooke
CI	Confidence interval
CISSS	Integrated health and social services centre
CIUSSS	Integrated university health and social services centre
CLSC	Local community service centre
CMQ	Collège des médecins du Québec
CPG	Clinical practice guideline
DAPM	Direction des affaires pharmaceutiques et du médicament
DBBM	Direction de la biovigilance et de la biologie médicale
DESS	Advanced graduate diploma
DGAPSP	Direction générale adjointe de la protection de la santé publique
e-CPS	Online Compendium of Pharmaceuticals and Specialties
EM	Erythema migrans
FDA	Food and Drug Administration
FMG	Family medicine group
FMOQ	Fédération des médecins omnipraticiens du Québec
FMSQ	Fédération des médecins spécialistes du Québec
FOPQ	Fellow de l'Ordre des pharmaciens du Québec
GDS	German Dermatological Society
HAS	Haute Autorité de Santé
IDSA	Infectious Diseases Society of America
ILADS	International Lyme and Associated Diseases Society

INESSS	Institut national d’excellence en santé et en services sociaux
INSPQ	Institut national de santé publique du Québec
KT	Knowledge transfer
LD	Lyme disease
LSPQ	Laboratoire de santé publique du Québec
MADO	Reportable diseases
MSSS	Ministère de la Santé et des Services sociaux
MUHC	McGill University Health Centre
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
OIIQ	Ordre des infirmières et des infirmiers du Québec
OMU	Optimal medication use
OPQ	Ordre des pharmaciens du Québec
OR	Odds ratio
PCNP	Primary care nurse practitioner
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PHAC	Public Health Agency of Canada
PR	Prevalence ratio
RAMQ	Régie de l’assurance maladie du Québec
R-AMSTAR	Revised Assessment of Multiple Systematic Reviews
RCT	Randomized controlled trial
RPAM	Public prescription drug insurance plan
RR	Relative risk
RRR	Relative risk reduction

GLOSSARY

Definitions in this glossary, as pertaining to Lyme disease, were formulated based on data and information extracted from the literature and the advisory committee's experiential knowledge and contextualized for the Quebec practice. For more details, refer to the supporting report for clinical decision support tools for diagnosis and treatment [INESSS, 2019a]. Other definitions are sourced from specialized dictionaries and glossaries.

Collective prescription

A prescription that covers a group of people or one or several clinical situations and may be carried out by professionals legally authorized to do so and designated in the prescription. A collective prescription allows an authorized person or professional designated in the prescription to exercise certain medical activities without having to obtain an individual prescription from a physician, under the conditions and in the clinical circumstances specified therein (adapted from the CMQ, 2017).

Early disseminated stage

Stage of Lyme disease that is generally reached when the localized infection has not been detected or effectively treated and that is characterized by the spread of bacteria through the bloodstream. It generally develops a few weeks after the transmission of bacteria by an infested tick. The clinical presentation may include systemic symptoms along with cutaneous, neurological, musculoskeletal, cardiac and/or ocular manifestations. Erythema migrans may or may not be present.

Erythema migrans

An isolated erythematous skin lesion that generally appears between 3 and 30 days following the transmission of bacteria by an infested tick and that persists and may even evolve over several days. An erythema migrans rash usually spreads concentrically from the site of the bite to a diameter that exceeds 5 cm and may or may not cause pain or itching. However, its characteristics (size, shape and appearance) and duration vary considerably from one individual to another. While a bull's eye rash (concentric rings) may also be caused by other factors, this type of lesion is highly suggestive of a Lyme disease infection when the affected individual has been in a high-risk area.

Late disseminated stage

Stage of Lyme disease generally characterized by the progression of the disseminated stage and that is generally reached when the infection has not been detected or effectively treated. It develops a few months after the transmission of bacteria by an infested tick. Lyme arthritis is the most common manifestation of this stage in North America.

Localized stage

Stage of Lyme disease (sometimes called early stage) at the beginning of the infection, before the dissemination of bacteria. A solitary erythema migrans rash is the primary skin lesion observed at this stage, though it may not always be present or noticed. When present, the rash appears in the four weeks after the transmission of bacteria by an infested tick.

Lyme disease

Infectious disease caused by bacterial genospecies of *Borrelia burgdorferi* that are transmitted to humans by infested black-legged ticks (*Ixodes scapularis* in Quebec). The clinical presentation of affected individuals depends on the bacterial species and the stage of the disease and may include cutaneous, neurological, musculoskeletal, cardiac and/or ocular manifestations.

Post-exposure prophylaxis

Preventive treatment (e.g., a vaccine or course of antibiotics) begun shortly after exposure to a pathogenic agent in order to reduce a patient's risk of developing an infection or certain effects of an illness.

Provincial medical protocol

Reference document that professionals and competent persons must use to determine the clinical content of prescriptions. Only protocols published by INESSS are mandatory. These provincial medical protocols are available on the INESSS website [CMQ, 2017].

Sensitivity

Measure of the performance of a diagnostic test, defined as the proportion of ill individuals who test positive for a condition. Sensitivity is calculated as follows: [number of true positives ÷ (number of true positives + number of false negatives)].

Signatory physician

The signatory physician or physicians of a collective prescription are physicians who adhere to the collective prescription and, by so doing, give their approval and permission to a professional or another capable individual to engage in a professional activity with patients covered by the prescription [CMQ, 2017].

Specificity

Measure of the performance of a diagnostic test, defined as the proportion of healthy individuals who test negative for a condition. Specificity is calculated as follows: [number of true negatives ÷ (number of true negatives + number of false positives)].

INTRODUCTION

Research topic

In the space of a few years, Lyme disease has become a pressing public health concern. The number of human cases reported in Quebec rose from 5 to 301 between 2011 and 2018,[1] and there is a risk of developing disabling and difficult-to-treat complications as a result of contracting the disease. In addition, Lyme disease has been the subject of media controversy. By far, the most effective means of preventing the spread of this disease are avoiding tick bites and reducing the population of ticks in the environment. A complementary prevention measure can also be offered to individuals bitten by ticks in specific geographic areas: single-dose doxycycline post-exposure prophylaxis (PEP).

In 2006, the Infectious Diseases Society of America (IDSA) developed eligibility criteria for this type of PEP [Wormser et al., 2006]. The criteria were adapted to the Quebec context by a group of experts mandated by the Institut national de santé publique du Québec (INSPQ) [Adam-Poupart et al., 2017]. As a result, in Quebec, doxycycline PEP may be provided to asymptomatic individuals bitten by a tick when all of the following criteria are met: 1) less than 72 hours have elapsed between the removal of the tick and the start of PEP, 2) the tick remained attached to the skin for 24 hours or more, 3) the individual does not present any contraindications to doxycycline and 4) the bite occurred in one of the geographic areas eligible for PEP. Currently, these areas are: certain sectors of Estrie, Montérégie, and Outaouais in Quebec, as well as high-risk areas in other Canadian provinces and in the United States.[2]

Due to climate change, it is expected that in the coming years *Ixodes scapularis*, the vector tick for Lyme disease, will continue to spread into various areas of the province. It is therefore likely that the number of geographic areas eligible for PEP will increase. To facilitate access to PEP, collective prescriptions were implemented in Estrie and Montérégie in 2018 that allow community pharmacists and or/nurses practising in these regions to provide PEP to individuals that meet the criteria. However, in other areas of the province without such a collective prescription, these same professionals are unable to provide PEP to individuals who meet the criteria.

Pregnant women, breastfeeding women and, particularly, children under 8 years of age who are exposed to ticks are currently excluded from the PEP criteria. In fact, monographs for doxycycline-based medications warn that use of these medications during tooth development may cause permanent tooth staining. This warning applies to all antibiotics in the tetracycline drug class, regardless of their individual affinity for calcium, the prescribed dose or the length of exposure. At the 2018 European Congress of Clinical Microbiology and Infectious Diseases, it was announced that the American Academy of Pediatrics had come out in favour of allowing the use of doxycycline in children under 8 years of age to treat Lyme disease, and particularly as a prophylactic treatment.

[1] Ministère de la Santé et des Services sociaux (MSSS). Maladie de Lyme. Tableau des cas humains – Bilan 2018 [website, French only]. Available at http://www.msss.gouv.qc.ca/professionnels/zoonoses/maladie-lyme/tableau-des-cas-humains-bilan.

[2] Ministère de la Santé et des Services sociaux (MSSS). Maladie de Lyme. Prophylaxie postexposition [website, French only]. Available at http://www.msss.gouv.qc.ca/professionnels/zoonoses/maladie-lyme/prophylaxie-postexposition/.

Context

In Quebec, the Direction générale adjointe de la protection de la santé publique (DGAPSP), under the Ministère de la Santé et des Services sociaux (MSSS), and the INSPQ are responsible for monitoring Lyme disease through the notifiable diseases (MADO) system and for monitoring ticks, but no public institution is mandated to address the clinical and therapeutic aspects of the disease. To remedy the absence of clear guidelines for treating Lyme disease patients in Quebec, the DGAPSP, in concert with the MSSS's Direction de la biovigilance et de la biologie médicale (DBBM) and the Direction des affaires pharmaceutiques et du médicament (DAPM), called on INESSS to issue recommendations and develop knowledge transfer tools pertaining to PEP as a means to prevent Lyme disease and diagnose and treat Lyme disease patients, in an effort to equip Quebec health professionals, particular primary care professionals, to manage this emerging disease. The DGAPSP and INESSS agreed that work on the controversial form of the disease (sometimes referred to as "chronic") and co-infections transmitted by ticks would be published in a second report in 2020.

The first mandate, focusing specifically on PEP, consisted in a review of all available scientific data on this intervention in order to modify or complete, as required, existing pharmacological recommendations. This mandate was broadened to include the development of a provincial medical protocol for PEP and a corresponding collective prescription template.

Deliverables

The first component is divided into five main deliverables:

- a notice including implementation recommendations
- a supporting report on knowledge transfer tools concerning the overall care of Lyme disease patients at the localized or disseminated stage, from diagnosis to treatment
- a state of knowledge report on the validity/performance of laboratory analyses
- a supporting report on knowledge transfer tools concerning post-tick bite PEP (including a clinical decision support tool, a shared decision support tool, a provincial medical protocol and a collective prescription template)
- a state of practice report on the presumed use of doxycycline to prevent Lyme disease in patients insured under Quebec's public prescription drug insurance plan.

Objectives

This project on the use of PEP for Lyme disease prevention has the following objectives:

- complete a systematic review of the scientific literature on the efficacy, safety and good practices of the studied PEP antibiotics used to prevent Lyme disease
- develop clinical recommendations for PEP based on these data, contextual information and experiential knowledge of Quebec patients, clinicians and experts
- develop a provincial medical protocol and a corresponding collective prescription template integrating the clinical recommendations for PEP
- produce knowledge transfer tools.

Excluded topics

The analysis will not concern the concept of providing PEP in Quebec, the eligibility criteria for

PEP in Quebec, the methodology to be used to outline a Lyme disease risk map, the ways to prevent tick bites or the monitoring of Lyme disease, as these topics are under the purview of the DGAPSP and/or the INSPQ.

The controversial form of Lyme disease (sometimes referred to as “chronic”) and co-infections transmitted by ticks will be addressed in subsequent work (component II of INESSS’s project on Lyme disease).

1. METHODOLOGY

1.1. Decision-Making Question

Is antibiotic PEP a safe and effective way to prevent Lyme disease following a tick bite in a geographic area at high risk for Lyme disease, and what are the optimal conditions for the use of antibiotics for this indication in Quebec?

1.2. Assessment Questions

The assessment questions concerning efficacy and safety were formulated based on the PICOTS framework (patient population, intervention, comparator, outcome, timing and setting). The assessment questions concerning guidelines for good clinical practice and the use of antibiotic PEP were formulated based on the PIPOH framework (population, intervention, professionals targeted, outcome of interest and health care setting).

Pharmacological aspects

Question 1: Efficacy of the studied PEP antibiotics
What is the efficacy of studied PEP antibiotics used for Lyme disease caused by *Borrelia burgdorferi* sensu stricto in adults or children bitten by the tick *Ixodes scapularis* in a geographic area at high risk for Lyme disease, as compared to a placebo, no treatment or another antibiotic?

Question 2: Safety of the studied PEP antibiotics
What are the adverse effects associated with the studied PEP antibiotics used for Lyme disease caused by *Borrelia burgdorferi* sensu stricto in adults or children bitten by the tick *Ixodes scapularis* in a geographic area at high risk for Lyme disease, as compared to a placebo, no treatment or another antibiotic?

Question 3: Safety of doxycycline in children and pregnant or breastfeeding women
What are the adverse effects associated with the use of oral doxycycline (for any indication) in children exposed in utero, during breastfeeding or before the age of 8, as compared to a placebo, no treatment or another antibiotic?

Epidemiological aspects

Question 4: Risk of contracting Lyme disease
What is the risk of contracting Lyme disease after being bitten by *Ixodes scapularis* in a geographic area at high risk for Lyme disease?

Clinical aspects

Question 5: Recommendations on the use of PEP
What are the positions of learned societies and health technology assessment agencies on the use of Lyme disease PEP and, if applicable, what are their eligibility criteria?

Question 6: Optimal use of PEP
To promote the optimal use of PEP, what clinical procedure should be followed by primary care health professionals consulted about a tick bite? Specifically: a. What should be done about the tick? b. What aspects of the circumstances surrounding the bite should be investigated and documented? c. What is the procedure for the use of single-dose doxycycline PEP for Lyme disease (dosage, absolute and relative contraindications, precautions)? d. What aspects of the patient's medication history should be investigated? e. How should the professional assess the patient's asymptomatic condition? f. What points should be discussed with the patient when they are deciding whether to take PEP? g. What instructions and information should be given to the person exposed to ticks and their family?

Professional and organizational aspects

Question 7: Access to PEP
a) What are the professional and organizational challenges involved in dispensing PEP? b) What are the limitations or situations requiring a consultation with a physician or a primary care nurse practitioner when a person bitten by a tick seeks care from another type of care professional? What instructions and information should be transmitted to the person exposed to ticks and their family?

Pharmacoepidemiological aspects

Question 8: Overview of PEP usage in Quebec
What is the state of the presumed use of doxycycline for Lyme disease in people covered by Quebec's public prescription drug insurance plan (RPAM)?

The specific question concerning pharmacoepidemiological aspects was the subject of a state of practice detailed in a separate report [INESSS, 2019b].

The methods used to examine the assessment questions meet INESSS's quality standards and include the triangulation of scientific, contextual and experiential data. The data were analyzed within the context of Quebec practice, in particular through consultations with various stakeholders. The methodology for each type of information collected is described later in this report.

1.3. Research and Method for Synthesizing Published Scientific Information and Clinical Recommendations

The pharmacological aspects (questions 1 to 3) were examined using systematic reviews with a qualitative synthesis of the results. To better assess the level of scientific evidence associated with the efficacy of each of the studied antibiotics, the primary studies included in the systematic

reviews were reanalyzed. For epidemiological aspects (question 4), a literature review was completed with a qualitative synthesis based on relevant publications identified through cited references. For clinical aspects (questions 5 and 6), a systematic review of documents containing clinical recommendations and information was completed with a qualitative synthesis. For professional and organizational aspects (question 7), refer to the section on research and method for synthesizing contextual information and experiential knowledge.

1.3.1. Identification of published scientific information and clinical recommendations

A scientific information specialist developed a systematic research strategy to answer all the assessment questions included in the work on Lyme disease, and particularly questions 1, 2, 5 and 6 in this report. To minimize publication bias, research was done in English and in French in multiple databases: PubMed, Embase, Evidence-Based Medicine Reviews (EBM Reviews), Cochrane, NHS Economic Evaluation (strictly for economic aspects) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL, strictly for the patient perspective). A register of ongoing clinical studies (ClinicalTrials.gov) was also consulted.

A specific strategy was developed by the scientific information specialist to answer the question about the safety of doxycycline in specific populations (question 3). For this strategy, PubMed, Embase and EBM Reviews were used.

For questions 1 and 2, the literature search prioritized systematic reviews published in the last 10 years that aligned with the exclusion and inclusion criteria listed in Table 1 of this document. If a systematic review of sufficient methodological quality was identified, the objective was to update it by consulting the primary studies published since the systematic review was produced. To answer question 3, all systematic reviews and primary studies that aligned with the inclusion and exclusion criteria were reviewed, regardless of the date of publication.

A manual search was done to identify clinical practice guidelines (CPGs) and other documents relevant to the research questions by consulting the websites of health technology assessment agencies and those of agencies, organizations, institutions and learned societies recognized in the fields of microbiology / infectious diseases and public health.

To answer research question 3, specialized works on the use of medication during pregnancy or breastfeeding were consulted [Briggs et al., 2017; Taketomo et al., 2014; Ferreira et al., 2013], as were the REPROTOX and TERIS databases. A manual search was also done to identify documents from recognized organizations on the use of doxycycline in children under 8 years of age and pregnant women to treat infectious diseases such as malaria and anthrax as well as rickettsial infections.

The following documents were also consulted: official monographs for antibiotics approved by Health Canada[3] or the Food and Drug Administration (FDA), documents published by INESSS directorates, and medication lists published by the Régie de l'assurance maladie du Québec (RAMQ) for institutions and for Quebec's public prescription drug insurance plan.

The bibliographies of selected publications were examined to identify other relevant documents. The stakeholders consulted were also asked to share any scientific documents that could help answer the assessment questions. For details on research strategies, refer to this report's supplementary appendices document.

[3] Via the Health Canada Drug Product Database and the online Compendium of Pharmaceuticals and Specialties (e-CPS).

1.3.2. Selection of documents

Documents were selected independently by two reviewers (FK, GM or GG). A first round of selection was done based on the titles and abstracts of documents identified during the systematic information search, based on the criteria in Table 1. A second round was done based on a complete read-through of the articles selected in the first round, again by two independent reviewers (FK, GG). Differences of opinion were resolved through consensus. A third opinion was not required. A flow chart based on the PRISMA method [Moher et al., 2009] illustrating the selection process for studies is presented in this report's supplementary appendices document, as is the list of excluded documents and the reasons for their exclusion.

Table 1. Document inclusion and exclusion criteria for completing systematic reviews

Inclusion criteria	
Question 1	
Population	Children and adults bitten by the tick species *Ixodes scapularis* in an endemic area for Lyme disease associated with *Borrelia burgdorferi* sensu stricto
Intervention	Post-exposure prophylaxis
Comparators	Placebo, no treatment, other antibiotic, different dosage of the same antibiotic
Outcomes	Absence of signs or symptoms of Lyme disease, dosage, administration route, duration, follow-up parameters
Design	Systematic reviews Primary studies: RCTs, cohort studies, case-control studies
Publication year	No limit up to May 2018
Question 2	
Population	Children and adults bitten by the tick species *Ixodes scapularis* in an endemic area for Lyme disease associated with *Borrelia burgdorferi* sensu stricto
Intervention	Post-exposure prophylaxis
Comparators	Placebo, no treatment, other antibiotic, different dosage of the same antibiotic
Outcomes	Any adverse effects
Design	Systematic reviews Primary studies: RCTs, cohort studies, case-control studies
Publication year	May 2008 to May 2018
Question 3	
Population	Children exposed to oral doxycycline (for any indication of doxycycline) in utero, while breastfeeding, or within their first eight years of life
Intervention	Oral doxycycline

Inclusion criteria	
Comparators	Placebo, no treatment, other antibiotic, different dosage of the same antibiotic
Outcomes	Any adverse effects, particularly dental adverse effects (e.g., permanent tooth staining, dental enamel hypoplasia) and congenital malformations
Design	Systematic reviews Primary studies: RCTs, cohort studies, case-control studies, quasi-experimental studies, case series
Publication year	No limit up to August 2018
Questions 4, 5 and 6	
Population	Children and adults bitten by a tick in an endemic area for Lyme disease
Intervention	Post-exposure prophylaxis
Comparators	N/A
Outcomes	Indications for prophylaxis (criteria), recommended antibiotic for specific populations, dosage, duration
Design	CPGs, expert consensus, guidelines
Publication year	January 2012 to May 2018
Exclusion criteria	
Population	Animal studies
Intervention	Other medication, natural products or preventive interventions (e.g., vaccines, insect repellant)
Type of publication	Other documents than those included (e.g., narrative review, case studies, editorials, theses and dissertations, opinion letters)

N/A: not applicable

1.3.3. Assessment of the methodological quality of documents

The quality of documents selected during the systematic reviews was assessed independently by two reviewers[4] (FK, GG, GM, MT, SL or SOD) using the following tools:

- Appraisal of Guidelines for Research and Evaluation II (AGREE II) for CPGs, expert consensuses and guidelines [Brouwers et al., 2010]
- Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) for systematic reviews [Kung et al., 2010]
- Critical Appraisal Skills Programme (CASP) [2018] for randomized controlled trials (RCTs)

[4] Descriptive studies were assessed by a single reviewer.

- the Public Health Agency of Canada (PHAC) tool [2014] for assessing analytical and descriptive studies.

Disagreements between the two reviewers were resolved through consensus. A third opinion was not required.

The methodological quality of documents selected to answer question 4, as well as CPGs that include recommendations on the use of doxycycline as prophylaxis in contexts other than Lyme disease, was not formally assessed, but an overall assessment was done.

The results of the assessments of the documents reviewed for this report are presented in the corresponding supplementary appendices document.

1.3.4. Extraction of information

The characteristics and results of the selected primary studies and systematic reviews were extracted by a science professional (GG) using pre-selected extraction tables tested on a number of publications to ensure their validity. 100% of the information was then validated by a second person (MT or SL). If relevant data were missing from the published version, the authors of the publication were contacted.

Pharmacological information was extracted from monographs by a single science professional (GG).

Clinical information and recommendations were extracted from CPGs by a single science professional (GG), using pre-set extraction forms that specify the organization, authors, publication year, recommendations, strength, supporting evidence, argument and author conclusions.

1.3.5. Analysis and synthesis of scientific data

Raw data, efficacy indicators calculated by the authors and conclusions were extracted from systematic reviews, RCTs and observational studies, then analyzed and presented based on parameters of the outcome of interest. For primary studies concerning the efficacy of antibiotics for PEP, the confidence interval (CI) of 95% was calculated using an exact method. For the group analysis of primary studies, a meta-analysis based on a random-effects model with inverse-variance weighting was used. All analyses were completed using the meta package version 4.5-0 with R available here: http://cran.r-project.org/web/packages/meta/index.html.

1.3.5.1. Evaluation of the level of scientific evidence

The evaluation of the level of scientific evidence for each of the assessment questions concerning the safety and efficacy of the studied PEP antibiotics for Lyme disease prevention relied on an assessment of all available scientific data by parameter of interest in the following four categories: the scientific and methodological limitations of studies, consistency/reliability, clinical impact and generalizability. These assessment criteria are described in Appendix A. Next, to support the scientific statements, an overall level of scientific evidence was assigned based on a scale: high, moderate, low or insufficient (Table 2). The overall level of scientific evidence integrates the results from the four assessment criteria to represent the overall confidence in the results of the scientific data. The statements and assigned levels of evidence are presented in the results section of this report.

Table 2. Overall evaluation of the level of scientific evidence

Level of Evidence	Definition
High	**Positive ranking in all criteria (methodological limitations, consistency/reliability, clinical impact, generalizability).** The reviewers have a high level of confidence that the effect estimate is comparable to the intervention's objectives. It is unlikely that conclusions drawn from this data will be significantly impacted by the results of future studies.
Moderate	**Positive ranking in the majority of criteria, including methodological limitations.** The reviewers have a moderate level of confidence that the effect estimate is comparable to the intervention's objectives. It is somewhat likely that conclusions drawn from this data will be significantly impacted by the results of future studies.
Low	**Negative ranking in all or most of the criteria.** The reviewers have a low level of confidence that the effect estimate is comparable to the intervention's objectives. It is very likely that conclusions drawn from this data will be significantly impacted by the results of future studies.
Insufficient	**The available data are insufficient.** The reviewers have no confidence in the relationship between the effect estimate and the intervention's objectives.

1.3.6. Analysis and synthesis of clinical information and recommendations from the literature

The definitions, information and clinical recommendations identified in CPGs, health technology assessment reports, expert panels, expert consensuses and consensus conferences, in addition to the guidelines informed by the level of scientific evidence and the main argument, were extracted in tables for comparison and the identification of similarities and differences. A qualitative synthesis was completed based on the aspects to be documented.

1.4. Research and Synthesis Methods for Contextual Information and Experiential Knowledge

After the review of the contextual information and experiential knowledge using various methods, a qualitative synthesis was completed and presented based on the aspects examined in this report.

1.4.1. Identification of contextual information in medico-administrative databases

To answer assessment question 8, and to contextualize the use of doxycycline PEP for Lyme disease in Quebec, an overview of doxycycline use was created using RAMQ administrative data from 2014 to 2018. The main results are summarized in section 2.5 of this report. For more details, refer to the report *Portrait de l'usage de la doxycycline en prévention de la maladie de Lyme chez les personnes couvertes par le régime public d'assurance médicaments du Québec* [Overview of the use of doxycycline to prevent Lyme disease in individuals covered by Quebec's public prescription drug insurance plan] [INESSS, 2019b].

1.4.2. Identification of contextual information in documents published in Quebec intended for clinicians

1.4.2.1 Information search and selection strategy

A single science professional used the Google search engine to locate documents relevant to the assessment questions and written by associations, professional orders and other organizations in Quebec, including the MSSS and the INSPQ. The websites of the MSSS and the regional public health directorates for Estrie and Montérégie were also consulted. A search was also completed to identify Quebec medical protocols and collective prescriptions published in 2018, as well as reports on the experience of using them. The stakeholders consulted were also asked to share information or documents relevant to the assessment questions.

1.4.2.2 Extraction

A single science professional extracted the information reviewed, with no validation by a second person.

1.4.2.3 Analysis and synthesis

The information collected was extracted into tables for comparison and identification of similarities and differences. A qualitative synthesis was completed based on the aspects to be documented.

1.4.3. Collection of experiential knowledge through consultations with stakeholders

The clinical recommendations developed by INESSS are the product of triangulating data from the scientific literature with experiential knowledge from Quebec experts, clinicians, patients and patient representatives and with Quebec-specific contextual elements. The contextual and experiential data were primarily obtained through consultations with stakeholders: working groups put together specifically for the project, standing INESSS committees, patient associations and key informants.

1.4.3.1. INESSS committees

To help guide its work on Lyme disease, INESSS formed an advisory committee of health professionals, experts recognized in the field and two patient partners. The procedure for recruiting patient partners was discussed and designed in collaboration with the Centre of Excellence on Partnership with Patients and the Public (CEPPP). Criteria were developed for identifying candidates who matched a desired profile: patients with disseminated-stage Lyme disease who were diagnosed in Quebec. To identify potential candidates, INESSS solicited assistance from the CEPPP and from microbiologist / infectious diseases specialists practising in high-risk areas who were not on the advisory committee. In addition, following the parliamentary proceedings on Lyme disease in March 2018, one candidate contacted the INESSS to express their interest in participating in the project. The CEPPP then conducted a series of interviews with potential candidates, and patient partners were chosen based on their overall score on a pre-selected list of criteria.

An advisory subcommittee was convened specifically to assist INESSS in developing the provincial medical protocol and collective prescription template for PEP.

These advisory committees' mandate was to ensure that the work was scientifically credible and clinically relevant as well as to contribute to achievability and ensure professional and social acceptability of clinical and implementation recommendations in addition to knowledge transfer tools. To accomplish this, the committees provided vitally important information, expertise, opinions and perspectives, as well as feedback at various stages of the project. Patient partners brought emerging concerns to the attention of the project team, particularly regarding persistent post-treatment symptoms, and shed light on challenges related to the applicability and social acceptability of the recommendations and tools developed.

INESSS also formed a monitoring committee of representatives from professional groups (orders, associations, federations and organizations) and representatives from the DGAPSP,

DBBM and Info-Santé, all three of which are under the MSSS, and from the INSPQ. This committee's mandate was to ensure that the project's mission and execution were in line with the needs of the community.

The Clinical Excellence Committee (CEC) on Optimal Medication Use was also consulted. This committee is tasked with ensuring the scientific rigour and professional and social acceptability of INESSS publications related to medication use.

Lastly, the MSSS's DAPM governance committee, whose mandate has a strategic scope, was consulted in order to address the challenges of the project and promote the effective adoption of preferred recommendations and measures among those put forward by INESSS.

The key takeaways from the discussions with committee members are synthesized in the paragraphs on experiential and contextual data in the results section of this report, as applicable. The committee members are listed in the front matter of this report.

1.4.3.2. Patient association

On December 6, 2018, a meeting was held with representatives of the Association québécoise de la maladie de Lyme (AQML), followed by email exchanges, in order to gather information on the association's concerns, viewpoints and needs regarding the treatment of Lyme disease in Quebec. A second meeting with the representatives was held on March 12, 2019, to share the results of the first component of this project.

1.4.3.3. Patients

To document the care experience of patients in Quebec, eight semi-structured interviews were held with individuals who had been diagnosed with Lyme disease in Quebec. Criteria were developed to identify candidates with the desired profile: patients with Lyme disease at the local or disseminated stage. These patients were recruited with the help of the Direction de santé publique (DSP) of Montérégie via the MADO registry and of specialized physicians who were or not members of the advisory committee. First, patients were contacted by their personal physician or a public health physician. If they agreed to participate, the INESSS team contacted them to plan the interviews and discuss the consent form that all patients were required to sign before participating. The interview plan focused on the patient's personal experience with Lyme disease in terms of diagnosis, treatment, care and quality of life. A narrative analysis of these interviews revealed a series of observations on the care experience in the Quebec health care system and the perception of the burden of the disease. Where these observations were relevant to the assessment questions, they were synthesized in the appropriate sections of this report.

1.4.3.4. Key informants

Seven community pharmacists—four from Estrie and Montérégie and three from outside of these regions—were interviewed about their procedures for doxycycline PEP for Lyme disease and, if appropriate, the application of current corresponding collective prescriptions. The Centre IMAGe, at the Ste-Justine university hospital centre (CHU), was also consulted for opinions about data on the use of doxycycline in pregnant women.

1.4.3.5. Confidentiality and ethical considerations

Any personal or medical information collected from the medico-administrative databases or provided by the stakeholders consulted was anonymized in order to protect the identity of the participants. Members of the project team, committees and the AQML were also required to adhere to the INESSS principles of discretion, confidentiality, integrity and respect. All INESSS members and partners in the work acknowledged and agreed to follow the code of ethics.

1.4.3.6. Preventing, disclosing and managing conflicts of roles and interests

All individuals who collaborated on this project was required to declare in advance any personal interests (commercial, financial, career-related, inter-personal or other) that may present a potential conflict of interest. They were also required to disclose any professional activities or roles that could present a potential conflict of roles. These disclosures were made using the standardized INESSS form. The sole exception to this requirement was key informants, who were interviewed on a specific one-time basis on the aspects mentioned above.

The disclosures were then assessed by INESSS in order to determine the appropriate course of action for managing any potential conflicts. In the interest of transparency, all conflicts of interest and conflicts of roles are publicly disclosed in the front matter of this report.

1.4.4. Analysis and synthesis of contextual information and experiential knowledge

Stakeholder contributions were documented using editable sheets and meeting minutes recorded in shared documents. The sheets contained the date, location and topic of the meeting, key takeaways from the meeting and details on the follow-up that was completed. The group consultations were also recorded with the consent of the participants. Privileged consultation and deliberation methods, as well as the decision-making process that led to the team's conclusions, were also documented.

1.5. Body of Evidence Integration Approach

1.5.1. Evaluation of the value of the body of evidence

In order to issue clinical recommendations regarding PEP for Lyme disease prevention, the body of evidence was evaluated according to the following five criteria:

- statement of scientific evidence and level of scientific evidence
- pharmacological, epidemiological, clinical, pharmacoepidemiological, professional and organizational aspects
- applicability of the intervention
- acceptability
- potential impacts of implementation.

These five decision-making criteria for assessing the value of the body of evidence are described in detail in Appendix A. The criteria were assessed by the INESSS project team in terms of the reliability and probative value of the elements of evidence considered relevant and were enhanced by members of the advisory committee.

Table 3. Summary of sources for collected information

Aspects	SOURCES OF INFORMATION			
	Scientific Literature	**Grey Literature**	**Consultations With Stakeholders**	**Medico-Administrative Databases**
Pharmacological	Systematic reviews, primary studies	CPGs/GLs, public health agencies, regulatory agencies (Health Canada and the FDA), monographs, reference works	AC, ASC-PCP, Centre IMAGe, AQML, patients, key informants	N/A
Epidemiological	Systematic and non-systematic reviews, primary studies	CPGs/GLs, INSPQ, LSPQ, PHAC, CDC	AC, ASC-PCP,	N/A
Clinical	Systematic reviews, primary studies	CPGs/GLs, public health agencies, regulatory agencies (Health Canada and the FDA), monographs, reference works	AC, ASC-PCP, MC, CEC-UOM	N/A
Professional and organizational	N/A	Websites of the MSSS, INSPQ and the DRSPs of Estrie and Montérégie, published PMPs and CPs, documents published by professional orders	AC, ASC-PCP, MC, CEC-UOM, key informants, AQML, patients	N/A
Pharmaco-epidemiological	N/A	N/A	N/A	RAMQ registries

Abbreviations: PHAC: Public Health Agency of Canada; AC: advisory committee; CEC-UOM: Clinical Excellence Committee on Optimal Medication Use; CDC: Centers for Disease Control and Prevention; CP: collective prescription; MC: monitoring committee; DRSP: regional directorate of public health; FDA: Food and Drug Administration; CPG: clinical practice guideline; INSPQ: Institut national de santé publique du Québec; GL: guidelines; LSPQ: Laboratoire de santé publique du Québec; PMP: provincial medical protocol; RAMQ: Régie de l'assurance maladie du Québec; ASC-PCP: advisory subcommittee on the provincial medical protocol and CP template; N/A: not applicable.

1.6. Deliberative Process and Formulation of Recommendations

The clinical recommendations for PEP were formulated in collaboration with the members of the advisory committee on Lyme disease. For each research question, a table containing the following information was presented to the advisory committee: 1) the scientific data, 2) recommendations for best clinical practices drawn from CPGs, 3) contextual and experiential data and 4) preliminary observations made by the project team after analyzing the body of evidence.

Committee members followed an informal deliberative process when discussing the body of evidence to formulate initial recommendations. Then, they gave their opinions on the final recommendations, either during deliberations or by email, depending on the degree of divergence between the initial opinions. Recommendations that were approved by at least 80% of the committee members were retained. In the event of a lack of consensus as to a recommendation's scope or relevance, the recommendation was withdrawn or reformulated.

Recommendations were developed taking into account the quality of scientific evidence (level of evidence), the trade-off between the advantages and disadvantages of each recommendation, the values and preferences of professionals and the applicability of the intervention in the context of practice.

The content of the provincial medical protocol and the collective prescription template for PEP was developed in collaboration with the subcommittee on the provincial medical protocol based

on clinical recommendations developed with the advisory committee, the data collected and the discussions held within the subcommittee on matters relating to clinical aspects.

1.7. Knowledge Transfer Tools

The stakeholders consulted were asked to identify their needs and determine what types of clinical tools could be useful and relevant for supporting first- and second-line health professionals. Next, considering the aspects documented during the first step, broad categories of clinical tools and their content were determined. Preliminary versions of knowledge transfer tools were developed around the clinical recommendations and information clinicians might deem essential, then proposed to the advisory committee. The committee members were asked to comment on and suggest changes to the tools based on their expertise and experience. A pre-final version of the knowledge transfer tools was presented to external readers (see below), members of the CEC-UOM, and the monitoring committee. As needed, the advisory committee members were consulted by email when changes were proposed by other stakeholders, in order to verify the relevance of the changes.

In addition to the provincial medical protocol, collective prescription template and liaison form template, three main PEP knowledge transfer tools were developed:

- the *Decision Support Tool* to guide and support practising health professionals in prescribing PEP for Lyme disease
- the *Follow-up Sheet* to inform patients about their condition and the actions to take depending on the progression of their condition
- the *Dialogue With Your Patient* tool to support discussions between health care professionals and the person eligible for PEP, and to incorporate the patient's preferences, values and perception of the risk of Lyme disease into the decision about whether or not to take PEP.

The last of these tools was developed from the Ottawa[5] decision aid template. This template supports an informed decision reached through a shared decision-making process in which the clinician and patient work together to determine: a) the available clinical options, b) the risks and benefits of each of these options, c) the patient's values and preferences when it comes to treatment options, to determine what is most important to the patient. In addition, the advantages and disadvantages directly associated with the risks and benefits of each option were identified based on the literature and consultations with stakeholders. These considerations serve to clarify the values and preferences of the patient when it comes to the proposed treatment options. Lastly, the clinically validated SURE Test scale was integrated to gauge the patient's level of comfort with the decision made [Légaré et al., 2010].

The source for the photos is listed in this report's supplementary appendices document.

To ensure that these tools would be useful in practice and adapted to the on-the-ground reality of health professionals, a number of potential future users from different regions in Quebec were consulted. An online survey was conducted in March 2019 to collect their comments on the tools. The list of survey respondents is presented in the front matter of this document, and the survey questions are listed in this report's supplementary appendices document. Comments from these future users were analyzed and integrated, as appropriate, by the project team.

[5] The Ottawa Hospital Research Institute. Patient Decision Aids [Website]. Available at: https://decisionaid.ohri.ca/methods.html.

1.8. Peer Validation

The preliminary results report, knowledge transfer tools, provincial medical protocol and collective prescription template were sent to three external readers, who assessed the relevance of the content and the overall scientific quality of the documents. The external readers were chosen based on their expertise (one microbiologist / infectious diseases specialist, one general practitioner with expertise in public health and one pharmacist) or their involvement in their field. They were also chosen for being representative of different regions in Quebec (Montréal, Sherbrooke and Gatineau). Their names and affiliations appear in the front matter of this document.

The project team analyzed their comments and integrated them into the final report as appropriate. They are reproduced in the summary table found in this report's supplementary appendices document.

1.9. Update

The need to update INESSS's work on Lyme disease PEP will be assessed based on future published CPGs/guidelines and on advances in scientific data.

2. RESULTS

2.1. Pharmacological Aspects

2.1.1. Results for research question 1: Efficacy of the studied PEP antibiotics

Question 1: Efficacy of the studied PEP antibiotics
What is the efficacy of the studied PEP antibiotics used for Lyme disease caused by *Borrelia burgdorferi* sensu stricto in adults or children bitten by the tick *Ixodes scapularis* in a geographic area at high risk for Lyme disease, as compared to a placebo, no treatment or another antibiotic?

2.1.1.1 Description of publications

The scientific information search identified 15,653 references (not counting duplicates) for all research questions related to the treatment (prophylactic or curative) and diagnosis of Lyme disease (see the flow chart in this report's supplementary appendices document). Of these, one systematic review of sufficient quality was retained for question 1. This review was completed by Warshafsky et al. [2010] and included four double-blind randomized controlled trials (RCTs) that assessed the efficacy of post-exposure prophylaxis for Lyme disease compared to a placebo [Nadelman et al., 2001; Agre and Schwartz, 1993; Shapiro et al., 1992; Costello et al., 1989]. The four RCTs were completed in the United States in high-risk areas for Lyme disease (Connecticut and New York state). In these geographic areas, as in Quebec, the bacteria responsible for Lyme disease is *Borrelia burgdorferi* sensu stricto,[6] and the vector that transmits the bacteria to humans is the black-legged tick, *Ixodes scapularis.*

Warshafsky and his co-authors excluded two studies from their systematic review [Maraspin et al., 2002; Korenberg et al., 1996] that did not randomly assign participants to separate groups and did not compare results to a placebo group. These two studies were also judged irrelevant to this systematic review, as they were conducted in Slovenia and in Russia, regions where the vector ticks for Lyme disease are, respectively, *I. ricinus* and *I. persulcatus,* and the infectious bacteria are *Borrelia afzelii* and *Borrelia garinii.*

No additional primary studies[7] were found that both met the inclusion criteria for this review and were published after Warshafsky's research period[8] for his review, apart from a study on an azithromycin gel administered locally to the site of the bite [Schwameis et al., 2017]. This study was not included in the current systematic review because it was terminated early due to the absence of observed improvement in the primary endpoint in the azithromycin group and because there are no Health Canada-approved topical forms of azithromycin. No ongoing clinical studies on PEP for Lyme disease were found in the ClinicalTrials.gov database.[9]

Given that the four RCTs included in Warshafsky's systematic review [2010] were heterogenous in terms of the antibiotics studied, the outcomes and the length of the follow-up period, it was deemed appropriate to extract the characteristics and results of each of the four studies individually.

Their main characteristics are summarized in Table 4 below. Note that the appearance of an erythema migrans rash at the site of the bite was the primary outcome of the Nadelman study

[6] For the sake of readability, *Borrelia burgdorferi* sensu stricto will be referred to as *B. burgdorferi*.
[7] RCTs, cohort studies or case-control studies.
[8] Between 2009 and 2018.
[9] Research conducted on October 12, 2018.

from which the sample size to be included was calculated, but in three of the other studies, there was no formally defined primary outcome or calculated sample size; these three studies documented the development of an EM rash or extracutaneous manifestations of Lyme disease. The occurrence of seroconversion was studied in the four studies, but the definitions and tests used differed, and in only two of these studies, positive or inconclusive immunofluorescence serology was confirmed by a western blot test [Nadelman et al., 2001; Shapiro et al., 1992]. The rate of infestation of *Ixodes scapularis* by *Borrelia burgdorferi* was evaluated in both of the studies conducted in Connecticut [Shapiro et al., 1992; Costello et al., 1989].

Table 4. Summary of the main characteristics of the four RCTs on post-exposure prophylaxis for Lyme disease

Author, year, country	Type of study	Total no. of patients included	Inclusion criteria	Intervention	Main reported outcome	Length of follow-up period	Quality (CASP)
Agre and Schwartz, 1993, US (NY state)	Double-blind RCT versus placebo	184 (179 analyzed)	- Bitten by *I. scapularis* in the last 72 hours - Age: 3–19	Penicillin (age < 9) or tetracycline (age > 9) 250 mg, QID for 10 days	EM or extracutaneous symptoms of LD	12–36 months	Average
Costello et al., 1989, US (Connec-ticut)	Double-blind RCT versus placebo	68 (56 analyzed)	- Bitten by *I. scapularis* in the last 72 hours - Age: 5 and up	Penicillin 250 mg, QID for 10 days	EM or extracutaneous symptoms of LD	6–12 months	Average
Nadelman et al., 2001, US (NY state)	Double-blind RCT versus placebo	506 (482 analyzed)	- Bitten by *I. scapularis* in the last 72 hours - Age: 12 and up	Doxycycline 200 mg, single dose	EM at the site of the bite	1.5 months	Average
Shapiro et al., 1992, US (Connec-ticut)	Double-blind RCT versus placebo	387 (365 analyzed)	- Bitten by *I. scapularis* in the last 72 hours - Age: 1 and up	Amoxicillin 250 mg, TID for 10 days	EM or extracutaneous symptoms of LD with seroconversion	6–12 months	Average

Legend: CASP: Critical Appraisal Skills Programme, EM: erythema migrans, US: United States, *I.: Ixodes*, LD: Lyme disease, No.: number, NY: New York

The four RCTs are described in detail in this report's supplementary appendices document.

2.1.1.2 Results for amoxicillin, penicillin and tetracycline

In the RCTs conducted by Agre and Schwartz [1993], Costello [1989] and Shapiro [1992], no erythema migrans was observed in the groups that received prophylaxis with amoxicillin, penicillin or tetracycline. In contrast, cases of erythema migrans were reported in the placebo group at a frequency of between 1.1% and 3.4%, depending on the study. No cases of extracutaneous manifestations of Lyme disease with seroconversion documented by the appropriate tests were observed. Overall, no statistically significant difference was found between the groups studied in the three trials. The number of patients included was limited, and few events were reported. Thus, the strength of these studies was likely insufficient. Limitations found to be common across the three studies were: absent or insufficient information on the comparability of the included groups, absence of information on the disease stage, duration of

tick attachment and level of tick engorgement, and a failure to account for all of the patients admitted to the trial in the analyses. In addition, the study by Agre and Schwartz did not include an analysis of the results by antibiotic administered (i.e., penicillin in individuals under age 9 and tetracycline in individuals 9 and up). The results of these studies are summarized in Table 5. The full results of these studies are available in this report's supplementary appendices document.

2.1.1.3 Results for doxycycline

The only RCT to find a statistically significant difference between the treated group and the placebo group, according to the authors' calculations, is Nadelman [2001]. Given that IDSA uses this study as the basis for its recommendation for the use, under certain conditions, of a single 200 mg dose of doxycycline to prevent Lyme disease following a bite from a black-legged tick, the results of this study are described in particular detail in this report. The study was conducted in Westchester County, New York, where the rate of *B. burgdorferi* infestation in ticks is reported by the authors as 25% for nymphs and 50% for adults, with an incidence of Lyme disease of 0.5 to 1 case per 1,000 people per year. Though 506 people age 12 and up were included in the study, 24 people (12 in each group) were not included in the efficacy analysis, because the tick species they were bitten by was not identified by the medical entomologist as *Ixodes scapularis*. A total of 482 participants were accounted for in the analysis for the primary outcome (erythema migrans at the site of the bite after 6 weeks): 235 in the doxycycline group and 247 in the placebo group. It should be noted that 11% of participants in the doxycycline group and 10% of participants in the placebo group did not complete the three planned visits (at inclusion, after 3 weeks and after 6 weeks). The demographic characteristics of the participants at inclusion are reported by the authors as being similar. The median age of participants was 41 in both groups. Nearly 10% have a medical history of Lyme disease and approximately 7% were considered seropositive for *B. burgdorferi*. In over 50% of cases, the tick that caused the bite was a nymph, and the median duration of attachment[10] was 30 hours. Both the doxycycline and placebo capsules were swallowed by patients under the direct supervision of the study personnel.

2.1.1.3.1. Results on the development of erythema migrans at the site of the bite

Of the 235 participants included in the doxycycline group, 1 single participant developed an erythema migrans rash at the site of the bite after 6 weeks, versus 8 out of 247 participants in the placebo group. The difference between the groups was statistically significant (0.4% vs. 3.2%, $P < 0.04$). The authors estimated the effect size by calculating the relative risk reduction (RRR) associated with the administration of a 200 mg dose of doxycycline. The RRR was estimated at 87% (CI 95%: 25%–98%).

2.1.1.3.2. Other results presented by the authors

The authors [Nadelman et al., 2001] completed analyses based on the disease stage and level of tick engorgement (partially engorged or unfed). It was shown that, for participants in the placebo group, erythema migrans developed at the site of the bite more frequently after a bite from a nymph than after a bite from an adult female (8/142 [5.6%] vs. 0/97 [0%], $P = 0.02$). Erythema migrans developed away from the site of the bite in 2 study participants (1 from each group). The authors attributed this fact to a new tick bite unknowingly sustained by the participant after the initial tick bite. They noted that subsequent bites sustained during the study were frequent, as 18.2% of participants reported new bites during the six-week follow-up period. In the placebo group, 2 participants developed a viral-like illness without erythema

[10] As estimated by the medical entomologist based on the scutal index

migrans and with confirmation of a *B. burgdorferi* infection; in the first case, by the passage from a negative result to an equivocal result for the ELISA test and negative result to a positive result for the IgM western blot, and in the second case, by a positive blood culture for *B. burgdorferi* and negative serological test. One participant in the doxycycline group also developed a viral-like illness without erythema migrans, with seroconversion documented only by the ELISA test (no confirmation by IgM western blot). No extracutaneous manifestations of Lyme disease (meningitis, oligoarthritis, facial nerve paralysis, heart block) or cases of asymptomatic seroconversion were observed.

2.1.1.3.3. Comments on and limitations of the Nadelman study

The Nadelman study [2001] has a number of limitations that merited comment. These limitations are presented by theme.

Imprecise results:

Though the strength of the Nadelman study [2001] was sufficient to detect a significant difference in the primary outcome between the two groups, it should be noted that the number of observed events (erythema migrans at the site of the bite) is low (1 event in the doxycycline group vs. 8 in the placebo group). Given this, the 95% confidence interval for the relative risk reduction (RRR) for erythema migrans at the site of the bite is broad, as it includes values ranging from 25% to 98%, according to the authors' calculation. In other words, a single 200 mg dose of doxycycline may reduce occurrences of erythema migrans at 6 weeks by 87%, but it is not possible to exclude the fact that this reduction may, in reality, be smaller (at worst, 25%) or larger (at best, 98%). The extent of this effect is therefore imprecise, and there is a degree of uncertainty around the true value of the effect of PEP administered via a single 200 mg dose of doxycycline. In addition, according to Cameron [2014], the 95% confidence interval calculated by Nadelman is incorrect. Using an exact[11] method, as Nadelman did, Cameron obtained a confidence interval of 95% for an odds ratio of 0.003 to 0.968, which corresponds to a confidence interval of 3.2% to 99.7%[12] for the RRR. This confidence interval is broader than that calculated by Nadelman and suggests the possibility that doxycycline only reduces the risk of erythema migrans at the site of the bite by 3.2% compared to the placebo. Note that the values of the confidence interval for the odds ratio calculated by INESSS following the exact method using the Nadelman data match those obtained by Cameron (refer to table 5).

It should also be noted that a change in the results of a single study participant could have a considerable impact on the conclusion of this study. As Cameron [2014] observes, if a single case of erythema migrans had been omitted from the doxycycline group, the statistical test for the primary result would not have been significant.[13] According to Cameron, this possibility cannot be ruled out, given that 11% of participants did not complete all three visits as part of the study and it is not known whether any of them developed erythema migrans.

Pertinence of the measure for effect size:

Recall that a statistically significant effect is not necessarily clinically significant. It is the effect size that determines clinical significance, not the presence of statistical significance. To assess the effect size, several indicators may be calculated from the same baseline data: relative risk

[11] A method for calculating a 95% confidence interval that is often preferred to other methods when the number of events is low.

[12] The RRR confidence interval from which the odds ratio is obtained through the following formula: lower bound = 1 – 0.968, upper bound = 1 – 0.003.

[13] Based on calculations by INESSS, a single additional event in the doxycycline group would bring the odds ratio to 0.26 (CI 95: 0.03, 1.30), and the P value for Fisher's exact test would be 0.106 6.

reduction (RRR), odds ratio (OR), relative risk (RR), absolute risk reduction (ARR), and the number needed to treat (NNT). Nadelman and his co-authors chose to express the effect size of prophylactic treatment with 200 mg doxycycline in terms of the RRR. However, RRR is a multiplicative indicator that does not account for the baseline risk in the population. This value tends to paint an optimistic—perhaps too optimistic—picture of efficacy when baseline risk is low. In the Nadelman study, an RRR of 87% with doxycycline indicates relatively high efficacy, while the baseline risk of erythema migrans at the site of the bite at 6 weeks is rather low, at 3.2% [Gonzalez, 2003]. ARR is considered a more clinically relevant indicator because it provides a measure of the absolute benefit of the intervention.[14] When expressed in terms of ARR, the result of the Nadelman study is 2.8%[15] (CI 95%: 0.5%–5.2%), which gives a much more conservative picture of the effects of doxycycline than RRR. NNT is also a relevant indicator of efficacy from a clinical and public health standpoint. It represents the number of patients who need to be treated in the group receiving the intervention to prevent one additional bad outcome in comparison to the placebo group over a given time period. In Nadelman, the NNT is estimated at 36 (CI 95%: 19–220). In Gonzalez's opinion [2003], it is important for clinicians to familiarize themselves with these indicators, as they are often used indiscriminately in clinical trial analyses. Gonzalez adds that based on empirical data, readers' perception of the efficacy of an intervention depends on how the result is reported. Nadelman's efficacy rate of 87%, as expressed by the RRR, is more impressive than an ARR of 2.8%. According to Gonzalez, the way in which the results were reported in the Nadelman study could predispose clinicians to routinely use doxycycline for post-exposure prophylaxis when the value of this intervention is uncertain. The results of the Nadelman study expressed in terms of the efficacy indicators calculated by the authors and by INESSS are presented in Table 5.

Relevance of the main clinical outcome:

ILADS [Cameron et al., 2014] showed that prevention of the appearance of erythema migrans at the site of the bite was not a reliable surrogate criterion for the prevention of Lyme disease, as erythema migrans does not develop in roughly 30% of cases. The study authors [Nadelman et al., 2001] recognized the limitations of this outcome and noted that it may have led to an underestimation of the true incidence of infections caused by *B. burgdorferi*. However, they defended their choice with the argument that erythema migrans at the site of the bite is the clinical manifestation most commonly associated with *B. burgdorferi* infections and that it is the only reliable indicator of infection.

Length of follow-up period:

According to several authors, the six-week follow-up period is not sufficient to conclude whether prophylaxis via a single 200 mg dose of doxycycline can prevent the development of Lyme disease at its various stages [Hofmann et al., 2017; Cameron et al., 2014; Maloney, 2011; Meyerhoff, 2002; Leenders, 2001]. According to the study's authors [Nadelman et al., 2001], this interval was chosen deliberately to reduce the risk of confusion caused by the development of Lyme disease from a subsequent bite.

[14] ARR represents the difference between the absolute risk in the treated group and the control group.

[15] Calculated by subtracting the frequency of erythema migrans at the site of the bite in the placebo group (3.2%) from that of the doxycycline group (0.4%).

Table 5. Effect of post-exposure prophylaxis for Lyme disease according to indicators calculated by study authors and by INESSS

Author, year	Intervention	Frequency of events[16] n/N(%)		Effect calculated by the authors Indicator (CI 95%)	Effect calculated by Warshafsky et al., 2010 Indicator (CI 95%), P value	Effect calculated by INESSS[17] Indicator (CI 95%), P value
		Intervention	Comparator			
Primary studies						
Agre and Schwartz, 1993	Penicillin or tetracycline, 1000 mg/day for 10 days	0/89 (0.0)	1/90 (1.1)	Not available	OR = 0.00 (0.00, 39.42), P = 1.00	Not applicable[18]
Costello et al., 1989	Penicillin, 1000 mg/day for 10 days	0/27 (0.0)	1/29 (3.4)	Not available	OR = 0.00 (0.00, 41.90), P = 1.00	Not applicable[18]
Nadelman et al., 2001	Doxycycline, 200 mg dose	1/235 (0.4)	8/247 (3.2)	RRR = 87% (25; 98)	OR = 0.13 (0.003, 0.97), P = 0.045	OR = 0.13 Exact CI = (0.003; 0.97), P = 0.0447 ARR = -2.8% Exact CI = (-11.7, 6.1), P = 0.0614 RRR = 87% Exact CI = (3.2, 99.7), P = 0.0447 NNT = 36 (19, 220)
Shapiro et al., 1992	Amoxicillin, 750 mg/day for 10 days	0/192 (0.0)	2/173 (1.2)	RRR = 100% (-379; 100)	OR = 0.00 (0.00, 4.80), P = 0.45	Not applicable[18]
Group analysis of the 4 primary studies						
Warshafsky et al., 2010	See above	1/543 (0.2)	12/539 (2.2)	Not applicable	OR = 0.084 (0.002, 0.57), P = 0.003 7 ARR = not avail. NNT = 49 (45-106)	OR = 0.083 (0.01, 0.64), P = 0.017 1 ARR = -1.7 (-3.0, -0.004), P = 0.010 9 NNT = 109 (101; 281) if baseline risk is 1% or NNT = 36 (34, 95) if baseline risk is 3% (see figure 1)

Legend: CI: confidence interval, NNT: number needed to treat, OR: odds ratio, ARR: absolute risk reduction, RRR: relative risk reduction

[16] "Event" refers to the development of erythema migrans at the site of the bite or an objective extracutaneous clinical manifestation consistent with early or late Lyme disease confirmed by seroconversion.

[17] For primary studies, the CI of 95% was calculated using an exact method. For the group analysis of the four primary studies, a meta-analysis based on a random-effects model with inverse-variance weighting was used. All analyses were completed using the General Package for Meta-Analysis, version 4.5-0, with R available at http://cran.r-project.org/web/packages/meta/index.html.

[18] The effect was not calculated. In fact, the measure of the effect size is imprecise as no cases of erythema migrans were observed in the group that received prophylaxis.

Generalizability of results:

Nadelman and his co-authors [2001] raised several points related to the generalizability of the results of their study: 1) patients and clinicians may have difficulty distinguishing *Ixodes scapularis* from other species of ticks and arthropods, or even from debris or scabs, 2) the efficacy of doxycycline in preventing other infections transmitted by *Ixodes scapularis* (such as babesiosis or human granulocytic ehrlichiosis) is not known and should not be assumed, and 3) neither should it be assumed that other antibiotics or dosing regimens for doxycycline (for example, 100 mg twice daily) have a similar efficacy to that of a single 200 mg dose of doxycycline for the prevention of Lyme disease.

The argument that it is difficult to identify ticks was examined and commented on by several authors. The results of the Nadelman study are considered translatable to situations in which the tick species, tick life stage and level of tick engorgement can be reliably identified. However, it appears that in common practice, this information is generally lacking [Maloney, 2011; Levy et al., 2001; Shapiro, 2001]. It was also noted that the generalizability of the results of the Nadelman study was limited to people bitten by *Ixodes scapularis* [Cameron et al., 2014] and regions where the prevalence of tick infestation and the incidence of Lyme disease are on the same order as those observed in the north of Westchester County [Shapiro, 2001].

Impact on the presentation of the disease:

Several authors, particularly the authors of the ILADS CPGs, brought up the possibility that a single dose of doxycycline may prevent the development of erythema migrans, inhibit a serological response and allow the development of late-onset manifestations of the disease [Cameron et al., 2014; Maloney, 2011; Volkman, 2008; Volkman, 2007; Bellovin, 2001]. There is some debate surrounding this hypothesis, and it is opposed by Nadelman [2001] and certain authors of IDSA's CPGs [Wormser et al., 2007], on the grounds that:

- In the Nadelman study, non-specific febrile illnesses were not more frequent in the doxycycline group than in the placebo group (2.1% [n = 5] vs. 1.6% [n = 4], a non-significant difference). In addition, there was no asymptomatic seroconversion suggestive of a subclinical infection where relevant; yet it should be noted that in the opinion of the advisory committee members, the tests used at the time were less sensitive, and it is difficult to exclude the absence of a current infection in patients who do not present with erythema migrans based on these tests.
- No extracutaneous manifestations were observed in the Nadelman study or in the three other RCTs on post-exposure prophylaxis, which had follow-up periods ranging from six months to three years.
- It is unlikely that a physiopathological mechanism would allow the proliferation and dissemination of *B. burgdorferi* resulting in a clinical illness in the absence of seroconversion.
- Seronegative Lyme disease is not a medically recognized phenomenon, and the T-cell proliferation assays on which diagnosis relies are considered non-specific.

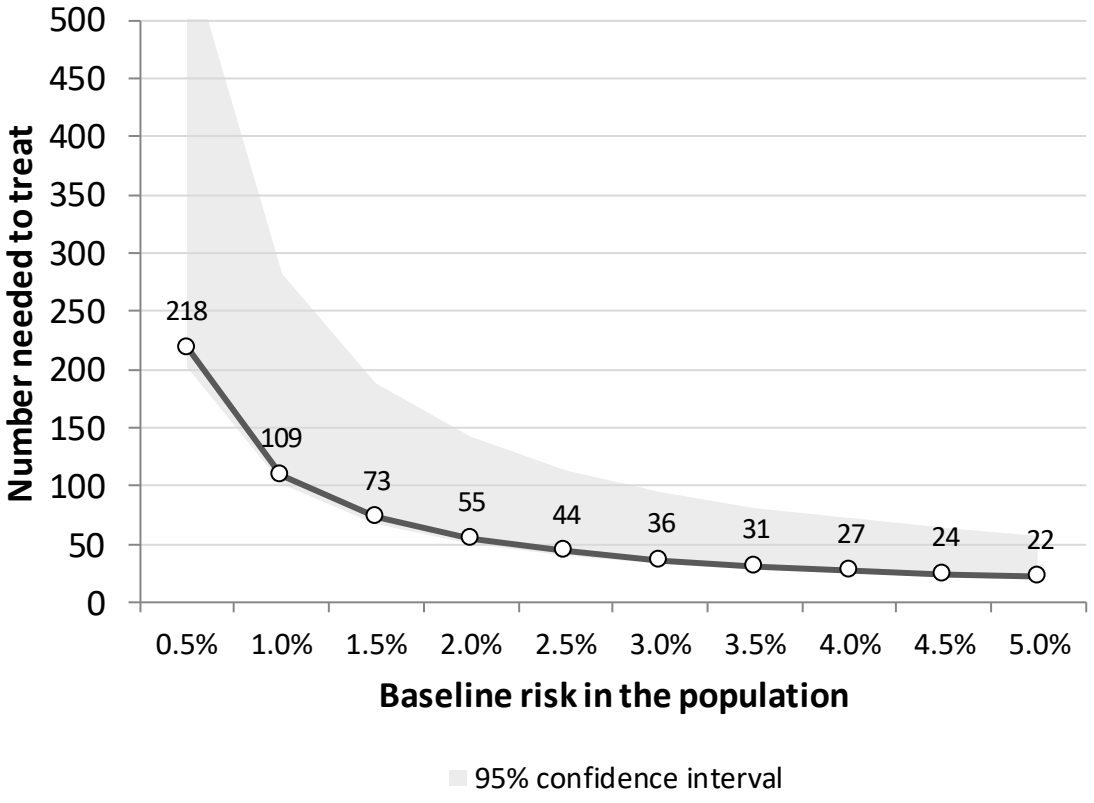
2.1.1.4 Results on the group analysis of studies on post-exposure prophylaxis for Lyme disease

In 1996, Warshafsky and his co-authors published the results of a first meta-analysis that included the three RCTs described above that examined prophylaxis via beta-lactam antibiotics (or tetracycline, for 30 patients in the study) over extended periods of time. The results were inconclusive, as the authors did not find a statistically significant reduction in the risk of contracting Lyme disease when compared with the placebo group [Warshafsky et al., 1996].

An update to this meta-analysis was later published [Warshafsky et al., 2010] to integrate the results of the Nadelman study [2001]. The event considered by Warshafsky when calculating efficacy was the development of erythema migrans at the site of the bite or an objective clinical manifestation consistent with early or late extracutaneous Lyme disease confirmed by seroconversion. The authors did not account for cases of viral-like illness with no erythema migrans with laboratory evidence of an infection by *B. burgdorferi.* They justify this choice on the grounds that: 1) tick bites are frequent in endemic zones, and therefore it was possible for participants to be bitten again without their knowledge after receiving prophylaxis (or the placebo) and subsequently develop antibodies against *B. burgdorferi* as a result of the second bite, and 2) serological tests are not precise enough to categorically establish a diagnosis of Lyme disease in these patients. To illustrate the second argument, the authors state that a two-step ELISA test paired with an immunoblot test has a sensitivity of 53% and a specificity of 98%, which places the combined positive predictive value of these tests at 37%, assuming that the prevalence of Lyme disease is 2.2%. Thus, 63% of positive results would be false positives, meaning that the majority of cases of viral-like illness with no erythema migrans with laboratory evidence of a *B. burgdorferi* infection would not be true cases of Lyme disease.

The results of this meta-analysis place the estimated overall risk of developing Lyme disease after a bite from *Ixodes scapularis* at 2.2% (CI 95%: 1.2, 3.9) in the placebo group and 0.2% (CI 95%: 0.0–1.0) in the prophylaxis group. The corresponding odds ratio (OR) is estimated at 0.084 (CI 95%: 0.002 0, 0.57, P = 0.0037) according to the authors' calculations. The authors also stated that 49 people bitten by *Ixodes scapularis* in an endemic zone would need to be treated to prevent one additional case of Lyme disease (CI 95%: 45, 106). These results should be interpreted with caution given that, firstly, this meta-analysis is based on several studies with a low number of participants, which does not allow for an adequate assessment of the effect of the intervention and secondly, it grouped studies that were heterogenous in terms of antibiotics, dosing regimens and follow-up periods. It should also be noted that the baseline risk of developing Lyme disease varies between the studies, from 1.1% to 3.4%. Consequently, the NNT varies considerably depending on the expected risk in the population, as illustrated by Figure 1. This figure shows that, as the baseline risk in the population decreases, the NNT increases, as does the level of uncertainty surrounding the results (represented by the grey area in Figure 1).

Figure 1. Number needed to treat as calculated by INESSS from the data in the meta-analysis by Warshafsky and his co-authors vs. baseline risk in the population



2.1.1.5 Statement of scientific evidence and level of scientific evidence for the efficacy of antibiotics studied for Lyme disease PEP

As discussed in the methodology section, the quality of scientific evidence was assessed based on four criteria, detailed in Appendix A. Each antibiotic studied for Lyme disease PEP was assigned a level of scientific evidence accompanied by a statement of evidence. The results of this assessment are summarized in the boxes below. The detailed tables for the assessment of scientific evidence are available in this report's supplementary appendices document.

Single-dose Doxycycline

Adults and children ≥ 12

Statement of evidence: According to the results of a single study, a single 200 mg dose of doxycycline administered within 72 hours of removing a tick identified as *Ixodes scapularis* reduces the absolute risk of developing erythema migrans at the site of the bite by 2.8% (CI 95%: -11.7, 6.1, P = 0.061 4) in adults and children age 12 and up, when the baseline risk of developing erythema migrans at the site of the bite is approximately 3.2% and the *B. burgdorferi* infestation rate for ticks is high (> 25%). The follow-up period for the study, which was limited to 6 weeks, was not sufficient to evaluate the efficacy of this treatment in preventing the appearance of other manifestations of Lyme disease. Though the tick (*I. scapularis)* and bacteria responsible for Lyme disease (*B. burgdorferi* sensu stricto) in Quebec are the same as those in the Nadelman trial, there is some doubt as to the generalizability of the results of this trial when the tick species, tick life stage and level of tick

engorgement cannot be reliably identified and when the tick infestation rate and baseline risk of developing erythema migrans are lower than those observed in this trial.

Level of evidence: Low for the outcome of erythema migrans at the site of the bite; insufficient for other manifestations of Lyme disease

Children < 12, pregnant or breastfeeding women

Statement of evidence: No data available in the literature reviewed

Level of evidence: Insufficient

Amoxicillin, Penicillin and Tetracycline

Adults and children (≥ 1 year for amoxicillin, ≥ 5 years for penicillin, and ≥ 9 years for tetracycline)

Statement of evidence: The data available do not allow for the assessment of the efficacy of 250 mg of amoxicillin TID, 250 mg of penicillin QID or 250 mg of tetracycline TID, administered for 10 days to prevent Lyme disease. In the three available RCTs, no statistically significant difference was observed between the groups in terms of the development of erythema migrans or extracutaneous symptoms of Lyme disease after 6 to 12 months. The number of participants and of events was too low to reveal statistically significant differences. In addition, these studies have limitations that compromise the validity of the results.

Level of evidence: Insufficient

Pregnant or breastfeeding women, children (≤ 1 year for amoxicillin, ≤ 5 years for penicillin, and ≤ 9 years for tetracycline)

Statement of evidence: No data available in the reviewed literature

Level of evidence: Insufficient

2.1.1.6 Contextual data

No contextual data were collected on the efficacy of antibiotics studied for Lyme disease PEP.

2.1.1.7 Experiential data

The majority of the advisory committee members were familiar with the Nadelman study, but the reanalysis of the data from INESSS brought to their attention the low level of evidence for the scientific data that serve as the basis for the recommendation of single-dose doxycycline PEP. The results were seen as disappointing when expressed in terms of ARR because they reveal that: 1) doxycycline only caused a 2.8% absolute reduction in the baseline risk for erythema migrans at the site of the bite, which is already low (3.2%), and 2) there is a high degree of uncertainty about the results, given the breadth of the confidence interval. The advisory committee members were asked to comment on the level of evidence for the results of the Nadelman study on the primary study outcome. A majority of members stated that the level of evidence was low, while one in three found it to be insufficient.

The generalizability of the results of the Nadelman study to the Quebec context was broadly discussed by the advisory committee. According to some members, in areas such as Granby and Cowansville, where roughly 90% of the ticks analyzed are *Ixodes scapularis* and the tick infestation rate is between 25% and 40%, it is likely that, for single-dose doxycycline, the NNT to

prevent one case of erythema migrans would be similar to that observed in the Nadelman study. As for the other areas eligible for PEP, some committee members expressed doubt that the tick infestation rate and proportion of *Ixodes scapularis* to other tick species would be as high as those in Granby and Cowansville. In these areas, given that ticks are not identified before PEP is prescribed, the NNT may be higher than that for the Nadelman study.

Of the eight patients consulted, only one had received PEP and, in their opinion, it had not been effective, as erythema migrans developed 18 days later. This patient did not receive PEP after sustaining a subsequent tick bite.

2.1.2. Results for question 2: Safety of the studied PEP antibiotics

Question 2: Safety of the studied PEP antibiotics
What are the adverse effects associated with the studied PEP antibiotics used for Lyme disease caused by *Borrelia burgdorferi* sensu stricto in adults or children bitten by the tick *Ixodes scapularis* in a geographic area at high risk for Lyme disease, as compared to a placebo, no treatment or another antibiotic?

2.1.1.8 Description of publications

The search for scientific information did not reveal any additional relevant documents to the four RCTs described above [Nadelman et al., 2001; Agre and Schwartz, 1993; Shapiro et al., 1992; Costello et al., 1989] that would help answer question 2.

2.1.1.9 Results from the randomized controlled trials on post-exposure prophylaxis for Lyme disease

In the Costello study [1989] and the Shapiro study [1992], the adverse effects reported are maculopapular skin rashes: 1 case with penicillin (3.7%) and 2 cases with amoxicillin (1%) were observed respectively in these two studies. In the Agre and Schwartz study [1993], no adverse effects attributable to penicillin were observed.

In the Nadelman study [2001] on the use of a single 200 mg dose of doxycycline, adverse effects related to treatment were more frequent in the doxycycline group than in the placebo group (30.1% vs. 11.1%, $P < 0.001$). The events observed were primarily nausea (15.4% vs. 2.6%, $P < 0.001$) and vomiting (5.8% vs. 1.3%, $P = 0.06$). According to the authors, taking doxycycline with food improved tolerance of the antibiotic with only a minimal decrease in the peak serum concentration. The extraction tables for all of the results on the safety of antibiotics studies for Lyme disease PEP are presented in this report's supplementary appendices document.

2.1.1.10 Statement of scientific evidence and level of scientific evidence for the safety of doxycycline for Lyme disease PEP

The assessment of scientific evidence for the safety of antibiotics studied for Lyme disease PEP was done only for doxycycline, the only antibiotic whose use is recommended in Quebec for this indication and for which the level of scientific evidence for efficacy was not deemed insufficient by a majority of the advisory committee members.

Doxycycline

Adults and children ≥ 12

Statement of evidence: According to the results of one study with a 6-week follow-up period, a single 200 mg dose of doxycycline administered within 72 hours of removing an *Ixodes scapularis* tick is not associated with severe adverse effects, but may lead to gastrointestinal adverse effects in close to one third of adults and children ages 12 and up (primarily nausea and vomiting).

Level of evidence: Low

Children < 12, pregnant or breastfeeding women

Statement of evidence: No data available in the reviewed literature

Level of evidence: Insufficient

2.1.1.11 Contextual data

No contextual data were collected on the safety of antibiotics studied for Lyme disease PEP.

2.1.1.12 Experiential data

The advisory committee members did not bring up any particular issues related to the safety single-dose doxycycline in adults and children over 8 years of age. They did, however, discuss the safety of this treatment in children under 8 years of age and in pregnant women. This information is detailed in the following section.

2.1.3. Results for question 3: Safety of doxycycline in children and pregnant or breastfeeding women

Question 3: Safety of doxycycline in children and pregnant or breastfeeding women
What are the adverse effects associated with the use of oral doxycycline (for any indication) in children exposed in utero, during breastfeeding or before the age of 8, as compared to a placebo, no treatment or another antibiotic?

2.1.3.1. Description of publications

The search for scientific information revealed 440 references (not including duplicates) that relate to research question 3 (see the flowchart in this report's supplementary appendices document). Of these references, the following were retained:

- Two systematic literature reviews, one by Cross [2016] on the use of doxycycline during pregnancy and in young children, and one by Meaney-Delman [2013] on the safety of antibiotics (including doxycycline) recommended for post-exposure prophylaxis and treatment of anthrax in pregnant women.
- Six primary studies that examined the possible occurrence of tooth staining and other dental effects after exposure to doxycycline in children under 8 years of age[19] [Pöyhönen et al., 2017; Todd et al., 2015; Volovitz et al., 2007; Lochary et al., 1998; Poloczek, 1975; Forti and Benincori, 1969].
- Six primary studies on doxycycline exposure during pregnancy, five of which examined the possible occurrence of congenital malformations [Muanda et al., 2017a; Cooper et al.,

[19] The Poloczek study included children exposed from the age of 1 month to 12 years, but the study was still included, as the average age was 29 months.

2009; Kazy et al., 2007; Czeizel and Rockenbauer, 1997; Horne and Kundsin, 1980] and one of which examined the risk of spontaneous abortion [Muanda et al., 2017b].

2.1.3.2. Problems associated with the use of doxycycline during pregnancy, while breastfeeding or in children before the age of 8

Doxycycline is an antibiotic in the tetracycline medication class. In the 1950s, tetracycline was the first antibiotic in this class to be commercialized. In the early 1960s, cases of permanent tooth staining and dental enamel hypoplasia were reported in children exposed to this drug. Because of these adverse effects, the use of all antibiotics in the tetracycline class—including doxycycline, which was developed later—was discouraged during tooth formation.

The at-risk period includes the prenatal period of the second and third trimesters of pregnancy and the post-natal period extending to the age of 8. According to the information reported by Cross [2016], calcification begins around the twelfth week of fetal life for deciduous teeth and between three and four months after birth for permanent teeth.[20] This means that in utero exposure to tetracyclines is likely to cause staining in only the deciduous teeth. Post-natal exposure to tetracyclines between the ages of 3 months and 8 years could lead to permanent staining of the permanent teeth, depending on the dose and length of exposure. After the age of 8, the crowns of the teeth are calcified, and permanent tooth staining attributable to tetracyclines is no longer observed.

The phenomenon of tooth staining is related to the fact that tetracyclines form a complex with calcium (orthophosphate) that is incorporated into calcifying tissues. Tetracyclines incorporated into the bones are released during the normal process of bone resorption, but they remain in the dental enamel and dentine if these tissues were in the process of calcifying at the time of exposure. This results in permanent staining of permanent teeth [Cross et al., 2016]. It should be noted that doxycycline has a lower affinity for calcium than tetracycline [Gaillard et al., 2017], and as such, it is less likely than tetracycline to cause tooth staining or enamel hypoplasia.

Beyond tooth staining, concerns were also raised about the risk of delayed skeletal maturation. In one study [Cohlan et al., 1963], tetracycline was associated with an inhibition of skeletal growth of the fibula in children born prematurely who received oral doses of 25 mg/kg every 6 hours during one or three periods of 9 to 12 days each. This effect was reversible after treatment was discontinued, with a rapid compensation in bone growth. No such cases were reported with doxycycline, and no published data have shown permanent skeletal structural abnormalities related to exposure to tetracyclines in humans [Cross et al., 2016].

2.1.3.3. Use of doxycycline in children under 8 years of age

2.1.3.3.1 Recommendations for use sourced from monographs, specialized works and grey literature

Monographs for doxycycline state that the administration of this antibiotic to children under the age of 8 is not recommended given that its safety for these patients has not been proven. The specialized work by Taketomo [2014] on the use of medication in pediatrics also recommends against administering doxycycline to this population, but it lists several exceptions based on recommendations from the Centers for Disease Control and Prevention (CDC).

The search of grey literature revealed that the CDC recommends the use of doxycycline given orally to young children for a number of infectious diseases: anthrax, Q fever, plague, tularemia, typhus (scrub, murin, and exanthematic) and rickettsial diseases transmitted by ticks (Rocky Mountain spotted fever and other fevers in the boutonneuse group, ehrlichiosis and

[20] Muthu and Sivakumar, 2009; Lunt and Law, 1974; Kraus, 1959; Logan and Kronfeld, 1933, all cited by Cross et al., 2016, p. 373.

anaplasmosis). The duration of treatment recommended by the CDC ranges, depending on the disease, from 5 to 60 days for post-exposure prophylaxis for anthrax, and the most frequently recommended dosage is 2.2 mg/kg per dose (maximum of 100 mg per dose) twice daily.

In the 2018 edition of the *Red Book*, the American Academy of Pediatrics (AAP) liberalized its recommendations for the use of doxycycline in children of all ages for short durations (up to 21 days depending on the condition). The AAP justifies the revised recommendation by stating that "recent comparative data in younger children suggest that doxycycline is not likely to cause visible teeth staining or enamel hypoplasia in children younger than 8 years." The recommendation on the use of doxycycline in children under 8 includes the indication for PEP in high-risk areas for contracting Lyme disease (30% to 50% of ticks infested), via a single 200 mg dose, or a dose of 4.4 mg/kg for a body weight under 45 kg, when multiple criteria are met (bite from *Ixodes scapularis*, tick attached for 36 hours or more and 72 hours elapsed since tick removal) [Kimberlin et al., 2018]. It should be noted that the 2018 *Red Book* does not provide any references for the recent comparative data on young children to which it refers.

2.1.3.3.2 Results from primary studies on the dental effects of doxycycline

The six primary studies that examined the dental effects of doxycycline in children exposed to the drug before the age of 8 were published between 1967 and 2017 and were conducted in the following countries: the United States, Italy, Germany, Finland, and Israel.[21] In these studies, information related to the exposure of children to doxycycline (and other tetracyclines, as the case may be) were researched retrospectively, and a cross-sectional dental assessment was completed on average 1 year to 9.5 years after exposure, depending on the study. Four of the six studies assessed the effects of doxycycline on permanent teeth, but two assessed these effects primarily on deciduous teeth [Poloczek, 1975; Forti and Benincori, 1969].

None of the six selected studies had a design that was considered strong,[22] as no randomized controlled trials or meta-analyses were identified. However, three of the six studies are analytical studies (exposed/unexposed cohort studies) considered moderate in design strength [Todd et al., 2015; Volovitz et al., 2007; Lochary et al., 1998]. The three other studies are descriptive studies with a cross-sectional evaluation and no control group [Pöyhönen et al., 2017; Poloczek, 1975; Forti and Benincori, 1969]. This type of design is considered weak.

The primary characteristics of these studies, their methodological quality and the primary results are presented in Table 6. The completed extraction tables are available in this report's supplementary appendices document.

Results from analytical studies

Of the three exposed/unexposed cohort studies, the largest study, and that with the highest methodological quality, is the study by Todd et al. [2015]. This study examined 271 children ages 8 to 16 living on an American Indian reservation with a high incidence of Rocky Mountain spotted fever. These children were assigned to groups based on whether they had been exposed to doxycycline before the age of 8, as documented by medical and pharmacy records. None of the study participants had been exposed to another antibiotic in the tetracycline class. In the end, 58 children who had received doxycycline before the age of 8 were compared to 213 unexposed children. Doxycycline had been administered twice daily at an average dose of 2.3 mg/kg (0.3 to 2.9) and for an average treatment duration of 7.3 days (1 to 10). The children had received an average of 1.8 treatments of doxycycline, which brings the total length of exposure to 13 days on average. A dental examination of the children was conducted by five dentists, blinded to the

[21] Note that the Poloczek study [1975] included children exposed to doxycycline between the ages of 1 month and 12 years.

[22] Based on the design strength assessment grid created by the Public Health Agency of Canada.

exposure status of participants and trained to recognize typical signs of tooth staining caused by tetracyclines. Tooth shade was measured through spectrophotometry, and could vary between 1 (lightest) to 16 (darkest). The average age of exposure to doxycycline was 4.5 years (0.2 to 7.9). At the time of the dental exam, the children in the group exposed to doxycycline were younger (9.8 years ± 1.7) than the children in the unexposed group (11.8 years ± 2.2) by a statistically significant margin ($P < 0.001$). Oral hygiene practices, consumption of coloured drinks and tobacco use were comparable between the two groups both before and after adjusting the results to control for age at the time of the dental exam. Tooth staining consistent with that seen with tetracycline was not observed in any of the study participants. The age-adjusted analyses did not show a significant difference between the children exposed to doxycycline and the unexposed children when it came to tooth shade, occurrence of dental enamel hypoplasia or fluorosis. It should be noted that the number of participants included was sufficient to demonstrate a difference in the average shade of teeth of 1.0 shade (on a scale of 1 to 16) with a power of 80% or an average difference of 1.3 for a power of 95%. Thus, with an average measured tooth shade of 9.5 (± 2.5) in the group exposed to doxycycline and 9.0 (± 2.3) in the unexposed group, the difference was not statistically significant, and the power of the study was sufficient to conclude that there is no difference. This study does have certain limitations, in particular the fact that the actual level of compliance with the doxycycline dosage regimen is not known, as it is in all the studies completed based on information from databases. In addition, the inter-rater variability for the visual dental examination and the use of a spectrophotometer was not studied.

The second exposed/unexposed cohort study, of moderate quality, was carried out by Volovitz et al. [2007]. It included 61 children ages 8 to 16, of whom 31 had been treated with doxycycline before the age of 8 for atypical therapy-resistant asthma and 30 of whom had not been treated with doxycycline for asthma of the same severity. Doxycycline had been administered at a dose of 4 mg/kg BID on the first day, followed by a single daily dose of 2 mg/kg for 9 days. The children who had not completed all 10 days of treatment were excluded from the analysis. The participants had received an average of two doxycycline treatments, which brings the total length of exposure to 20 days on average. For 55 of the children, the dental examination was completed by one dentist, blinded to exposure status. The remaining six children in the group exposed to doxycycline were examined by their own dentist. Tooth shade was assessed using the Lumin Vacuum shade guide with 16 shades ranging from brightest (white) to darkest (grey). The children's average age at the time of exposure to doxycycline was 4.1 years (2 to 7.7), whereas their average age at the time of the dental examination was 10.4 years (8 to 16). The two groups were comparable in terms of age at the time of the dental examination, age when the asthma began, oral hygiene practices, a history of neonatal jaundice, previous trauma to the teeth, and excessive drinking of coloured beverages. No visible tooth staining was observed in the exposed group or the unexposed group. In addition, no statistically significant difference was observed between the two groups in terms of proportion of children with bright teeth, and no dark teeth were observed. This study has several limitations, notably that the number of participants included is limited, and no calculation of power is available. No information is given about the possible administration of other antibiotics in the tetracycline class. In addition, the tooth shade results are given only for 25 of the 31 participants exposed to doxycycline—the missing data concerning, in theory, the children examined by their own dentist.

The third exposed/unexposed cohort study, of low quality, was conducted by Lochary et al. [1998]. It included 30 children who had been diagnosed with Rocky Mountain spotted fever, of whom 10 were treated with doxycycline. Each of the 10 children was paired with two control subjects who were not treated with doxycycline. Pairing was done based on exposure to fluoride, chronological age, and the level of dental development. Note that exposure to other tetracyclines was an exclusion criterion in both groups, as was the presence of braces, a history of trauma or the presence of dental restoration material on the tooth under evaluation and the

presence of clinically apparent dental fluorosis. Doxycycline had been administered at a dosage of 30 to 200 mg per day for a duration of 2 to 10 days, but the authors do not specify the average dosage in relation to body weight. Tooth staining was assessed, based on photos, by five dentistry residents independent from one another and blinded to exposure to doxycycline. At the time of exposure to doxycycline, the children had an average age of 5.1 years (4 to 8), whereas at the time of the dental examination, they had a mean age of 13.7 years (11 to 19). The study authors report that the results analysis completed using the median values from the shade score does not reveal a significant difference between the exposed group and the unexposed group in terms of incidence or degree of tooth staining. This study has several limitations, in particular the fact that the number of participants included is limited, and no calculation of power is available. Tooth staining was assessed based on photos rather than on direct clinical observation. In addition, the ordinal scale used (ranging from 0 to 3) does not allow for a precise measurement of the degree of tooth staining. In addition, inter-rater variability was examined, but it appears that the staining score assigned by the five raters was the same for only 11% of the teeth rated. Lastly, the actual compliance with the doxycycline dosage regimen is unknown.

Table 6. Summary of characteristics and results of studies on the dental effects of doxycycline in children exposed before the age of 8

Author (year) Research design	Total no. of pts studied No. of pts exposed to doxycycline	Average age (range): - exposure to doxycycline - dental examination	Doxycycline treatment: - average dose (range) - average duration (range) - no. of treatments/patient	Results	Quality of study
Effects on permanent teeth					
Analytical studies with control group					
Lochary [1998] Exposed/unexposed cohort	N total = 30 N doxy = 10	- 5.1 yrs (4 to 8) - 13.7 yrs (11 to 19)	- 30 to 200 mg/day - 6.2 days (2 to 10)[23] - not avail.	No significant difference between groups in terms of the incidence or degree of staining of permanent teeth.	Low
Todd [2015] Exposed/unexposed cohort	N total = 271 N doxy = 58	- 4.5 yrs (0.2 to 7.9) - 9.8 yrs (8.1 to 15.6)	- 2.3 mg/kg/dose (0.3 to 2.9) BID - 7.3 days (1 to 10) - 1.8 treatments/patient	No visible staining of permanent teeth observed. No significant difference between groups in terms of tooth shade or occurrence of dental enamel hypoplasia or fluorosis	High
Volovitz [2007] Exposed/unexposed cohort	N total = 61 N doxy = 31	- 4.1 yrs (2 to 7.7) - 10.4 yrs (8 to 16)	- 4 mg/kg BID first day followed by 2 mg/kg/day for 9 days (N/A) - 10 days (N/A) - 2 treatments/patient	No visible staining of permanent teeth observed. No significant difference between groups in terms of proportion of participants with light teeth. No dark teeth observed.	Moderate
Descriptive study with no control group					
Pöyhönen [2017] Case series	N total = 38 N doxy = 38	- 4.7 yrs (0.6 to 7.9) - 14.2 yrs (8.3 to 22.6)	- 10 mg/kg/day (8 to 10) for 2 to 3 days, then 5 mg/kg/day (2.5 to 10) - 12.5 days (2 to 28) - 1 treatment/patient (except 1 patient who had 2 treatments)	No visible staining of permanent teeth or dental enamel hypoplasia observed.	Moderate
Effects on deciduous teeth					
Descriptive studies with no control group					
Forti and Benincori [1969] Case series	N total = 25 N doxy = 25	- 4 to 55 days of life (children born prematurely) – approx. 1 yr[24] (not avail.)	- 2 mg/kg/day 1st day, then 1 mg/kg/day - not avail. (6 to 17) - not avail.	1 case (4%) of slight mottled staining on the upper incisors, associated with low fluorescence under a black light	Low
Poloczek [1975] Case series	N = 282 N doxy = 282	- 2.4 yrs (1 month to 12 yrs) - approx. 3.4 yrs[25] (not avail.)	- 4 mg /kg 1st day, then 2 mg/kg the following days - not avail. (5 to 8) - repetition of treatment for 41 patients	3 cases (1.1%) of staining and hypoplasia related to doxycycline.	Low

Legend: no.: number, pts = patients, not avail.: not available, N/A: not applicable, yr: year

[23] Average calculated from raw data presented in the publication [Lochary et al., 1998].

[24] Age not noted by the authors, but calculated based on the fact that the dental examination was completed one year after the treatment.

Results from descriptive studies:

In the Pöyhönen study [2017], of moderate quality, no visible tooth staining or dental enamel hypoplasia was observed after an average follow-up period of 9.6 years in 38 children exposed to oral or intravenous doxycycline before the age of 8 to treat a suspected infection of the central nervous system. In this study, the dosages of doxycycline were relatively high, as a loading dose of 10 mg/kg (8 to 10) per day was administered for two to three days, followed by an average dose of 5 mg/kg per day (2.5 to 10), for an average total treatment duration of 12.5 days (2 to 28).

Lastly, the only two studies in which dental effects were observed after exposure to doxycycline are the studies of the lowest quality. In the Forti and Benincori study [1969], of 25 children born prematurely and treated with doxycycline between the ages of 4 days and 55 days, one single child developed slight mottled discoloration on the upper incisors associated with low fluorescence under a black light, observed one year after treatment. In the Poloczeck study [1975], of 282 children exposed to doxycycline at an average age of 29 months (1 month to 12 years) to treat various infections, dental discoloration was observed one year after treatment in 5 of the participants (1.8%). However, in only 3 of the participants (1.1%) were the effects (discoloration observed by fluorescence and hypoplasia) considered by the authors to be related to doxycycline. In both of these studies, the effects were observed in deciduous teeth, as the children were assessed at an average age of 1 year and 3.4 years. Yet, it cannot be assumed that staining observed in deciduous teeth would necessarily correlate to staining in the corresponding permanent teeth. The two studies had the same limitation: a follow-up period too short (1 year) to assess the effects of doxycycline on permanent teeth and on all teeth in process of calcifying at the moment of exposure.

2.1.3.3.3 Results from the Cross systematic review (2016)

The systematic review by Cross et al. [2016] was deemed by INESSS as moderate quality based on the R-AMSTAR grid (for details on the characteristics of this review, see this report's supplementary appendices document). This review included the three main studies on tooth staining in children following exposure to doxycycline—by Todd [2015], Volovitz [2007] and Lochary [1998]—but it did not include two of the three descriptive studies, as one [Poloczek, 1975] was published in German, and the other [Pöyhönen et al., 2017] was published after Cross's systematic review.

According to the authors, the data collected in this systematic review suggest that doxycycline is not associated with permanent tooth staining when used in pregnant women or in children under 8 years of age, nor is it associated with a permanent inhibiting effect on bone growth. They state that based on the available data, the risk of adverse effects associated with teeth and bones is negligible, though no quality data is available on this subject. The authors conclude that the use of doxycycline should be considered when the risk of rare and non-severe adverse effects is outweighed by the risk of complications related to an infection.

2.1.3.3.4 Statement of scientific evidence and level of scientific evidence for the safety of doxycycline in children under 8 years of age

Doxycycline

Children < 8 years

– Onset of staining in permanent teeth

Statement of evidence: According to the results of three studies that included a total of 370 children, of whom 127 were exposed to doxycycline before the age of 8 at average doses of 2 to 10 mg/kg/day for

average total durations of 12.5 to 20 days, and for indications other than Lyme disease PEP, doxycycline does not cause staining of permanent teeth.

Level of evidence: Low

– Changes in the shade of permanent teeth

Statement of evidence: According to the results of three studies that included a total of 362 children, of whom 99 were exposed to doxycycline before the age of 8 at average doses of 2 to 8 mg/kg/day for average total durations of 6.2 to 20 days, and for indications other than Lyme disease PEP, doxycycline does not cause visible changes in the shade of permanent teeth compared to children not exposed to this antibiotic.

Level of evidence: Low

– Enamel hypoplasia of permanent teeth

Statement of evidence: The results of a single study that included 271 children, of whom 58 were exposed to doxycycline before the age of 8 at an average dose of 4.6 mg/kg/day for an average total duration of 13 days did not show a statistically significant difference in the risk of dental enamel hypoplasia in permanent teeth compared to children not exposed to this antibiotic. These data are, however, insufficient to draw conclusions regarding this outcome.

Level of evidence: Insufficient

2.1.3.4. Use of doxycycline during pregnancy

2.1.3.4.1. Recommendations for use sourced from monographs, specialized works and specialized databases

According to Ferreira et al. [2013], exposure to a tetracycline in the first trimester does not require any particular obstetric care, but tetracyclines should be particularly avoided from the gestational age of 16 weeks due to a risk of tooth staining in children exposed in utero beginning at this time. Consistent with Ferreira's recommendations, Briggs et al. [2017] and the e-CPS [CPhA, 2016] note that the use of tetracyclines is contraindicated during the second and third trimesters of pregnancy. On the risk of congenital malformations, Taketomo et al. [2014], like TERIS, concludes that it is unlikely that therapeutic doses of doxycycline during pregnancy pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk. REPROTOX similarly concludes that based on experimental studies on animals and data on humans, there is no expected increase in the risk of congenital malformations with doxycycline (refer to the full extraction table in this report's supplementary appendices document). Note that none of these specialized works or specialized databases refer to the two studies by Muanda et al. [2017a; 2017b], described below.

2.1.3.4.2. Results from primary studies

Of the six primary studies that examined the adverse effects of doxycycline following fetal exposure, four concern the risk of congenital malformations [Muanda et al., 2017a; Cooper et al., 2009; Czeizel and Rockenbauer, 1997; Horne and Kundsin, 1980], one examines the outcomes of weight and age of children at the time of birth [Kazy et al., 2007], and one examines the risk of spontaneous abortion [Muanda et al., 2017b]. These studied were published between 1980 and 2017 and were carried out in Canada, the United States and Hungary. No studies on dental or skeletal effects following in utero exposure to doxycycline were identified.

None of the six studies identified had a research design considered to be strong.[25] However, five are analytical studies with a design judged as moderate in strength, as they are exposed/unexposed cohort studies or case-control studies. Of these, the Kazy study [2007] was published in a letter to the editor and contains few details on methodology, statistical analyses and results. Its methodological quality was not assessed and the results are presented for reference only. The methodological quality of the other four studies with moderate design strength was evaluated using the critical appraisal tool for analytical studies designed by the Public Health Agency of Canada. It revealed that the study with the highest methodological quality is the Cooper study [2009] (high quality), follow by the two Muanda studies [2017a; 2017b] and the Czeizel and Rockenbauer study [1997] (moderate quality for all three). The sixth study is part of a case series. Its methodological quality was not assessed, and its results are presented for reference only.

The extraction tables of the characteristics and results of these studies are available in this report's supplementary appendices document.

Results on the risk of congenital malformations:

The three main studies on the risk of malformations linked to fetal exposure to doxycycline are the two cohort studies by Cooper [2009] and Muanda [2017a] and the case-control study by Czeizel and Rockenbauer [1997].

The study with the highest number of children exposed in utero to doxycycline is Cooper et al. [2009], which included 30,049 children covered by Tennessee's Medicaid program and born between 1985 and 2000. Children exposed in utero to medications known to be teratogenic and children with diabetic mothers were excluded. Of the participants, 24,521 had been exposed in utero to an antibiotic likely to be used in the event of a bioterrorism attack (ciprofloxacin, azithromycin, doxycycline or amoxicillin), 2,128 had been exposed in utero to erythromycin (including as positive controls) and 3,400 had not had fetal exposure to antibiotics. Of the children exposed to an antibiotic in utero, 1,843 had been exposed to doxycycline only (that is, no fetal exposure to another antibiotic). Doxycycline had been administered to the mother during pregnancy at an average dose of 194 mg/day for an average duration of 9.6 days. The results for the adjusted[26] hazard ratio (HR) did not show a rise in the overall risk of major congenital malformations (of any type) in children exposed in utero to doxycycline during the first four lunar months of pregnancy versus children with no fetal exposure to antibiotics (adjusted HR = 0.85 [CI 95%: 0.59, 1.23]). Similar results were found for fetal exposure to doxycycline at any point during pregnancy (adjusted HR = 0.84 [IC 95%: 0.59, 1.19]). Note that according to the authors, the power of this study was sufficient to detect a twofold increase in the risk of malformations of any type. In addition, no increase was observed in the risk of developing specific malformations of the following types: cardiovascular, genitourinary, central nervous system, gastrointestinal, and musculoskeletal. A nearly threefold increase in the risk of orofacial anomalies was observed with doxycycline, but the difference compared to the unexposed group was not statistically significant. The result for the risk of increased orofacial anomalies is imprecise, as the 95% confidence interval is broad considering the small number of reported events (5/1,691 in the group exposed during the first four lunar months, 4/3,400 in the unexposed group, adjusted hazard ratio = 2.96 [CI 95%: 0.75, 11.67]). Note that the power of the subgroup

[25] Based on the design strength assessment grid created by the Public Health Agency of Canada.
[26] Adjusted to account for the following potentially confounding variables: year of birth, maternal age, race, residence in a rural area, income quartile, chronic maternal diseases (hypertension, epilepsy, sickle-cell anemia, asthma, kidney disease, neoplastic disease, cardiovascular disease other than hypertension and diabetes, HIV infection, cystic fibrosis, autoimmune diseases, chronic mental illness, obesity, migraine, Crohn's disease, organ transplant, ulcerative colitis), and birth in a hospital with a level III neonatal intensive care unit.

analyses, such as the analysis of orofacial malformations, was potentially insufficient to show statistically significant differences between the groups. One of the limitations of this study, and of all the studies based on databases, is the fact that it is impossible to know whether the doxycycline prescribed was actually taken by the mother. Some potentially confounding factors, such as alcohol consumption, folic acid intake, exposure to teratogenic chemicals and the indication for the use of doxycycline, were not taken into account. In addition, multiple pregnancies were not excluded, even though according to Muanda, they are a known risk factor for major congenital malformations. The generalizability of the results to the general Quebec population is questionable in that the study looked at people enrolled in Medicaid, and of the mothers to whom doxycycline was prescribed during pregnancy, 63% were black and 25% were smokers, with an average age at birth of 22.6 years.

The Czeizel and Rockenbauer study [1997] is a case-control study completed based on data from the Hungarian Case-Control Surveillance of Congenital Abnormalities (1980–1992). This study included 32,804 children born with no congenital malformations, of whom 63 (0.19%) had been exposed in utero to doxycycline, and 18,515 children with congenital malformations, of whom 56 (0.30%) had been exposed in utero to doxycycline. The cases and controls were paired based on sex, week of birth and parents' area of residence. In the majority of cases, doxycycline had been administered to the mother during pregnancy at a 100 mg dose twice daily on the first day, then at 100 mg per day the following days, for a total duration of 6 to 14 days. The conditional logistic regression analysis for paired cases, adjusted for the age of the mother and use of other medications, revealed a statistically significant increase in the risk of congenital malformations (of any type) when exposure to doxycycline at any point during pregnancy was considered ($p = 0.03$). However, this result is not statistically significant when considering only exposures that occurred during the second or third month of pregnancy ($p = 0.22$). The authors also completed subgroup analyses by type of malformation. No statistically significant result was observed. Still, no conclusions can be drawn from these analyses, as the confidence intervals are very broad considering the very low (even nonexistent) number of events observed. This study has several limitations; in particular, the data on exposure to medications was obtained primarily through a questionnaire completed by mothers, which means that the possibility of information bias cannot be excluded; in addition, the response rate for the questionnaire was lower in the control group than in the case group (67% vs. 81%). The odds ratios calculated using McNemar's test for paired data were not adjusted for potentially confounding factors such as the age of the mother or intake of other medications. Moreover, certain potentially confounding factors such as alcohol consumption, tobacco use and the indication for the use of doxycycline were not considered in any of the analyses. Multiple pregnancies were also not excluded. Note that the intake of medications known to be teratogenic was not an exclusion criterion for the study, though of the main medications consumed by study participants during pregnancy that are listed by the authors, none are known to be teratogenic.

A third large-scale study was recently published on the risk of congenital malformations following fetal exposure to antibiotics. This study was conducted by Muanda et al. [2017a] on a cohort of pregnancies in Quebec that included only pregnant women covered by Quebec's public prescription drug insurance plan (RPAM) between 1998 and 2009. Four databases accessible via a single identification code were used as the data sources for the Muanda study: RAMQ (diagnosis, medical interventions, socioeconomic status of the women and the prescribers), the RPAM database (medication names, start date, dose and duration), MED-ECHO for hospitalization data (diagnosis related to hospitalization, interventions, gestational age), and the database of statistics on Quebec (sociodemographic data on patients and birth weight). The Muanda study excluded multiple pregnancies, pregnancies exposed to medications known to be teratogenic during the first trimester, pregnancies with chromosomal

abnormalities or minor malformations, as well as pregnancies exposed to more than one antibiotic or other anti-infective during the first trimester. Exposure to antibiotics during the first trimester of pregnancy only was considered during this study. In total, 15,469 pregnancies exposed to an antibiotic, of which 164 were exposed to doxycycline, were included in the analysis, as were 124,469 pregnancies that were not exposed to antibiotics. In this study, in utero exposure to doxycycline during the first trimester of pregnancy was associated with a statistically significant increase in the risk of circulatory system defects (adjusted[27] OR = 2.38 [CI 95%: 1.21, 4.67]), heart defects (adjusted[29] OR = 2.46 [CI 95: 1.21, 4.99]) and septal defects (adjusted[29] OR = 3.19 [CI 95%: 1.57, 6.48]). No statistically significant increase in the risk of other organ defects of any kind or in the risk of other major congenital malformations of any kind was observed. This study has several limitations, including a lack of information on the dose and duration of the doxycycline treatment. In addition, certain potentially confounding factors such as alcohol consumption, tobacco use, folic acid intake and exposure to teratogenic chemicals could not be taken into account. Moreover, as with all the studies done based on databases, it is impossible to know whether the doxycycline prescribed was taken by the mother. Given that multiple comparisons were done, it is not possible to exclude the possibility that certain results were produced by chance. Lastly, the results may not be generalizable to women with private prescription drug insurance of a higher socioeconomic status than the women covered by the public prescription drug insurance plan.

Lastly, in one case series [Horne and Kundsin, 1980] that looked at 43 children exposed in utero to doxycycline for 10 days (dosage varied from 100 to 300 mg/day depending on the weight of the mother), no congenital malformations were reported by the mothers one year after birth.

Results on the risk of spontaneous abortion

Muanda et al. published a second study on the cohort of pregnancies in Quebec (1998–2009) with the goal of quantifying the association between exposure to antibiotics during pregnancy and the risk of spontaneous abortion. In this study, each case of pregnancy that ended in spontaneous abortion before the 20th week was paired with 10 controls based on gestational age and year of the pregnancy. Pregnancies exposed to a medication known to be teratogenic and pregnancies terminated through a planned abortion were excluded. Exposure to antibiotics was defined as at least one prescription for antibiotics issued between the first day of the pregnancy and the date of the spontaneous abortion, or a prescription for antibiotics begun before pregnancy, but that continued past the first day of pregnancy. The study included 8,702 pregnancies that ended in spontaneous abortion before the 20th week of pregnancy, of which 36 had been exposed to doxycycline. The control group included 87,020 pregnancies. Overall, in this study, exposure to doxycycline was associated with a statistically significant increase in the risk of spontaneous abortion before the 20th week of pregnancy (adjusted OR = 2.81 [CI 95%: 1.93, 4.10]). This study has the same limitations as the aforementioned study by Muanda et al.: the average dose and duration of doxycycline treatment are not given; certain potentially confounding factors such as alcohol consumption, tobacco use, folic acid intake and exposure to teratogenic chemicals could not be taken into account; it is impossible to know whether the prescribed treatment was actually taken; and the results may not be generalizable to women with private prescription drug insurance.

[27] The odds ratios were adjusted to account for maternal age on the first day of gestation, the marital status of the woman, reception of social assistance during pregnancy, the calendar year of the birth, the sex of the child, level of education (≤ 12 years or > 12 years), place of residence on the first day of gestation (rural or urban), the presence of chronic maternal comorbidities, endometriosis or a maternal infection, and the use of health services the year preceding the pregnancy.

Results on weight and age at birth

The Kazy study [2007] was published in a letter to the editor in which few details are given as to the methodology, statistical analyses completed and the results. Thus, the results of this study are given for reference only. Like the Czeizel and Rockenbauer study [1997], this study was done based on data from the Hungarian Case-Control Surveillance of Congenital Abnormalities (1980–1996). It included 38,151 children with no congenital abnormalities, of whom 78 had been exposed in utero to doxycycline and 38,073 had not been exposed in utero to the same antibiotic. Doxycycline had been administered at a dose of 200 mg the first day, then at 100 mg the following days for a total duration of 6 days. In this study, no statistically significant difference was observed between children exposed in utero to doxycycline and unexposed children in terms of gestational age and average weight at birth, the rate of premature births or the rate of children with a low birth weight.

2.1.3.4.3. Results on published systematic reviews

The systematic review by Meaney-Delman [2013] on the safety of antibiotics recommended for anthrax treatment and post-exposure prophylaxis in pregnant women was assessed as moderate in quality by INESSS based on the R-AMSTAR grid. All the studies described above were included in this systematic review, with the exception of the two studies by Muanda et al., as these were published after the review. The authors conclude that doxycycline is generally avoided during pregnancy due to concerns about the risk of tooth staining, delayed fetal growth and hepatotoxicity in the mother that are founded in data on the use of tetracycline during pregnancy and animal studies. Studies on prenatal use of doxycycline do not report any cases of tooth staining or delayed growth in newborns, nor do they report any cases of maternal hepatotoxicity, which suggests that the risk associated with these adverse effects is likely low. The authors of this review call into question the increased risk of cleft lip and cleft palate associated with the use of doxycycline, citing the results of the Cooper study [2009] described above. They note that it is difficult to draw a clear distinction between the effects of the antibiotic treatment and the effects of the underlying infection, considering that febrile disease in the mother is associated with an increased risk of cleft lip and cleft palate and congenital abnormalities. Considering the low prevalence of cleft lip and cleft palate (11/10,000 births) and the potential impact of the infection in the mother, the authors point out that the absolute risk of orofacial malformations associated with exposure to doxycycline is likely low. Lastly, the authors conclude that new data are needed to inform the selection of doxycycline doses for pregnant women, but that based on the few data available, dosage adjustments may not be required.

For their part, Cross et al. [2016] conclude that the available data support a loosening of restrictions on the use of doxycycline during the first trimester or first half of pregnancy.

2.1.3.4.4. Statement of evidence and level of evidence for the use of doxycycline during pregnancy

Doxycycline

Pregnant women

– Major congenital malformations during the first trimester

Statement of evidence: Based on the results of three studies, in utero exposure to doxycycline at a dose of 100 to 200 mg/day for 6 to 10 days during the first trimester of pregnancy is not associated with a statistically significant increase in the risk of major congenital malformations when these are analyzed as a whole, regardless of type.

Level of evidence: Low

– Major congenital malformations at any time during pregnancy

Level of evidence: The results of two studies do not point to any conclusions regarding the risk of major congenital malformations when these malformations were analyzed as a whole, regardless of type, following in utero exposure to doxycycline at any time during pregnancy at an average dose of 100 to 200 mg/day for 6 to 14 days (absence of statistically significant difference in one study, slight statistically significant increase in the second study).

Level of evidence: Insufficient

– Specific congenital malformations

Statement of evidence: The results of one study demonstrated a statistically significant increase in the risk of circulatory system defects (adjusted OR = 2.38 [CI 95%: 1.21, 4.67]), heart defects (adjusted OR = 2.46 [CI 95%: 1.21, 4.99]), and septal defects (adjusted OR = 3.19 [CI 95%: 1.57, 6.48]) after in utero exposure to doxycycline during the first trimester. The results of one other study showed a statistically significant increase in spontaneous abortions before the 20th week of pregnancy (adjusted OR = 2.38 [CI 95%: 1.21, 4.67]). Doses and durations of the doxycycline treatment are unknown in both of these studies. However, the data are insufficient to draw conclusions about these outcomes.

Level of evidence: Insufficient

2.1.3.5. Use of doxycycline while breastfeeding

2.1.3.5.1. Data from monographs and specialized works

According to the monograph from the e-CPS [CPhA, 2016] and the work by Ferreira [2013], short-term use of tetracyclines is not contraindicated (Ferreira lists a maximum duration of three weeks, whereas the e-CPS lists a treatment duration of 7 to 10 days).

However, long-term use is not recommended due to theoretical concerns about effects on growth or tooth staining in the exposed child [Ferreira et al., 2013]. Briggs et al. [2017] see this risk as negligible because, as is also stated in the e-CPS, while tetracyclines can be found in low concentrations in breast milk, no detectable traces are found in the serum of exposed children. In 2001, the American Academy of Pediatrics classified tetracyclines as medications compatible with breastfeeding, a recommendation that is echoed by Briggs et al. [2017]. Concerning doxycycline specifically, REPROTOX cites the 2001 conclusions of the World Health Organization (WHO) working group on medication and breastfeeding, according to which short-term use of doxycycline (one week) is likely safe. The National Institutes of Health (NIH) site LactMed also states that short-term use of doxycycline is acceptable in breastfeeding women. The full extraction table of information from monographs and specialized works is available in this report's supplementary appendices document.

2.1.3.5.2. Scientific data from primary studies and systematic reviews

No studies on the risk of tooth staining or the occurrence of other effects in children exposed to doxycycline while breastfeeding were identified.

2.1.3.6. Contextual data

2.1.3.6.1. Children under 8 years of age

The clinical decision support tool created by the Children's Hospital of Eastern Ontario entitled "Algorithm for Prophylaxis of Lyme Disease in Pediatric Patients" [CHEO, 2018] has already integrated the 2018 *Red Book*'s new recommendations on the use of doxycycline for Lyme disease PEP in children of any age.

There are no commercial preparations of doxycycline adapted for administration to young children. In its clinical guide on Lyme disease [Renaud et al., 2018], CHU Ste-Justine advises cutting doxycycline tablets, while the collective prescriptions for Estrie and Montérégie recommend the following magistral preparation: a 5 mg/ml doxycycline oral suspension. Based on the information gathered from community pharmacists, the formula for this magistral preparation is simple (doxycycline tablets crushed and mixed with ORA-Blend) and accessible via RxVigilance, a software program widely used in pharmacies. It can be prepared in 20 minutes or less. The oral suspension is not generally made in advance, as it does not have extended stability (up to 15 days).

2.1.3.6.2. Pregnancy and breastfeeding

No contextual data were collected on the use of doxycycline during pregnancy or while breastfeeding.

2.1.3.7. Experiential data

2.1.3.7.1. Children under 8 years of age

The consultation with members of the advisory committee revealed heterogenous practices for prophylaxis in children under 8 years of age, a population for whom doxycycline PEP is currently contraindicated and for whom the only recommended course of action is monitoring for symptoms suggestive of Lyme disease. Because they are unable to prescribe doxycycline, some members said they had prescribed amoxicillin to these children. Other members stated that they did not use amoxicillin, as it is not recommended in their establishment for PEP out of a fear of inducing resistance with a 10-day treatment regimen and due to an absence of probative data on its efficacy.

In response to the scientific data presented by INESSS, a majority of the advisory committee members stated that they would feel comfortable providing single-dose doxycycline PEP to children under the age of 8 who meet the criteria. One committee member, however, stated that the data currently available are insufficient to formulate any recommendations on prophylaxis in children.

As for the dose of doxycycline that should be administered in young children, advisory committee members said they preferred to follow the 2018 *Red Book* recommendation: 4.4 mg/kg for patients under 45 kg (up to 200 mg per day). They pointed out that contrary to what is instructed by INSPQ and the collective prescriptions for Estrie and Montérégie, this amount should not be divided into two doses given 12 hours apart in order to avoid the risk of the second dose being forgotten or given at the wrong time. In addition, in the Nadelman study, doxycycline was administered in a single dose, and the study's authors clearly stated that it cannot be assumed that the efficacy of other doxycycline dosage regimens (for example, 100 mg twice daily) would be similar to that of a single 200 mg dose of doxycycline for preventing Lyme disease.

The advisory committee was asked whether a minimum age should be set for prescribing PEP in children. This idea was rejected, as infants and children under 1 year old do not walk, and thus the possibility of them being bitten by a tick is low. In addition, the *Red Book* and the CHEO do not list a minimum age for doxycycline PEP.

As part of the consultations to create the provincial medical protocol and collective prescription template for PEP, the question of whether to exclude children under 8 years old from collective prescriptions was debated. The advisory committee agreed on recommending the use of PEP for children under 8 years old on a case-by-case basis outside the framework of a collective prescription. However, some stakeholders consulted made the point that excluding children under the age of 8 would create inequity in terms of care and access to PEP. If this group were excluded, children under 8 that meet the criteria for PEP would be required to see a doctor or a specialized nurse practitioner (SNP). Some of them would not be able to receive PEP, either due to the family's inability to see a medical professional within the required timeframe or because doctors or SNPs who are unfamiliar with the scientific data would not know what to do. In light of this, and considering the data on the dental effects of doxycycline in children under 8 along with the American Academy of Pediatrics' position, a majority of those consulted felt that the inclusion of children under 8 in the collective prescriptions on PEP was acceptable as long as the decision to begin treatment is arrived at through a shared decision-making process involving the family and the appropriate advice is provided. However, there was only a 60% consensus on this question among the people consulted. Those against including children under 8 in collective prescriptions for PEP had three main arguments: 1) there is insufficient scientific data concerning, in particular, the efficacy of PEP in this population, 2) there is a risk of medico-legal consequences if a child develops problems after taking doxycycline, 3) the collective prescriptions for Estrie and Montérégie currently exclude children under 8, and based on the experience of applying these prescriptions, it appears that people are not frustrated by the fact that they cannot receive PEP as long as they receive the appropriate advice.

2.1.3.7.2. Pregnancy

The advisory committee members said that they did not have experience with prescribing PEP to pregnant women, who primarily seek care for tick bites from primary care physicians. In response to the data presented by INESSS, a number of committee members felt that prescribing a 200-mg dose of doxycycline would likely be safe during the second and third trimesters of pregnancy, but that during the first trimester, this should be avoided due to concerns about the risk of malformations and spontaneous abortion raised by the studies by Muanda et al. Other members stated that, in general, they would not prescribe doxycycline to pregnant women. All the members agreed on the need for additional studies on the subject. In the meantime, committee members felt it was best not to systematically recommend the use of doxycycline in pregnant women. However, if a pregnant woman met the criteria and was very worried about the potential consequences of Lyme disease, a thorough assessment of the potential risks and benefits could be done by a physician to help the patient decide on the best option. If in doubt, the physician could seek the opinion of a microbiologist / infectious diseases specialist, obstetrician-gynecologist, or centre specializing in pregnancy, such as the Centre IMAGe at CHU Ste-Justine. The advisory committee members stated that pregnant women, like children under the age of 8, should be excluded from the scope of any collective prescription for PEP.

2.1.3.7.3. Breastfeeding

The majority of the committee members have never had to assess the indication of PEP in breastfeeding women. Of those who have, some prescribed 200 mg of doxycycline, and others recommended only monitoring for the appearance of symptoms.

2.2. Epidemiological Aspects

2.2.1. Results for question 4: Risk of contracting Lyme disease

2.2.1.1. Scientific data

Question 4: Risk of contracting Lyme disease
What is the risk of contracting Lyme disease after being bitten by *Ixodes scapularis* in a geographic area at high risk for Lyme disease?

2.2.1.1.1. Overall risk assessed from RCTs

The overall risk of contracting Lyme disease after being bitten by *Ixodes scapularis* in a high-risk geographic area may be assessed using the results observed in the placebo group of the four RCTs described in section 2.1.1. Lyme disease[28] developed in: 1.1% (1/90) of participants in the Agre and Schwartz study [1993], 1.2% (2/173) of participants in the Shapiro study [1992], 3.2% (8/247) of participants in the Nadelman study [2001], and 3.4% (1/29) of participants in the Costello study [1989]. The Nadelman study specifies that the rate of 3.2% includes all life-cycle stages and engorgement levels of *Ixodes scapularis* ticks. In the other three studies, information on the life-cycle stage and level of engorgement was not documented. Note that in all four studies, the *Borrelia burgdorferi* infestation rate for *Ixodes scapularis* was at least 12% and reached 50% in two studies. Warshafsky [2010], who completed a group analysis of the results of these four studies, concluded that the overall risk of contracting Lyme disease after being bitten by *Ixodes scapularis* was 2.2% (CI 95%: 1.2 to 3.9%).

A complementary publication on the duration of tick attachment as a predictor of the risk of Lyme disease [Sood et al., 1997], identified through reference citations, provides data consistent with these figures. In one region of the United States where 14% of ticks were infested with *Borrelia burgdorferi*, 0.9% (2/225) of study participants bitten by a black-legged tick developed erythema migrans. Two cases of asymptomatic seroconversion confirmed by an immunoenzymatic test or immunoblot test were also observed in this study, bringing the final infection rate to 3.3% (4/119).[29]

Ixodes scapularis nymphs and adult females are associated with a greater risk of infection [Sood et al., 1997], while larvae are not considered a relevant vector for Lyme disease [Wormser et al., 2006]. Note that in the Nadelman study [2001], all cases of erythema migrans observed were caused by *Ixodes scapularis* ticks at the nymph stage. One possible explanation for this is that adult ticks are larger and thus more quickly identified and removed than nymphs.

2.2.1.1.2. Risk in relation to duration of attachment

<u>Studies on humans</u>

In two US studies on humans, an attachment duration of 72 hours or more was associated with a higher risk of infection compared to an attachment duration of under 72 hours [Nadelman et al., 2001; Sood et al., 1997]:

- In the Nadelman study, the risk of developing erythema migrans after being bitten by an *Ixodes scapularis* nymph attached for more than 72 hours was 25% (3/12), vs. 0% (0/48) for attachment durations below 72 hours.
- In the Sood study, the risk of infection by *Borrelia burgdorferi*, defined as the occurrence of erythema migrans and/or seroconversion, was 20% (3/15) after being bitten by an *Ixodes*

[28] Erythema migrans is the only manifestation of Lyme disease observed in these studies.
[29] Only 119 of 225 participants had a serologic test at both assessments.

scapularis female or nymph attached for 72 hours or more, vs. 1.1% (1/94) for attachment durations below 72 hours.

Studies on animals

A recent review summed up the existing experimental data on the risk of *Borrelia burgdorferi* transmission in relation to the duration of attachment of *Ixodes scapularis* [Eisen and Eisen, 2018]. This review reported three main findings:

- The most relevant experimental studies are those involving a single infested tick, as this is the most likely scenario in humans.
- In four studies that included a total of 87 rodents exposed for 24 hours to a single *Ixodes scapularis* nymph infested by *Borrelia burgdorferi*, no transmission (0/87) was observed during the first 24 hours [Hojgaard et al., 2008; Piesman and Dolan, 2002; Des Vignes et al., 2001; Piesman et al., 1987]. Researchers observed transmission rates of close to 10% (13/115) at 48 hours, 53% (32/60) at 63 to 67 hours, 73% (62/85) at 72 hours, and 94% (17/18) after a full feeding. There are no data from experimental studies involving a single infested tick that look at the risk of transmission between 24 and 48 hours. Thus, it is impossible to know whether transmission begins just after 24 hours of attachment or just before 48 hours of attachment.
- While there is no evidence for transmission in the first 24 hours in experimental studies involving a single infested tick, the possibility of transmission occurring during this window under specific conditions cannot be excluded. The authors of the aforementioned review [Eisen and Eisen, 2018] cite the example of a tick that begins feeding on an animal and then bites a human to complete feeding.

2.2.1.2. Contextual data

Twelve tick species have been identified in Quebec,[30] but *Ixodes scapularis* is the only one that can transmit the bacteria responsible for Lyme disease to humans. Based on data from the passive tick surveillance program led by the LSPQ, it appears that nearly 50% of ticks submitted by hospitals and veterinarians are not *Ixodes scapularis*. Of the ticks collected from humans that are not *Ixodes scapularis*, the most frequently submitted species are *Ixodes cookei* and *Dermacentor variabilis* [Gasmi et al., 2018].

It should be noted that the group of experts mandated by the INSPQ to issue a scientific notice on PEP suggested offering PEP in CLSC service areas in which at least one municipality has a proportion of ticks infested with *Borrelia burgdorferi* greater than or equal to 20% [Adam-Poupart et al., 2017]. Given that there are limitations to using human-based active and passive acarological surveillance to determine this rate, according to the information provided in the notice, the INSPQ experts suggested that PEP also be offered to people bitten by a tick in a CLSC service area where an average of three cases of Lyme disease, or 10 cases per 100,000 residents, have been documented over three years. This means that in Quebec, the geographic areas eligible for PEP would not overlap with the areas classified as “high risk” or “endemic” by the INSPQ, as the criteria used to identify these areas differ. For endemic areas, for example, the rate of *Ixodes scapularis*[31] ticks infested with *Borrelia burgdorferi* is not considered. Based on the

[30] Institut national de santé publique du Québec (INSPQ). Guide d’identification des tiques du Québec [website, French only]. Available at https://www.inspq.qc.ca/guide-d-identification-des-tiques-du-quebec.

[31] Areas with a “high risk” of Lyme disease contraction are defined by the INSPQ as follows: at least three cases of Lyme disease documented locally in the last five years (municipalities < 100,000 residents) OR at least 23 human-based submissions of *Ixodes scapularis* ticks in the last year obtained through passive surveillance (municipalities < 100,000 residents) OR all three life-cycle stages of the tick *Ixodes scapularis* collected in one

information reported by the stakeholders consulted, the coexistence of the list of municipalities eligible for PEP and the map of areas at risk for contraction of Lyme disease may cause confusion for on-the-ground professionals, as they present seemingly similar information, which may be misleading.

2.2.1.3. Experiential data

According to information provided by a member of the advisory committee, the tick infestation rate in Granby varies between 25% and 40% depending on the year, and over 90% of ticks identified are *Ixodes scapularis*.

In Summary:

- According to human studies, the overall risk of contracting Lyme disease after being bitten by a black-legged tick (all life-cycle stages and engorgement levels included) is between 1% and 3% in high-risk geographic areas (12% to 50% of ticks infested).
- The risk of *Borrelia burgdorferi* transmission from a bite from an infested black-legged tick increases with the duration of tick attachment.
- No human studies were found that examined the risk of *Borrelia burgdorferi* transmission during the first 24 hours of attachment. The animal studies that are the most applicable to humans (bite from a single infested tick) did not find evidence of transmission during this window. However, the possibility of transmission occurring during this window under specific conditions cannot be excluded.
- According to human studies, the risk of transmission may reach 25% after 72 hours of attachment following a bite from an infested black-legged tick in a high-risk geographic area (14% to 50% of ticks infested). Data on animals show transmission rates of approximately 75% after 72 hours of attachment when a tick is infested.

year through active surveillance, with at least one nymph testing positive for *Borrelia burgdorferi*. (Source, French only: Carte de risque d'acquisition de la maladie de Lyme selon les municipalités du Québec, 2018, https://www.inspq.qc.ca/sites/default/files/documents/zoonoses/carte-maladie-lyme-juillet2018.pdf.)

2.3. Clinical Aspects

2.3.1. Results for question 5: Recommendations on the use of PEP

Question 5: Recommendations on the use of PEP
What are the positions of learned societies and health technology assessment agencies on the use of Lyme disease PEP and, if applicable, what are their eligibility criteria?

2.3.1.1. Description of publications

The search for scientific information led to the selection of seven sets of clinical practice guidelines (CPGs) or other guidelines on Lyme disease, of which four address post-exposure prophylaxis:

- two sets from North America:
  - one from the Infectious Diseases Society of America (IDSA) [Wormser et al., 2006][32]
  - one from the International Lyme and Associated Diseases Society (ILADS) [Cameron et al., 2014]
- two sets from Europe:
  - one from the German Dermatological Society (GDS) [Hofmann et al., 2017]
  - one from the Haute Autorité de Santé [HAS, 2018] in France.

The CPGs published by IDSA in 2006 were considered by INESSS to be of low methodological quality based on the AGREE II grid, while the other three sets of CPGs were deemed moderate in quality.

Note that the AAP's Lyme disease recommendations that appear in the 2018 edition of the *Red Book* [Kimberlin et al., 2018] were considered, as this is a reference work for the treatment of pediatric infectious diseases.

2.3.1.2. Synthesis of published recommendations

In brief, the two sets of North American CPGs (IDSA, ILADS) recommend dispensing prophylaxis after a tick bite, though under different conditions and using different procedures, whereas the two sets of European CPGs (HAS, GDS) do not recommend it, regardless of the age or condition of the person bitten (see Table 6 of this report and the full extraction of recommendations in this report's supplementary appendices document).

Table 7. Summary of recommendations from clinical practice guidelines on post-exposure prophylaxis for Lyme disease prevention and the corresponding level of evidence

Author, year (country)	Target population	Recommendation	Level of evidence according to the authors
North America			
IDSA 2006 (United States)	Not specified	Not recommended: **systematic** prophylaxis after a tick bite	E-III ("strongly against" recommendation, opinions of respected authorities and clinical experience or descriptive studies)

[32] The CPGs from IDSA were selected even though they were published prior to 2012 (an exclusion criterion), as this document continues to be used as a reference by clinicians. IDSA announced on its website that it would be publishing an update to this guide in the future.

Author, year (country)	Target population	Recommendation	Level of evidence according to the authors
	Adults and children ≥ 8 years	May be offered: single-dose doxycycline (adults: 200 mg, children: 4 mg/kg up to 200 mg) if: • Tick is reliably identified as *I. scapularis* at the adult or nymph stage and attachment duration is ≥ 36 hours • AND prophylaxis can be started within 72 hours of removing the tick • AND the local tick infestation rate is ≥ 20% • AND doxycycline is not contraindicated	B-I ("moderately in favour" recommendation, at least one RCT)
	Children < 8 years, pregnant and breastfeeding women	Relative contraindication for doxycycline. Amoxicillin should not replace doxycycline.	D-III ("moderately against" recommendation, opinions of respected authorities and clinical experience or descriptive studies)
ILADS 2014 (United States)	Not specified	Not recommended: single 200 mg dose of doxycycline	Very low
	Not specified	Should be offered promptly: 100–200 mg doxycycline BID for 20 days if bitten by an *Ixodes* tick and if there is evidence of engorgement (regardless of degree and of local tick infestation rate). Other therapeutic options may be appropriate depending on the patient.	Very low
AAP, *Red Book* 2018 (United States)	Children of all ages	May be used in high-risk areas (tick infestation rate of 30% to 50%) after a bite from *Ixodes scapularis*: single-dose doxycycline for children of all ages (200 mg or 4.4 mg/kg if weight < 45 kg). The benefits of prophylaxis outweigh the risks when: • The tick is engorged (attached for ≥ 36 hours) • AND prophylaxis can be started within 72 hours of removing the tick Not recommended: prophylaxis with amoxicillin	Not available
	Pregnant women	Doxycycline has not been sufficiently studied during pregnancy to issue recommendations on its use.	Not available
Europe			
HAS 2018 (France)	Not specified	Recommended: no treatment and close monitoring	Not available
GDS 2017 (Germany)	Not specified	Not recommended: local or systemic prophylaxis after a tick bite	Not available

Legend: AAP: American Academy of Pediatrics, HAS: Haute Autorité de Santé, IDSA: Infectious Diseases Society of America, ILADS: International Lyme and Associated Diseases Society, LD: Lyme disease, GDS: German Dermatological Society

IDSA recommends against systematically administering prophylaxis after a tick bite ("strongly against" recommendation based on opinions of respected authorities). However, it does state that a single dose of doxycycline may be offered after a tick bite in adults (200 mg dose) and in children 8 and older (dose of 4 mg/kg up to 200 mg) provided that four criteria are met: 1) the tick can be reliably identified as the species *Ixodes scapularis* at the adult or nymph stage and the attachment duration is ≥ 36 hours, 2) prophylaxis can be started within 72 hours of removing the tick, 3) the local tick infestation rate is ≥ 20%, and 4) doxycycline is not contraindicated. IDSA is "moderately in favour" of this recommendation and assigns it the highest level of evidence in its ranking system. In support of the minimum attachment duration of 36 hours, IDSA cites the results of experimental studies that show that transmission of *Borrelia burgdorferi* to lab animals is rare when *Ixodes scapularis* adults or nymphs are attached for under 36 hours. This "grace period" corresponds with the time required for spirochetes to migrate from a tick's digestive tract to the salivary glands once it has begun feeding. The 72-hour window between

removing the tick and beginning doxycycline treatment is proposed because there is no data on the efficacy of prophylaxis administered beyond 72 hours after removing the tick.

IDSA states that doxycycline is a relative contraindication in pregnant women, breastfeeding women and children under 8 years old.[33] The organization recommends against replacing doxycycline with amoxicillin for such patients because of the absence of data on the efficacy of a short-term treatment regimen for amoxicillin prophylaxis, the excellent efficacy of antibiotic treatment in people who develop Lyme disease and the extremely low risk of developing serious complications from Lyme disease after a recognized tick bite ("moderately against" recommendation, based on opinions of respected authorities).

For single-dose doxycycline prophylaxis to be prescribed selectively as needed, IDSA recommends that health professionals learn to identify *Ixodes scapularis* ticks at the different stages of its development and to recognize when the tick is at least partially engorged. For all cases, IDSA recommends closely monitoring people who have removed a tick for the appearance of signs and symptoms of tick-borne diseases, particularly erythema migrans at the site of the bite, for up to 30 days.

Opinions are divided on the use of single-dose doxycycline to prevent Lyme disease after a tick bite, as, unlike IDSA, ILADS expressly recommends **against** using this PEP treatment. Nonetheless, both North American learned societies cite the same study (Nadelman [2001]) to support their recommendations. It should be noted that ILADS performed a more in-depth analysis of this study than did IDSA. In its assessment of the overall quality of evidence, ILADS discussed in detail the risk of bias and the precision, consistency and generalizability of results. ILADS determined that the evidence provided in the Nadelman study was "very low." IDSA, on the other hand, ranked the study's level of evidence at the top of its three-tier scoring system. For ILADS, the determining factor appears to have been the risk of a single dose of doxycycline causing a seronegative disease state if the prophylaxis fails. This is where IDSA and ILADS diverge in their interpretation, as according to the authors of IDSA's CPGs, late-onset seronegative Lyme disease is not a proven medical phenomenon [Wormser et al., 2007]. In the opinion of ILADS, the harm associated with the potential development of a seronegative disease state outweighs the benefits of offering prophylaxis via a single 200 mg dose of doxycycline, which it views as uncertain. In place of this treatment, it recommends promptly offering prophylaxis via a 100- to 200 mg dose of doxycycline twice daily for 20 days after a bite from an *Ixodes* tick, if there is evidence of engorgement (regardless of the degree or the local tick infestation rate). This recommendation is based on two murine model trials that studied the effects of an injectable form of long-acting doxycycline, though this form is not yet available for use in humans. It does, however, consider the level of evidence for the recommendation to be "very low," and encourages the National Institutes of Health to fund appropriately designed studies. ILADS also notes that some CPGs recommend using an estimation of the tick attachment duration based on their scutal index[34] to decide whether to administer prophylaxis, though it is of the opinion that this estimation requires specific expertise to complete and it is unrealistic to assume that all clinicians can or will acquire such skills. Lastly, ILADS recommends that the clinician and patient engage in a shared decision-making process to determine whether to use prophylactic antibiotics following a tick bite. ILADS does not provide any specific recommendations for children or pregnant and breastfeeding women.

[33] Relative contraindications of a treatment are distinct from absolute contraindications. A treatment should not be used in patients who present absolute contraindications to that treatment, whereas for relative contraindications, a treatment may be used with caution if the benefits outweigh the potential risks for the patient.
[34] Ratio of a tick's body length to its scutum width.

As previously mentioned in section 2.1.3, the *Red Book* states that single-dose doxycycline may be provided as PEP for Lyme disease in children, regardless of their age, when multiple criteria are met.

The HAS recommends [Translation] “no therapy with close monitoring, on the express condition of the absence of erythema migrans or other symptoms related to tick-borne diseases.” It supports this recommendation with the fact that there is a single positive study of good quality conducted in the United States [Nadelman et al., 2001] whose results are difficult to translate to Europe (different ecology, study completed in a highly endemic area). The HAS does not provide any specific recommendations for pregnant women, children under 8 or immunosuppressed patients, but it notes that a specialized opinion may be sought for these populations.

Lastly, the GDS does not recommend Lyme disease PEP and notes that this applies to antibiotics administered systemically or topically. The GDS brings up the fact that the Nadelman study [2001] had a follow-up period limited to six weeks, and that because of this, no conclusion can be reached as to the efficacy of a single 200 mg dose of doxycycline to prevent a late-onset infection. It adds that, due to the low risk of infection, doxycycline would need to be unnecessarily administered to a high number of people in order to prevent one potential case of infection. It also refers to the risk of impacting intestinal flora and of contributing to bacterial resistance.

2.3.2. Contextual data

As mentioned in the introduction, the access criteria for PEP in Quebec were developed by the INSPQ based on recommendations from IDSA, with some variations. In Quebec:

- There is no requirement to identify the tick to ensure that it is in fact an *Ixodes scapularis* tick at the adult or nymph stage before prescribing PEP. The reasons for this are that the tick is often not present at the appointment with the health professional and that identifying ticks is not a simple task, as primary care health professionals have neither the expertise nor the equipment required to do so [Adam-Poupart et al., 2017].
- The minimum duration of tick attachment was set at 24 hours, rather than the 36 hours cited in the IDSA CPGs, to make it easier for clinicians and people who have been bitten to work backward and determine how long the tick was attached [Adam-Poupart et al., 2017].
- The decision-making algorithm provided to clinicians specifies a maximum window of 72 hours between removing the tick and seeing a health care professional, whereas IDSA specifies a 72-hour limit between removing the tick and beginning PEP, per the study cited for this criterion. It should be noted that in the INSPQ’s opinion, the two recommendations are functionally the same.
- The recommended dosage of doxycycline for PEP is 200 mg for people over the age of 12, or 4 mg/kg/day divided into two doses for one day for children ages 8 to 12 (maximum 100 mg/dose). IDSA does not mention the possibility of dividing the doxycycline dose into two separate doses for children.

As for the identification of ticks, the INSPQ published the *Guide d’identification des tiques au Québec* [Identification guide for ticks in Quebec] to help health professionals identify specimens that are brought to them by their patients. The guide describes how to observe the specimen to determine whether it is a tick, provides a detailed description of the tick species *Ixodes scapularis*, and shows health professionals how to distinguish it from other species and types of tick that are most commonly found in Quebec. However, this guide seems to be relatively unknown and underused by primary care professionals. Based on the results of a survey of 31

emergency physicians conducted for this project by a member of the advisory committee, 55% of respondents (12/22) were unaware of the guide. After learning about it, 82% (18/22) stated that they would not use it, primarily out of a fear of misidentifying a black-legged tick potentially carrying *Borrelia burgdorferi*.

2.3.3. Experiential data

Based on advisory committee members' experience with applying Quebec's criteria for receiving PEP, it appears that:

- In general, primary care professionals are familiar with and apply these criteria.
- The duration of tick attachment is the most difficult criterion to assess in practice.
- Clinicians tend to prescribe PEP rather than abstaining from treatment when there is uncertainty about a given criterion.
- People who fulfill the criteria for receiving PEP are not given the option of only monitoring for symptoms. PEP is prescribed in an emotionally charged atmosphere, as patients are worried about the consequences of Lyme disease, and they are generally happy to be offered PEP because they feel like they're "doing something."
- Ticks are not identified by health professionals.

To this last point, the majority of clinicians consulted for this project said that they did not feel comfortable identifying ticks, because they were not trained to do so. A number of them mentioned that it would be desirable for there to be a validated application for smartphones and tablets that helps them identify ticks within the timeframe for prescribing PEP. Applications of this type already exist, but it is difficult to assess whether they meet the aforementioned conditions. Some do not identify the species and only allow the user to confirm whether the specimen is a tick (for example, the Detectick application developed in Quebec). The website etick.ca is a free validated platform that identifies tick species from submitted photos. However, the response time is 24 hours, which may be too long in the context of PEP.

In summary:

- Lyme disease PEP is recommended in North America, but not in Europe, because the vector tick and bacteria responsible for the disease are not the same and because the only positive clinical study on PEP was completed in a North American context and had limitations.
- The two major North American learned societies that have drafted recommendations on PEP specify different dosage regimens: IDSA recommends a single 200 mg dose of doxycycline by mouth based on the results of the clinical study described above, whereas ILADS recommends a 100–200 mg dose of doxycycline BID by mouth for 20 days, based on animal studies looking at the effect of an injectable form of long-acting doxycycline.
- In Quebec, single-dose doxycycline PEP by mouth may be provided according to the adapted IDSA criteria.
- In 2018, the American Academy of Pediatrics recommended administering doxycycline to children of all ages, including those under the age of 8, for various infectious diseases and specifically for Lyme disease PEP in high-risk areas when multiple criteria are met.

- In situations in which doxycycline is contraindicated, IDSA and the American Academy of Pediatrics recommend against replacing doxycycline with amoxicillin, as it has not been sufficiently studied for Lyme disease PEP.

2.3.4. Results for question 6: Optimal use of PEP

Question 6: Optimal use of PEP
To promote the optimal use of PEP, what clinical procedure should be followed by primary care health professionals consulted about a tick bite? Specifically: a. What actions should be taken concerning the tick? b. What aspects of the circumstances surrounding the bite should be investigated and documented? c. What is the procedure for using single-dose doxycycline PEP for Lyme disease (dosage, absolute and relative contraindications, precautions)? d. What aspects of the patient's medication history should be investigated? e. How should the professional assess the patient's asymptomatic condition? f. What points should be discussed with the patient when they are deciding whether to take PEP? g. What instructions and information should be given to the person exposed to ticks and their family?

The information gathered to answer the sub-questions for question 6 was sourced primarily from CPGs, best practice documents published in Quebec (by the MSSS, public health branches, INSPQ), experiential knowledge from consulted stakeholders and monographs for doxycycline-based medication. The collective prescriptions on PEP for Estrie and Montérégie were also consulted. The sections are not divided by type of data, but the summary specifies the source where appropriate.

2.3.4.1. Actions to be taken concerning the tick

2.3.4.1.1. Removing the tick

The first action that should be taken when a person presents with a suspected tick attached to the skin is removing the specimen as quickly as possible, as there is a correlation between the duration of tick attachment and the risk of *Borrelia burgdorferi* transmission from the tick [HAS, 2018]. According to the MSSS brochure [2018], grooming tweezers should be used to remove it, whereas the collective prescriptions for Estrie and Montérégie recommend using fine point tweezers (for example, splinter forceps or other tweezers designed for removing ticks). Several learned societies recommend the use of a tick remover [HAS, 2018]. There are several tick removers on the market in Quebec. Based on the experience of members of the subcommittee on the provincial PEP medical protocol, fine point tweezers are less suited to effectively removing ticks than tick removers, except in cases where the tick is not engorged. It was decided that the medical protocol should give the option of using either fine point tweezers or a tick remover.

2.3.4.1.2. Identifying the tick

According to the current criteria for offering PEP in Quebec, health professionals do not need to verify that the collected specimen is a tick belonging to the species *Ixodes scapularis*. However, in conversations with stakeholders, it became apparent that a step should be added to the process for assessing the indication of PEP: verifying that the specimen is in fact a tick, without going so far as to identify the species. Based on information from the LSPQ, of specimens sent in for analysis, scabs are the most commonly misidentified "culprit."

2.3.4.1.3. Analyzing microbic agents in ticks

Since the fall of 2018, the results of molecular analysis (PCR) tests used to determine whether ticks are carrying microbic agents are no longer sent to clinicians by the LSPQ. The CDC [2019] does not recommend using microbic agent detection tests in ticks, as these are not diagnostic tests and are therefore not subject to the same strict quality standards applied to the latter. Thus, a positive result for the presence of *Borrelia burgdorferi* would not necessarily mean that a person has been infected. Health professionals may still continue to submit ticks to the LSPQ's passive surveillance program for black-legged ticks according to the procedures of their institutions.

In Quebec, there are commercially available tests sold in pharmacies that claim to quickly identify the presence of *Borrelia burgdorferi* in ticks. At first glance, the prospect of using these tests to better identify patients who qualify for PEP and thus reduce unnecessary exposure to doxycycline appears promising. However, it is not recommended that these tests be used to inform the care of individuals exposed to ticks. According to the LSPQ, these tests produce false negatives [Sprong et al., 2013] and likely false positives. Moreover, a positive result would not necessarily indicate that *B. burgdorferi* transmission has occurred.

Members of the advisory subcommittee on the provincial PEP medical protocol felt it relevant to include this information in the protocol.

2.3.4.2. Aspects of the circumstances surrounding the tick bite that should be documented

The PEP information form annexed to the collective prescriptions for Estrie and Montérégie includes fields for the date and time that the tick was discovered, the date and time the tick was extracted, the part of the body that was bitten, and the area where the tick bite occurred (municipality and region/country). It also has a field for a description of the circumstances leading to the tick bite, such as outdoor activities. These elements were deemed relevant to the PEP medical protocol.

2.3.4.3. Procedures for the use of single-dose doxycycline PEP

2.3.4.3.1. Dosage

In the Nadelman study [2001], doxycycline was administered in a single 200 mg dose in adults and children age 12 and up. According to the study's authors, it cannot be assumed that other dosage regimens for doxycycline (for example, 100 mg twice daily) would be as efficacious as a single 200 mg dose of doxycycline at preventing Lyme disease. For Lyme disease PEP, IDSA recommends a single 200 mg dose in adults and children age 8 and up (4 mg/kg, up to 200 mg). In the 2018 *Red Book*, the American Academy of Pediatrics also recommends a single 200 mg dose, but for children under 45 kg, it recommends a dosage of 4.4 mg/kg, rather than 4.0 mg/kg.

In Quebec, the INSPQ currently recommends administering PEP via a single 200 mg dose for patients over the age of 12 [Adam-Poupart et al., 2017]. For children ages 8 to 12, the INSPQ recommends a total of 4 mg/kg divided into two doses for one day (up to 100 mg/dose). The collective prescriptions for Estrie and Montérégie also recommend these dosages.

In following the Nadelman study, the advisory committee members stated that doxycycline should be given in a single dose. For children, they advised following the dosage recommended by the American Academy of Pediatrics (a single dose of 4.4 mg/kg). They noted the risk of the second dose being forgotten or given at the wrong time if the dose of doxycycline were divided into two doses taken 12 hours apart.

2.3.4.3.2. Absolute and relative contraindications

The monographs for doxycycline-based medications list a number of contraindications: a history of allergic reaction to tetracyclines, myasthenia gravis, and the intake of isotretinoin. The precautions sections of these monographs also list relative contraindications: age below 8, pregnancy, breastfeeding and anomalies of the esophagus.

The collective prescriptions for Estrie and Montérégie do not mention isotretinoin intake, but they do list additional contraindications: a history of liver failure, a history of active esophagitis or esophageal ulcers, and a history of hypersensitivity to sunlight.

The advisory committee and the subcommittee on the provincial medical protocol gave the following opinions on contraindications in the context of a single 200 mg dose of doxycycline:

- A history of allergic reaction to tetracyclines is an absolute contraindication.
- Myasthenia gravis is a relative contraindication in the opinion of the neurology expert consulted, and a single 200 mg dose of doxycycline would be compatible with the majority of myasthenic patients; according to the same expert, only cases of poorly controlled or decompensated myasthenia would require an individual clinical assessment, but there are exceptions; it should be noted that the guide on medications contraindicated for myasthenia published by CHU de Québec – Université Laval also lists tetracyclines under precautions rather than formal contraindications [Dionne and Breton, 2015].
- Intake of isotretinoin is not a contraindication in the opinion of an expert dermatologist consulted, as in the 20 years that the drug has been used for acne, no detrimental effects have been observed when isotretinoin and doxycycline have been prescribed simultaneously in error.
- Anomalies of the esophagus are a relative contraindication.
- It is unlikely that a single dose of doxycycline would have a significant impact on the liver. According to information from the website Livertox,[35] in rare cases, doxycycline has been associated with liver damage following treatments lasting for several days or weeks. However, for the sake of caution, the committee members felt it wise to include active liver disease in the list of relative contraindications, especially severe cases.
- It is unlikely that a single dose of doxycycline would have a significant impact on the occurrence of a photosensitivity reaction. Out of caution, the patient should be asked about prior cases of photosensitivity and, as applicable, it would be wise to stress the need to avoid exposure to sunlight and ultraviolet rays or use a full-spectrum sunblock before exposure to sunlight. However, photosensitivity is not a contraindication.
- Active esophagitis or esophageal ulcers are not a contraindication, but if certain health conditions are present, it would be wise to stress the need to take doxycycline with food and a glass of water and to avoid lying down after taking it.

Doxycycline use during pregnancy, while breastfeeding and in children under the age of 8 is discussed in section 2.1.3 of this report. In brief, pregnancy is a relative contraindication,

[35] LiverTox. Doxycycline [website]. Available at https://livertox.nih.gov/Doxycycline.htm.

whereas breastfeeding and an age below 8 are not contraindications when doxycycline is administered in a single dose.

In general, the members of the subcommittee on the provincial medical protocol felt that it was essential to draw up an exhaustive list of patient history details. They noted that it is particularly important to consider potential complications related to the use of single-dose doxycycline in the context of PEP following a tick bite, given the low risk of developing Lyme disease, uncertainty surrounding the efficacy of single-dose doxycycline at preventing Lyme disease, and the preventive nature of the intervention. Furthermore, they noted that in the context of applying a collective prescription, signatory physicians may be held liable, and it is best to work with the most complete verification list possible.

2.3.4.3.3. Precautions

The monographs indicate that cases of illness caused by *Clostridium difficile* were reported with the use of several antibiotics, including doxycycline. However, based on the available scientific data, tetracyclines are associated with a low risk of *Clostridium difficile* infection compared to other antibiotics, and some publications even suggest that doxycycline has a protective effect. While members of the subcommittee had never observed a case of *Clostridium difficile* infection triggered by doxycycline, they felt it wise to exercise caution with patients who have experienced a severe or complicated episode in the past 30 days, as these patients are at risk for relapse.

To avoid gastric distress and esophageal lesions, monographs for doxycycline-based medications recommend taking the medication with food and a full glass of water. They also recommend remaining upright and avoiding lying down for two hours after taking a dose. Lastly, to avoid photosensitivity reactions, they advise using sunscreen before exposure to the sun or ultraviolet rays.

All of these precautions were deemed relevant to share with individuals to whom PEP is prescribed. It should be noted that the booklet on doxycycline for pharmacists that was published using the Vigilance Santé software program indicates that patients should wait 30 minutes before lying down, rather than 2 hours. Pharmacists on the committees felt it was best to use the 30-minute minimum timeframe.

As for the consumption of dairy products, contradictory information was found. The monographs for doxycycline-based medications indicate that the absorption of doxycycline is not significantly impacted by the ingestion of food or milk. The FDA recommends avoiding the consumption of dairy products one hour before and two hours after taking tetracycline, but says that minocycline and certain forms of doxycycline can be taken with milk [FDA and NCL, 2013]. The documents on doxycycline published by the CDC for patients specify to avoid milk and dairy products for a few hours before and after taking doxycycline [CDC, 2013]. The same goes for the information distributed by the National Health Service in the United Kingdom [NHS, 2018]. The pharmacists consulted were not all in agreement about the relevance of recommending spacing out the consumption of milk and dairy products when taking doxycycline. However, given the low level of evidence for the efficacy of doxycycline PEP, it was deemed appropriate to recommend spacing out consumption of dairy products when taking doxycycline to promote maximum absorption.

In a preliminary version of the provincial medical protocol, the list of medication interactions to consider was included in an appendix. However, it was decided that verifying drug interactions and establishing the procedure to address them are both regular duties of pharmacists and this list did not necessarily need to be included in the protocol.

2.3.4.4. Aspects of the patient's medication history to be investigated

The collective prescriptions for Estrie and Montérégie specify to verify whether any antipyretics/analgesics have been taken in the 6 hours prior to the consultation. The CPGs do not address this point, though it is still an important detail to verify, as certain medications could mask a fever that is potentially associated with a tick bite.

Neither the CPGs nor the current collective prescriptions address individuals who have been bitten by a tick multiple times in the same season. However, the members of the advisory subcommittee felt it would be appropriate to ask patients who seek care for a tick bite how often they have taken PEP during the current tick activity period. Members stated that undergoing more than two rounds of such treatment could indicate that primary prevention measures are not correctly understood and/or applied. In such a situation, the health professional should have a discussion with the patient to identify what is preventing them from implementing these measures. Health professionals play a critical role in patient education. In any case, in the opinion of the committee members, doxycycline may be prescribed again if all criteria to receive PEP are met.

2.3.4.5. Assessment of a patient's asymptomatic condition

According to the criteria set by the INSPQ, PEP may be provided only to "asymptomatic" individuals. In practice, it appears necessary to educate health professionals about the symptoms that must be checked for before prescribing PEP. The primary concern is ensuring that the person does not have symptoms suggestive of Lyme disease caused by either the tick bite that is the subject of the visit or a previous tick bite, in the case of people who have been exposed to black-legged ticks multiple times. In the opinion of the advisory committee members, administering PEP to a person with Lyme disease at the localized or early disseminated stage could be problematic, and any individual with symptoms suggestive of Lyme disease should undergo a clinical examination so they may receive the appropriate treatment if needed (rather than PEP).

2.3.4.5.1. Redness at the site of the bite

In the Nadelman study [2001], individuals who presented with clinical signs of Lyme disease, particularly erythema migrans, were excluded from participating. Yet, the study's authors do not at any point address the question of redness at the site of the bite that could be caused by a local hypersensitivity reaction.

None of the CPGs consulted specify the protocol to follow when redness is observed at the site of the bite while evaluating a patient for the indication of PEP. Some CPGs do discuss the differential diagnosis between erythema migrans and a hypersensitivity reaction to the bite:

- IDSA [Wormser et al., 2006] states that a hypersensitivity reaction is the most likely diagnosis (versus erythema migrans) if the redness appears when the tick is still present or if it develops within the first 48 hours after the bite. The organization notes that this reaction may sometimes resemble a rash, generally does not exceed 5 cm in diameter and subsides within 24 to 48 hours. In contrast, newly developing erythema migrans tends to spread over this same time period. To differentiate between the two, IDSA advises marking the outline of the red patch with ink and monitoring the area for one to two days without antibiotics.
- According to the HAS [2018], erythematous cutaneous reactions that develop immediately following the bite or within 24 hours of the bite and that clear in a few days are not compatible with a diagnosis of erythema migrans. The HAS notes that the clinical criterion that appears to be the most specific to erythema migrans is the progressive concentric expansion of the lesion, over several weeks, up to 30 cm in size at times.

- NICE [2018] notes that hypersensitivity reactions to a bite develop and clear within 48 hours of the bite, and they are more often associated with heat, pain and itching than with erythema migrans.

All three sets of CPGs, along with those from the GDS, specify that erythema migrans appears between 3 and 30 days post-bite.

In the PEP collective prescriptions for Estrie and Montérégie, the presence of an erythematous skin lesion is a contraindication for the application of these collective prescriptions, and the patient must be referred to a physician. Clinically evaluating an erythematous skin lesion is considered equivalent to issuing a diagnosis, an action that may not be performed by pharmacists or nurses. Yet, based on an assessment of the collective prescription's application in Estrie [Binet et al., 2018], only 32% (10/31) of participating pharmacists referred patients to a physician when they presented with redness. According to the authors, it appears that in the majority of cases, redness was not seen as a symptom of Lyme disease. The authors add that different information appears to have been circulated in Estrie, as some comments gathered from the questionnaire indicate that pharmacists decided whether to begin PEP based on the diameter of the red patch. The authors of the assessment recommended that redness, regardless of the size of the lesion, should always be considered a symptom of Lyme disease, and that its continued presence should be a contraindication for applying the collective prescription, as health professionals cannot differentiate between a hypersensitivity reaction and early-stage erythema migrans based only on the initial size of a lesion.

The procedure to follow in the context of PEP when redness is observed at the site of the bite has been the subject of much discussion and consultation with members of the advisory committee and the subcommittee on the provincial medical protocol on PEP. The following points emerged from these discussions:

- In practice, it is difficult to tell whether redness at the site of a tick bite is related to developing erythema migrans or to a hypersensitivity reaction to the bite. This is an important distinction, as a person presenting with erythema migrans should receive a full course of antibiotic treatment rather than PEP, whereas a patient with a local hypersensitivity reaction could be prescribed PEP.
- The size of a red patch is not the best criterion for assessing whether, shortly after the bite, the lesion could be early erythema migrans, as erythema migrans develops progressively and does not reach the targeted size of 5 cm or more right away. As stated by the HAS, progressive expansion is the clinical criterion most specific to erythema migrans.
- Before prescribing PEP, the best practice when redness is present at the site of the bite would be to outline the red patch with ink and monitor its evolution for 24 to 48 hours, as advised by IDSA. In some cases, the reassessment could be completed by the end of the 72-hour deadline for beginning doxycycline treatment after removing the tick. This would not be possible for people who see a doctor at the very end of this window.
- Patients may face barriers to access when trying to consult a health professional capable of completing a clinical evaluation of the red patch within 24 to 48 hours of removing the tick.
- The available scientific data do not allow for a conclusion to be drawn as to the safety of giving a single dose of doxycycline to a person with early erythema migrans.
- All of the members consulted agreed that true erythema migrans should be treated with a full course of antibiotics.
- Based on the experience of members who have applied the collective prescription on PEP, it is common to observe a small red patch at the site of the bite. However, due to a lack of

available epidemiological data, the exact frequency with which redness after a tick bite occurs is not known. Thus, it is not possible to say how many people would be deprived of access to PEP if redness were a contraindication for applying the collective prescription.

- In the context of applying the collective prescription, some members suggested taking an approach similar to the one adopted in cases of otitis—that is, providing PEP to people who fulfill the requirements regardless of the presence of a small red patch at the site of the bite, and giving these patients the appropriate instructions, such as outlining the red patch and taking the tablet only if the red patch does not expand after 24 to 48 hours. However, some of the members consulted were not in favour of this solution, notably because they feared the instructions would not be fully understood and followed.
- In the experience of some clinicians on the committees, in general, red patches caused by a hypersensitivity reaction would not exceed 1 cm in size. Thus, in their opinion, the collective prescription could be applied if a red patch did not exceed this size. However, several members were not comfortable with this solution, as the 1 cm threshold is not supported by any scientific data.

In the end, the consulted committee members were of the opinion that a number of variables should be taken into account (size of the red patch, evolution of the patch from the moment it is observed, time elapsed between the bite and the appointment, the patient's ease of access to a follow-up appointment, the patient's ability to follow the given instructions, etc.) and that situations should be handled on a case-by-case basis. In general, they feel that health professionals should exercise particular caution when a patient presents with redness at the site of the bite, and that clinical judgment should take precedence. A consensus was reached on a general statement that explains the reasoning underlying the decision regarding the prescription of PEP when there is redness at the site of the bite. However, due to a lack of sufficient scientific evidence, it was not possible to reach a consensus on the criteria that would allow pharmacists to administer PEP under a collective prescription when a patient presents with redness at the site of the tick bite.

2.3.4.5.2. Other symptoms suggestive of Lyme disease

Symptoms suggestive of Lyme disease whose presence must be ruled out before prescribing PEP were addressed in INESSS's research on the diagnosis of Lyme disease (for more details, see the report in support of tools for diagnosing and treating Lyme disease [INESSS, 2019a].

2.3.4.6. Points to be discussed with the patient

Of the CPGs reviewed, only those from ILADS address shared decision-making in the context of prescribing PEP. ILADS states that the majority of patients place great importance on preventing a "chronic" disease, but some prioritize the avoidance of unnecessary antibiotics and prefer not to take preventive antibiotics after a tick bite. Thus, ILADS recommends that prophylactic treatment options and their risks and benefits be weighed against the values and preferences of the patient in the context of a shared decision-making process between the clinician and their patient [Cameron et al., 2014].

With regard to existing uncertainty surrounding the true efficacy of PEP in the Quebec context, the consulted stakeholders strongly supported this recommendation. Reservations about PEP expressed by one of the patient partners and by the AQML (see section 2.1.1.7) also support the development of a shared decision-making process for prescribing PEP.

It also appears important to integrate information about the risk of Lyme disease transmission into the discussion between the health professional and the person bitten, in addition to the risks

and benefits of various treatment options. Members of the advisory committee noted that this risk was often overestimated.

For cases in which the person bitten is a child under the age of 8, the consulted stakeholders observed that the shared decision-making process took on even greater importance given the absence of data on the efficacy and safety of single-dose doxycycline PEP in this population, of which the family should be informed. The family should also be told of the concerns about dental effects from doxycycline and the fact that the available data on this topic are reassuring in the context of the administration of a single dose.

2.3.4.7. Instructions and information to be provided to patients exposed to ticks

IDSA recommends that all individuals bitten by a tick, including those who receive PEP, be closely monitored for 30 days for symptoms suggestive of tick-borne diseases, especially the development of an expanding erythematous skin lesion at the site of the bite [Wormser et al., 2006]. ILADS advises that during the initial appointment, clinicians should inform patients of ways to prevent future tick bites and educate them about early and late-onset manifestations of Lyme disease and manifestations of other tick-borne diseases [Cameron et al., 2014]. Both IDSA and ILADS recommend that people who develop manifestations associated with tick-borne diseases immediately seek medical attention.

The current recommendations in Quebec state to monitor for symptoms consistent with Lyme disease for 30 days, whether or not PEP has been administered [Adam-Poupart et al., 2017].

The advisory committee members believed it was important to monitor for and report symptoms that may appear in the first 30 days after a bite, but also symptoms that may develop later. In their point of view, this recommendation is especially important for people whose activities put them at risk for tick exposure, particularly those who have already been bitten by a tick multiple times during the current period of tick activity.

Discussions with the subcommittee on the provincial PEP medical protocol revealed the importance of specifying why people who receive PEP must also be monitored for symptoms: PEP is not guaranteed to prevent Lyme disease, and doxycycline has been recognized as ineffective at preventing other infections transmitted by ticks. It was noted, however, that symptoms associated with other tick-borne infections do not overlap with those of Lyme disease. Symptoms of other tick-borne infections will be discussed at a later date after INESSS has completed its work on potential co-infections.

Though it is the pharmacist's job to provide patients with information about potential adverse effects of medication and the primary precautions to take, a majority of clinicians felt it pertinent to include this information in the provincial medical protocol on PEP.

2.4. Professional and Organizational Aspects

2.4.1. Results for question 7: Access to PEP

Question 7: Access to PEP	
a)	What are the professional and organizational challenges involved in dispensing PEP?
b)	What are the limitations or situations requiring a consultation with a physician or a primary care nurse practitioner when a person bitten by a tick seeks care from another type of health care professional?

2.4.1.1. Professional challenges

The aforementioned report [Binet et al., 2018] that examined the implementation of the collective prescription in Estrie revealed a number of barriers to this implementation, which also pose professional challenges for pharmacists, including:

- a lack of compensation for PEP examinations
- the workload associated with applying the collective prescription
- the preparation time required for pharmacists to familiarize themselves with the collective prescription.

In addition, as previously noted, the results of this report indicate that in the majority of cases, redness was not interpreted by pharmacists as a symptom requiring referral to a physician. In fact, the pharmacists consulted as part of the current work are of the opinion that examining patients to differentiate between a hypersensitivity reaction and EM is beyond the scope of their expertise.

2.4.1.2. Organizational challenges

The main organizational challenge identified is the difficulty some people face when trying to access PEP outside of the network of community pharmacies. A single patient, out of the eight who were interviewed, had received PEP, and his account is telling: He was bitten at the end of 2017 in an area eligible for PEP and had to visit four different clinics before being able to get an appointment and being prescribed PEP. Access issues of this type are problematic in the context of PEP, as delays could lead to individuals seeing a health professional only after the recommended 72-hour time limit for PEP has passed. Difficulty referring patients to a physician is another organizational issue identified in the application of the collective prescription in Estrie [Binet et al., 2018].

2.4.1.3. Situations and limitations requiring a referral

The current collective prescriptions for Estrie and Montérégie specify to refer to a physician any person bitten by a tick who presents with symptoms suggestive of Lyme disease. The advisory committee members consulted felt it appropriate to include this recommendation in the proposed collective prescription template, with the addition of an option to refer patients to a primary care specialized nurse practitioner.

No consensus was reached among the advisory committee members regarding systematically referring pregnant women bitten by a tick to a physician. However, as PEP is broadly contraindicated in this population, it was not deemed appropriate to include such a recommendation in the collective prescription template, especially since, in cases in which the physician is not well versed in the risks and benefits of PEP in this population, they will tend not to prescribe PEP and the patient will have sought medical care unnecessarily.

2.5. Pharmacoepidemiological Aspects

2.5.1. Results for question 8: Overview of PEP usage in Quebec

Question 8: Overview of PEP usage in Quebec
What is the state of the presumed use of doxycycline for Lyme disease in people covered by Quebec's public prescription drug insurance plan (RPAM)?

To contextualize the use of doxycycline for Lyme disease PEP in Quebec, INESSS completed a descriptive cross-sectional study based on RAMQ databases for each of the years from 2014 to 2018. The targeted individuals had to have received at least one prescription for a single day of doxycycline treatment paid for by RPAM.[36] These individuals, designated as users, also had to be covered continuously by RPAM during the year being studied.

The main results of this study show that:

- The distinct number of users prescribed doxycycline for the presumed indication of PEP more than quintupled over the five years studied, from 182 in 2014 to 973 in 2018.
- Two spikes in the monthly number of users have been observed each year since 2016: one from April until August, and one from October to November.
- In terms of percentage of prescriptions issued, family physicians lost ground to physicians specializing in public health and preventive and occupational medicine. From 2014 to 2017, family physicians issued 90% of prescriptions, and in 2018 this figure dropped to 71%. Physicians specializing in public health and preventive and occupational medicine issued 19% of prescriptions (N = 185) in 2018. This result appears to be directly related to the implementation of the collective prescriptions in Estrie and Montérégie.
- Multiple PEP prescriptions for a single person were rare.
- The distribution of users by socio-sanitary region for 2017 and 2018 shows a concentration of cases in Estrie and Montérégie, the two geographic areas at highest risk for Lyme disease.

For the full results of this study, refer to the *Portrait de l'usage de la doxycycline en prévention de la maladie de Lyme chez les personnes couvertes par le régime public d'assurance médicaments du Québec* [Overview of the use of doxycycline to prevent Lyme disease in individuals covered by Quebec's public prescription drug insurance plan] [INESSS, 2019b].

[36] RPAM covers just over 40% of Quebec residents, including nearly 95% of people age 65 and over.

3. DISCUSSION

3.1. Summary of Main Findings

The results of the INESSS systematic review on the efficacy and safety of single-dose doxycycline PEP for Lyme disease prevention revealed that the recommendation to use this type of prophylaxis is based on data that the majority of the members of the advisory committee consider to be of a low level of evidence. While the authors of a double-blind RCT [Nadelman et al., 2001] reported that single-dose doxycycline had a statistically significant effect in preventing the appearance of erythema migrans at the site of the bite versus a placebo in subjects age 12 and over, significant limitations that impact the internal and external validity of this trial were observed. Approximately one third of the members of the advisory committee considered the level of scientific evidence for this study to be insufficient, echoing the opinion of the AQML. At the same time, a majority of the members stated that single-dose doxycycline PEP was likely useful when the criteria for dispensing PEP in Quebec were met, especially in areas where the ecological conditions are similar to those in the Nadelman study—that is, when the black-legged tick makes up the vast majority of the local tick population, as clinicians do not identify tick species—and when the tick infestation rate exceeds 25%. When these conditions are not all met, it is likely that the number of people who must be treated with single-dose doxycycline to avoid one case of erythema migrans will be higher than that observed in this study (average NNT: 36).

Due to uncertainty about the true efficacy and safety of PEP, it is particularly important for the clinician and the patient or family member, as the case may be, to decide whether to dispense PEP through a shared decision-making process. The various treatment options should be presented (PEP + symptom monitoring or symptom monitoring alone), and the risks and benefits of each option should be discussed, as should information about the risk of Lyme disease transmission. The members of the advisory committee noted that many people do not know that the overall risk of contracting Lyme disease is low, including in high-risk geographic areas. In addition, the emerging disease is the subject of a great deal of media coverage. Thus, as the committee members observed, PEP is often prescribed in a highly emotional context. Putting this risk into perspective may help reduce anxiety about the disease.

It emerged from discussions with stakeholders that implementing a shared decision-making process for PEP is yet more important when the person bitten is a child under the age of 8, given the lack of data on the efficacy and safety of this treatment in children under 12 and the low level of evidence for data that show an absence of dental effects on permanent teeth in children exposed to doxycycline before the age of 8. While a general consensus was reached on the concept of providing PEP on a case-by-case basis to children under 8, no consensus was reached as to the inclusion or exclusion of this population when PEP is administered by a pharmacist or nurse under the collective prescription. In the end, it was decided to allow regional public health directorates that will administer the PEP collective prescriptions to make this choice depending on the feasibility of referring patients to a local physician or specialized nurse practitioner within the required timeframe for beginning the treatment.

For pregnant women, concerns surrounding the use of doxycycline were twofold: the risk of dental staining in the developing fetus when exposed to doxycycline during tooth calcification (during the second or third trimester of pregnancy) and the risk of congenital malformations, primarily during the first trimester. The risk of dental staining does not appear particularly problematic, but the scientific data on the risk of malformations are not currently conclusive. The advisory committee members felt that, on the whole, it was best not to immediately provide PEP to pregnant women who meet the PEP eligibility criteria.

Lastly, it should be noted that the available scientific data for other antibiotics studied for Lyme disease PEP, including amoxicillin, are currently insufficient to recommend their use in populations for which doxycycline is contraindicated.

The clinical procedure proposed for the provincial medical protocol on PEP is based on the procedure in the collective prescriptions for Estrie and Montérégie, though the content has been adapted according to the results of the systematic reviews conducted by INESSS and the experiential knowledge of the consulted stakeholders. Particular care was taken in selecting and defining the medical conditions to look for in patients before prescribing PEP. The consulted committee members were concerned about making sure PEP is carefully prescribed within a framework that minimizes the potential side effects of doxycycline use. Thus, certain conditions were designated as relative contraindications for PEP where the data in the literature were inconclusive as to whether a dose of doxycycline could have a real clinical impact (e.g., active liver disease, or a recent history of a complicated or severe *Clostridium difficile* episode). In addition, the consulted stakeholders felt it important to exclude from the indication of PEP all individuals with symptoms that are suggestive of Lyme disease and may be associated with the known tick bite or a previous tick bite, in the case of repeated exposure to ticks.

Surprisingly, the CPGs reviewed and the existing PEP tools in other provinces in Canada and in the United States do not address the procedure to follow when deciding on the indication for PEP when redness is present at the site of the bite. However, this emerged as an issue of great importance during discussions with stakeholders. Clinical, professional and organizational challenges were also brought up during these discussions. The consulted clinicians validated the concept of conducting a clinical evaluation on a case-by-case basis and helped define the general guidelines for deciding whether to administer PEP when redness is present at the site of the bite. However, due to a lack of sufficient scientific data, it was not possible to reach a consensus on the criteria that must be fulfilled for a pharmacist to administer PEP under a collective prescription when the patient presents with redness at the site of the bite. Out of an abundance of caution, and given that establishing a differential diagnosis between early-stage erythema migrans and a hypersensitivity reaction is not within the scope of expertise of professionals capable of applying a collective prescription, it is suggested that any redness should constitute a contraindication for PEP, as is the case in the current collective prescriptions for Estrie and Montérégie.

Note that INESSS did not set out to modify the PEP access criteria. However, in the course of its work, INESSS found it pertinent to propose two adjustments to these criteria: the 72-hour timeframe should begin at the time the tick is removed and end at the moment doxycycline treatment is begun (rather than the moment of consultation) to account for delays that may occur between seeking medical care and beginning treatment, and to align with the findings of Nadelman's RCT on single-dose doxycycline. In addition, to reduce the number of people unnecessarily exposed to PEP, it recommended confirming that the bite was caused by a tick. To this end, simple, observable indicators that can, for example, be identified in a photo taken on a smartphone and enlarged, were defined with the assistance of the LSPQ.

3.2. Strengths and Limitations of the Assessment

One of the primary strengths of this report is its reliance on a rigorous and transparent methodology. CPGs and systematic reviews of primary studies, as applicable, were systematically searched by scientific information specialists in order to respond to all of the previously defined research questions. The quality of the body of literature was evaluated and an analytical synthesis of the results from the selected documents was completed. In addition, INESSS's research on Lyme disease, including PEP, was the subject of a number of consultations with stakeholders, including a large panel of first- and second-line health

professionals, along with patients and representatives from patient associations. These consultations brought to light a wide range of perspectives, experiences and challenges, which helped improve the relevance of the recommendations and tools developed. However, a number of limitations must be mentioned.

With regard to the low—at times, insufficient—level of evidence for available data on single-dose doxycycline PEP, and considering the opinions of the stakeholders consulted, it appears that the foundation for the very concept of providing PEP in Quebec is not as solid as previous work on this topic would suggest. Some stakeholders even suggested that PEP should be applied within a strict research framework only in the regions of Estrie and Montérégie, in order to document specific essential aspects (frequency of redness at the site of the bite, size of red patches, availability of the tick, side effects of PEP, symptoms, etc.).

Moreover, optimal use of single-dose doxycycline PEP cannot be dissociated from the ecological conditions of the areas in which it is applied. Based on contextual and experiential data collected, the ecological conditions in Granby and Cowansville are similar to those of the hyperendemic region of the United States in which the Nadelman study was conducted, as it has been reported that in both areas, the black-legged tick makes up the majority of the tick population and the prevalence of *Borrelia burgdorferi* is close to 30% on average. However, currently, available data on acarological surveillance in Quebec are insufficient to conclude whether the ecological conditions of the Nadelman study are present in all areas eligible for PEP.

3.3. Clinical and Organizational Impact

The publication of the INESSS provincial medical protocol and knowledge transfer tools concerning single-dose doxycycline PEP for Lyme disease should better equip health professionals, particularly primary care professionals, to treat individuals who seek care for a tick bite and determine whether PEP is appropriate. These documents specify the clinical procedure to adopt, the criteria for dispensing PEP and the circumstances under which PEP should not be initiated. They are also intended to increase the general level of knowledge about how Lyme disease transmission occurs and the risk of contracting Lyme disease. The ultimate goal is to reduce the number of cases of Lyme disease through proper application of PEP coupled with increased vigilance with respect to primary prevention measures and monitoring for symptoms suggestive of the disease.

Implementing collective prescriptions based on the INESSS provincial medical protocol should facilitate access to PEP in accordance with the standardized procedures of socio-sanitary regions. It should also reduce delays in receiving care—an important consideration, given the necessity of beginning doxycycline treatment within 72 hours of removing the tick after a bite.

3.4. Impact on Research

In order to enhance knowledge of PEP and improve the level of scientific evidence for PEP, and considering the availability of research funds earmarked for Lyme disease since 2018, researchers and research institutes may consider conducting studies on the true efficacy and safety of single-dose doxycycline PEP, its effects on the clinical presentation of subjects who have developed Lyme disease, the application of this type of PEP in Quebec and the efficacy and safety of other means of Lyme disease prophylaxis. It would also be useful to lead human studies to better assess the risk of Lyme disease transmission in relation to, for example, the duration of attachment of the infested tick.

RECOMMENDATIONS

Each of the clinical recommendations presented below was developed in consideration of the data from the scientific literature, recommendations for best clinical practices, contextual information and experiential knowledge from the consulted stakeholders.

1. Application of single-dose doxycycline PEP by population

Adults and children age 8 and up:

1.1. Single-dose doxycycline PEP for Lyme disease may be offered to adults and children age 8 and up bitten by a tick in a high-risk geographic area eligible for PEP as defined by the MSSS, provided that the following criteria are met:

- The specimen is still attached to the skin and has been identified as a tick, or the specimen has already been removed from the skin, but it is possible to determine that it is in fact a tick.
- AND the patient does not present any signs or symptoms suggestive of Lyme disease.
- AND 72 hours or less have elapsed between the moment the tick was removed and the moment PEP would be initiated.
- AND the tick was attached to the skin for 24 hours or more.

Children under the age of 8:

1.2. The available scientific data are insufficient to issue recommendations on the use of single-dose doxycycline PEP for Lyme disease prevention in children under the age of 8. However, considering the results on the efficacy and safety of a single 200 mg dose of doxycycline for this indication in individuals ages 12 and up, along with safety data that suggest an absence of visible dental effects on permanent teeth following exposure to doxycycline before the age of 8, doxycycline PEP may be considered on a case-by-case basis for children under 8 in the context of a shared decision-making process engaged in with the family when all of the criteria for receiving PEP are met.

Pregnant women:

1.3. Given the current state of knowledge, single-dose doxycycline PEP for Lyme disease prevention should not be systematically offered to pregnant women who meet the criteria for receiving it. When in doubt, health professionals should seek the opinion of a microbiologist / infectious diseases specialist, obstetrician-gynecologist or centre specializing in pregnancy before deciding whether to offer PEP.

Breastfeeding women:

1.4. For breastfeeding women, the use of single-dose doxycycline PEP for Lyme disease prevention may be considered under the conditions specified for adults and children age 8 and up.

2. Contraindications for providing single-dose doxycycline PEP

2.1. Single-dose doxycycline PEP should not be provided in the following situations:

- When the bite was sustained in a geographic area not eligible for PEP
- When the patient reports a recent history of a bite and it is not possible to determine that the specimen is in fact a tick

- When the patient presents with symptoms suggestive of Lyme disease
- When the patient has a history of allergic reaction to antibiotics in the tetracycline class (doxycycline, minocycline, tetracycline, etc.)

3. Health conditions to investigate before prescribing PEP that constitute contraindications for the use of single-dose doxycycline or that require certain precautions

3.1. Before beginning single-dose doxycycline PEP for Lyme disease prevention, the following health conditions should be looked for in patients:

- Breastfeeding
- History or active episode of esophagitis or esophageal ulcers
- History of allergic reaction to antibiotics in the tetracycline class (doxycycline, minocycline, tetracycline, etc.) (**absolute contraindication**)
- History of photosensitivity reactions following intake of doxycycline
- Severe or complicated case of *Clostridium difficile* infection that has been resolved for less than 30 days
- Pregnancy (**relative contraindication**)
- Active liver disease (**relative contraindication**)
- Poorly controlled or decompensated myasthenia gravis (**relative contraindication**)
- Obstructive esophageal conditions (stenosis, achalasia, etc.) (**relative contraindication**)

4. Verification of an individual's asymptomatic condition

4.1. Before beginning single-dose doxycycline PEP for Lyme disease prevention, the health professional should verify the absence of symptoms suggestive of Lyme disease (associated with the bite that prompted the patient to seek care or with a previous bite, if the person has a history of repeated exposure to ticks):

- skin manifestations: redness that may be indicative of EM at the site of the bite or elsewhere on the body
- musculoskeletal manifestations (e.g., significant swelling of the knee)
- neurological manifestations (e.g., facial paralysis)
- cardiac manifestations (e.g., chest pains, palpitations, dizziness)
- general systemic symptoms that developed after the bite (headache, fever/shivering, stiffness or pain at the nape of the neck, muscle or joint pain).

4.2. Any person presenting with symptoms suggestive of Lyme disease should not receive PEP and should undergo a clinical evaluation to receive the appropriate treatment as necessary.

5. Procedure to follow in the case of redness at the site of the bite

5.1. When redness is present at the site of the bite, a clinical assessment should be completed on a case-by-case basis.

5.2. Single-dose doxycycline PEP should not be administered if redness may be indicative of early-stage erythema migrans, as erythema migrans must be treated with a full course of antibiotics.

5.3. If the nature of the redness is unclear, it is recommended that the health professional monitor the evolution of the redness (outline the red patch) and wait 24 to 48 hours before beginning PEP if time permits (follow-up appointment or instructions to the person bitten).

5.4. For all cases, if a red patch is larger than 5 cm in diameter or if a red patch of less than 5 cm in diameter persists for more than 72 hours after the tick is removed, the patient should consult a physician or primary care specialized nurse practitioner to receive a full course of antibiotic treatment for the erythema, if appropriate.

6. Analysis of microbial agents in ticks

6.1. The results of microbial agent detection tests in ticks should not be used to decide whether to prescribe PEP or to issue a diagnosis of Lyme disease.

7. Shared decision

7.1. Single-dose doxycycline PEP for Lyme disease prevention should be initiated after a shared decision is reached through an informed discussion between the clinician and the person for whom the indication for PEP has been validated. This discussion should cover the risk of contracting Lyme disease, the different treatment options available and the potential risks and benefits of each option. The final decision should take into account the person's values and preferences.

8. Dosage

8.1. When indicated, doxycycline PEP should be prescribed in the following dosages:

- Age < 12, single dose PO:

− if weight ≥ 45 kg: 200 mg

− if weight < 45 kg: 4.4 mg/kg (maximum 200 mg)

- Age > 12, single 200 mg dose PO

8.2. Doxycycline should be taken within 72 hours of removing the tick.

9. Other antibiotics

9.1. For those who fulfil the criteria for Lyme disease PEP but who cannot be treated with doxycycline, the only course of action recommended is monitoring for the appearance of symptoms suggestive of Lyme disease, and the person should be instructed to seek care from a physician or primary care specialized nurse practitioner should these symptoms appear. No antibiotic, including amoxicillin, other than single-dose doxycycline has been proven effective at preventing Lyme disease.

10. Instructions and information to provide

10.1. All people who seek care for a tick bite, regardless of the region in which the bite was sustained or the decision concerning the dispensation of PEP, should receive:

- instructions to monitor for symptoms suggestive of Lyme disease that may appear within 30 days of the bite or later
- instructions to seek care from a physician or primary care specialized nurse practitioner if any of these symptoms appear
- information on how to avoid sustaining new tick bites.

10.2. All people who receive single-dose doxycycline PEP for Lyme disease prevention should be informed of the following:

- the time limit before which PEP should be taken, in consideration of the maximum limit of 72 hours after removing the tick
- the importance of monitoring for symptoms suggestive of Lyme disease that may appear, given that the efficacy of PEP is not guaranteed
- the main side effects of doxycycline
- the precautions that should be taken to avoid photosensitivity reactions and gastrointestinal distress.

CONCLUSION

INESSS's research on PEP for Lyme disease prevention made it possible to better define the absolute and relative contraindications to consider before prescribing single-dose doxycycline, and to define the recommended dosage in children. Drawing on the current collective prescriptions for Estrie and Montérégie, and taking into account the available scientific data and best practices, as well as experiential knowledge of Quebec clinicians, this project also helped define the clinical procedure to be followed when initiating single-dose doxycycline PEP. Considering the general low level of evidence for the available data and existing uncertainties about the benefits and risks of this intervention, it is suggested, at the end of this project, that once the indication is validated, PEP be initiated after a shared decision is reached between the clinician and the patient. Regardless of the decision made, this will also provide an opportunity to educate the patient about the importance of monitoring for the appearance of Lyme disease symptoms to ensure proper treatment. Lastly, the provincial medical protocol on PEP should facilitate the implementation of collective prescriptions by regional public health directorates through a unified provincial framework in order to provide faster access to PEP when required.

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APPENDIX A: Assessment criteria for the quality of scientific data, level of scientific evidence and value of the body of evidence

Table A-1. Assessment form for the quality of scientific evidence

Assessment criteria	Assessment scale
Methodological quality of studies • Number of studies included in the data synthesis • Optimal study design for answering the assessment question • Risk of bias / respect for methodological criteria • Accuracy (optimal sample size and statistical power)	**High quality** • At least one study or one synthesis of studies whose study designs are appropriate for answering the assessment or practice question, of good methodological quality with a low risk of bias. OR • Several studies or one synthesis of studies whose study designs are sufficiently appropriate for answering the assessment or practice question, of good methodological quality with a low risk of bias. **Moderate quality** • One or two studies whose study designs are sufficiently appropriate for answering the assessment or practice question, of good methodological quality with a low risk of bias. • One synthesis of studies whose study designs are not very appropriate for answering the clinical or assessment question, of good methodological quality with a low risk of bias. **Low quality** • Several studies or one synthesis of studies whose study designs are appropriate for answering the assessment or practice question, of medium methodological quality with a moderate risk of bias. • One or two studies whose study designs are not very appropriate for answering the assessment or practice question, of good methodological quality with a moderate risk of bias. **Very low quality** • Several studies or one synthesis of studies whose study designs are appropriate for answering the assessment or practice question, of low methodological quality with a major risk of bias. • Several studies or one synthesis of studies whose study designs are sufficiently appropriate for answering the assessment or practice question, of low methodological quality and a major risk of bias. • At least one study or synthesis of studies whose study designs are not very appropriate for answering the assessment or practice question, of low methodological quality with a major risk of bias.

Assessment criteria	Assessment scale
Consistency/reliability (dependability) • Consistency in the effect of the intervention, considering the comparability of populations, methods and measurement tools • Complementarity and diversity of methods and measures	**Very high consistency** • All studies are consistent. **High consistency** • Most studies are consistent, and inconsistency can be explained. **Moderate consistency** • Inconsistency reflects true uncertainty surrounding the clinical question. **Low consistency** • Studies are inconsistent. **Not applicable** (one single study)
Clinical or organizational impact • Clinical/organizational/social significance of the effect • Achievement of intervention objectives	**Very high impact** • The clinical impact of the results is very substantial. **High impact** • The clinical impact of the results is substantial or significant. **Moderate impact** • The clinical impact of the results is moderate. **Low impact** • The clinical impact of the results is limited or insufficient.
Generalizability/transferability • Similarity between the studied population and context and those targeted • Adaptability of the intervention	**Very high generalizability/transferability** • The studied population is the same as the target population. Thus, the results reported in the literature are generalizable to the target population. **High generalizability/transferability** • The studied population is similar to the target population. Thus, the results reported in the literature are generalizable to the target population, with some caveats. **Moderate generalizability/transferability** • The studied population differs from the target population. Thus, the results reported in the literature are not directly generalizable to the target population, but may be applied judiciously to the target population. **Low generalizability/transferability** • The studied population differs from the target population. Thus, the results reported in the literature are not directly generalizable to the target population and it is difficult to determine whether it is wise to apply them to the target population.

Table A-2. Level of evidence assigned based on evidence assessment criteria

Level of evidence	Definition
High	All criteria were positively assessed. The reviewers have a high level of confidence that the effect estimate is comparable to the intervention's objectives. It is unlikely that the conclusion drawn from the scientific data will be significantly impacted by the results of future studies.
Moderate	The majority of criteria were positively assessed. The reviewers have a moderate level of confidence that the effect estimate is comparable to the intervention's objectives. It is somewhat likely that the conclusion drawn from the scientific data will be significantly impacted by the results of future studies.
Low	All or most of the criteria were negatively assessed. The reviewers have a low level of confidence that the effect estimate is comparable to the intervention's objectives. It is very likely that the conclusion drawn from the scientific data will be significantly impacted by the results of future studies.
Insufficient	No scientific data are available, or the available data are insufficient. The reviewers have no confidence in the relationship between the effect estimate and the intervention's objectives or cannot draw a conclusion from the data presented.

Table A-3. Decision making criteria for assessing the value of the body of evidence

Decision making criteria	Definition
Statement of scientific evidence and level of scientific evidence	Observations from the analysis of scientific data and the overall quality.
Clinical, epidemiological and organizational aspects	Aspects deemed important in the decision-making process leading to the recommendations: natural history of the disease or condition, severity of the disease or condition, prevalence and effective alternative treatments available, etc.
Applicability of the intervention	Assessment of the pertinence of observations from the scientific evidence to the health care system or the clinical context in which the recommendations will be implemented. Assessment of the applicability of the proposed intervention (barriers and facilitating factors). Assessment of the applicability of the proposed intervention (available resources). Conformity to social norms and values and compliance with laws and regulations.
Acceptability	Accessibility of the proposed intervention (geographic, organizational, economic, sociocultural). Administrative convenience of the proposed intervention. Expectations, preferences and values of patients, users and/or family members concerning the effects, risks and costs of the intervention. Preferences and values of care workers in the health and social services system concerning clinical and practical procedures for administering the intervention.

Headquarters

2535 Laurier Boulevard, 5th floor

Québec, Quebec G1V 4M3

418-643-1339

Montréal office

2021 Avenue Union, 12th floor, suite 1200

Montréal, Quebec H3A 2S9

514-873-2563

Institut national d'excellence en santé et en services sociaux

Québec