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Lyme Disease, from diagnosis to treatment, at the localized and disseminated stages

Report in support of knowledge transfer tools for diagnosis and treatment

Produced by the Institut national d'excellence en santé et en services sociaux (INESSS)

Medication directorate

Québec

Lyme Disease, from diagnosis to treatment, at the localized and disseminated stages

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The mission of the Association québécoise de la maladie de Lyme (AQML) is to raise awareness of Lyme disease and its 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 they were not involved in developing recommendations:

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Dr. Amir Kadir: public position statements (advocacy in the Assemblée nationale for devoting more resources to Lyme disease patient care, treatment and research); clinic specializing in treating Lyme disease.

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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.

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SUMMARY

Introduction

Lyme disease, a vector-borne disease transmitted by the black-legged tick, is on the rise in Québec. The number of confirmed or probable cases recorded in Québec's reportable diseases (MADO, maladies à déclaration obligatoire) registry doubled between 2013 and 2017 (143 vs. 329 cases). While there seems to be a consensus in the medical and scientific community regarding the definition and features of the localized stage of the disease, this is not the case for the early and late disseminated stages. Indeed, the distinction between the disseminated stages, post-treatment Lyme disease syndrome and the controversial form of the disease (sometimes referred to as "chronic") is not altogether clear, both with regard to medical practice and in the scientific literature. To address the lack of clear guidance on managing patients with Lyme disease in Québec, the Direction générale adjointe de la protection de la santé publique (DGAPSP), in collaboration with the Direction de la biovigilance et de la biologie médicale (DBBM) and the Direction des affaires pharmaceutiques et du médicament (DAPM) of the Ministère de la Santé et des Services sociaux (MSSS), asked the Institut national d'excellence en santé et en services sociaux (INESSS) to make recommendations and create knowledge transfer tools concerning post-exposure prophylaxis (PEP) for preventing Lyme disease and the identification, diagnosis and treatment of patients with this disease. This will help Québec's health professionals, especially those in primary care, to deal with this emerging disease. It was agreed with the requester that the project would be carried out in two parts. The first would address PEP and the localized and disseminated stages of the disease, while the second would concern the controversial form of Lyme disease (sometimes referred to as "chronic") and tick-borne co-infections. Publication of the second part is scheduled for 2020.

Methodology

To carry out that part of the project specifically dealing with identification, diagnosis and treatment, INESSS gathered scientific data, best clinical practice recommendations published by learned societies and health technology assessment agencies, contextual information and experiential knowledge in order to document the pathophysiological, epidemiological, technological, pharmacological, clinical and professional and organizational aspects and the patient-related issues.

To this end, a systematic search of the scientific literature published in French, English and German was conducted on these aspects and for clinical practice guidelines and guidance documents published in North America, Europe and Oceania. An additional search, using the Google search engine, was conducted for reports, practice standards, regulations and guidance documents. This search was extended to include the government websites of Canadian, American, French, British, New Zealand and Australian public health agencies and departments of health. The websites of Québec's regional public health departments, the Institut national de santé publique du Québec (INSPQ), the MSSS's Direction générale de santé publique and public documents from the Association québécoise de la maladie de Lyme (AQML) were consulted as well.

To gather experiential knowledge, INESSS created an advisory committee consisting of clinicians, including specialists in different disciplines, an expert in laboratory tests and acarological surveillance, and two patient partners who had been diagnosed with Lyme disease. This was supplemented by consultations with representatives from the AQML and interviews with eight patients who had contracted Lyme disease.

To ensure that the recommendations and clinical decision support tools would be contextualized to Québec's needs, they were developed with the advisory committee using analysis and triangulation of the scientific, contextual and experiential data and the practice standards recommended by different learned societies and health technology assessment agencies in Canada and abroad. To ensure compliance with the statute and regulations governing reserved professional activities, as well as the feasibility, applicability and acceptability of the recommendations intended for decision-makers and different stakeholders, and to check that the potential impact of implementation was taken into consideration, a follow-up committee consisting of representatives from the INSPQ, the Collège des médecins, the Ordre des infirmières et infirmiers du Québec, the Ordre des pharmaciens du Québec, the federations of general practitioners and medical specialists as well as the MSSS's DGAPSP, DBBM and Info-Santé was created. INESSS's Comité d'excellence clinique en usage optimal du médicament and the governance committee of the MSSS's DAPM were invited to raise other issues from a societal and strategic perspective.

Results

Making the diagnosis is the main challenge in Lyme disease. Its clinical presentation varies from patient to patient, both in terms of the type of manifestations and their severity and the pace of disease progression. Since the manifestations of Lyme disease can be consistent with an array of other diseases, the clinician should, in the presence of these manifestations, examine the possibility of tick exposure, perform a complete physical examination in search of other manifestations suggestive of Lyme disease, and consider the other possible clinical conditions. The only manifestation of Lyme disease from which the diagnosis can be made in a patient whose clinical picture is consistent is the typical isolated erythema migrans. Since isolated erythema migrans does not always have a typical appearance and is not always present or notice its absence should not lead the clinician to rule out Lyme disease. Two-tier serology has low sensitivity during the onset of the infection but increases as the disease progresses, with the result that it is high in patients with Lyme arthritis. However, the level of scientific evidence for the diagnostic value of two-tier serology is low or insufficient, mainly because of the studies' designs. Because of the limitations of the serological tests, their results are used mainly to complement the clinical picture and should not be used alone to make or rule out the diagnosis.

The approach to treating localized or disseminated stage Lyme disease does not seem to pose any particular problems once a diagnosis has been made. The recommended antibiotics are generally similar from one guideline to the next, but the scientific evidence is weak. The differences reside mainly in the duration of treatment, the route of administration and the ranking of the lines of therapy.

The analysis shows that it is crucial to properly assess the patient's overall condition before deciding on the antibiotic and the manner in which it will be administered, since failure to notice

manifestations of the early disseminated stage could lead to the wrong choice of antibiotic or a duration of treatment that is inappropriate for the patient's condition. As well, if there are any doubts about the diagnosis of Lyme disease, the treatment approach decision should be made jointly with one or more medical specialists or experienced colleagues. It would be advisable for patients with the early or late disseminated stage or persistent symptoms after treatment that cannot be explained by other clinical conditions to be managed by one or more specialists.

Conclusion

Lyme disease can be clinically challenging when it exhibits atypical cutaneous manifestations or multisystem symptoms, and it can become more complex if diagnosed and treated late. With the exception of the high-risk regions, such as the Eastern Townships and the Montérégie, Québec clinicians' experience with this emerging disease is, on the whole, limited. The recommendations and clinical decision support tools developed by INESSS are therefore a first step that could lead to practice changes for a better care experience.

RÉSUMÉ

Du diagnostic au traitement de la maladie de Lyme aux stades localisé et disséminés – Rapport en soutien aux outils d'aide à la décision clinique sur le diagnostic et le traitement

Introduction

La maladie de Lyme, maladie à transmission vectorielle par les tiques à pattes noires, est en progression au Québec. Le nombre de cas confirmés ou probables inclus au registre des maladies à déclaration obligatoire du Québec a doublé entre 2013 et 2017 (143 vs 329 cas). Alors que le stade localisé de la maladie semble faire l'unanimité dans la communauté médicale et scientifique quant à sa définition et ses caractéristiques, la situation est différente pour les stades disséminés précoce et tardif. En effet, la distinction entre les stades disséminés, le syndrome post-traitement de la maladie de Lyme et la forme controversée de la maladie (parfois dite chronique) manque de clarté tant sur le plan de la pratique médicale que de la littérature scientifique. Afin de pallier l'absence de lignes directrices claires concernant la prise en charge des patients atteints de la maladie de Lyme au Québec, la Direction générale adjointe de la protection de la santé publique (DGAPSP), en collaboration avec la Direction de la biovigilance et de la biologie médicale (DBBM) et celle des affaires pharmaceutiques et du médicament (DAPM) du ministère de la Santé et des Services sociaux (MSSS), a sollicité l'Institut national d'excellence en santé et en services sociaux (INESSS) afin d'établir des recommandations et des outils de transfert de connaissances concernant la prophylaxie post-exposition (PPE) en prévention de la maladie de Lyme, la reconnaissance, le diagnostic et le traitement des patients atteints de cette maladie. Cet exercice permettra d'outiller les professionnels de la santé québécois, particulièrement ceux en première ligne, afin qu'ils puissent faire face à cette maladie en émergence. Il a été convenu, avec le demandeur, que les travaux seraient réalisés en deux volets, le premier devant aborder la PPE ainsi que les stades localisé et disséminés de la maladie et le deuxième ayant comme sujet la forme controversée de la maladie de Lyme (parfois dite chronique) et les co-infections transmises par les tiques. La publication de ce deuxième volet est prévue en 2020.

Méthodologie

Pour réaliser la partie du mandat portant précisément sur la reconnaissance, l'établissement du diagnostic et le traitement, l'INESSS a colligé les données scientifiques, les recommandations de bonne pratique clinique publiées par des sociétés savantes et des agences d'évaluation, l'information contextuelle et les savoirs expérientiels pour documenter les aspects physiopathologiques, épidémiologiques, technologiques, pharmacologiques, cliniques, professionnels et organisationnels de même que les enjeux des patients.

Pour ce faire, l'INESSS a réalisé une recherche systématique de la littérature scientifique publiée en français, en anglais et en allemand sur les aspects à documenter, puis des guides de pratique et lignes directrices publiés en Amérique du Nord, en Europe et en Océanie. Une recherche complémentaire au moyen du moteur de recherche Google a aussi été effectuée afin de repérer

des rapports, normes de pratique, règlements et lignes directrices publiés puis elle s'est étendue aux sites Web gouvernementaux des agences de santé publique et ministères de la santé canadiens, états-uniens, français, britanniques, néozélandais et australiens. Les sites Web des directions de santé publique régionales québécoises, de l'Institut national en santé publique du Québec (INSPQ) puis de la Direction générale de santé publique du MSSS ainsi que les documents publics de l'Association québécoise de la maladie de Lyme (AQML) ont aussi été consultés.

Pour recueillir les savoirs expérientiels, l'INESSS a créé un comité consultatif formé de cliniciens, dont des médecins spécialistes dans différentes disciplines, d'un expert en analyse de laboratoire et en surveillance acarologique, puis de deux patients partenaires qui ont reçu un diagnostic de maladie de Lyme. Des consultations avec des représentants de l'AQML puis des entrevues avec huit patients qui ont contracté la maladie de Lyme ont complété la collecte des savoirs expérientiels.

Pour que les recommandations ainsi que les outils d'aide à la décision clinique soient contextualisés par rapport aux besoins du Québec, ils ont été élaborés avec le comité consultatif à partir de l'analyse et de la triangulation des données scientifiques, contextuelles et expérientielles de même que des standards de pratiques recommandées par différentes sociétés savantes et agences d'évaluation au Canada et à l'international. Pour s'assurer de la conformité à la loi et aux règlements qui encadrent les activités professionnelles réservées, puis de la faisabilité, de l'applicabilité et de l'acceptabilité des recommandations destinées aux décideurs et à différentes parties prenantes de même que pour vérifier que les impacts potentiels de la mise en œuvre ont été considérés, un comité de suivi formé de représentants de la DGAPSP, de la DBBM et d'Info-santé du MSSS, de l'INSPQ, du Collège des médecins, de l'Ordre des infirmières et infirmiers du Québec, de l'Ordre des pharmaciens du Québec ainsi que des fédérations des omnipraticiens et des médecins spécialistes a aussi été créé. Le Comité d'excellence clinique en usage optimal du médicament et le comité de gouvernance de la DAPM du MSSS ont aussi été mis à contribution pour soulever d'autres enjeux dans une perspective sociétale et stratégique.

Résultats

L'établissement du diagnostic est l'enjeu principal de la maladie de Lyme.La présentation de la maladie varie d'un patient à l'autre, tant en ce qui concerne le type des manifestations que leur intensité et la vitesse de progression de la maladie. Comme les manifestations de la maladie de Lyme peuvent être compatibles avec une variété d'autres maladies, il convient en leur présence d'évaluer la possibilité d'exposition aux tiques, de faire un examen physique complet à la recherche d'autres manifestations évocatrices de la maladie et de considérer les autres conditions cliniques possibles. La seule manifestation de la maladie de Lyme qui permet d'établir le diagnostic chez un patient dont le tableau clinique est compatible est l'érythème migrant isolé typique. Puisque l'érythème migrant isolé n'a pas toujours un aspect typique et qu'il n'est pas toujours présent ni remarqué, son absence ne doit pas conduire à l'exclusion du diagnostic.

La sérologie à deux volets a une sensibilité faible au début de l'infection. Cette dernière augmente avec la progression de la maladie de sorte qu'elle est élevée chez les patients atteints d'arthrite de Lyme. Le niveau de preuve scientifique de la valeur diagnostique de la sérologie à deux volets est cependant faible ou insuffisant compte tenu principalement du devis des études.

En raison des limites des tests sérologiques, leurs résultats servent à complémenter le tableau clinique et ne devraient pas à eux seuls servir à établir le diagnostic ou à l'exclure.

La conduite thérapeutique à tenir pour traiter la maladie de Lyme aux stades localisé et disséminés ne semble pas poser un enjeu particulier lorsque le diagnostic a été établi. Les antibiotiques recommandés sont généralement comparables d'un guide de pratique à l'autre, mais les preuves scientifiques sont de faible niveau. Les variations se situent plutôt à l'égard de la durée du traitement, de la voie d'administration et de la hiérarchie des intentions de traitement.

Il ressort de l'analyse qu'une bonne évaluation de l'état général du patient est cruciale avant de choisir l'antibiotique et ses modalités d'usage puisque la présence de manifestations du stade disséminé précoce non repérées pourrait entraîner un mauvais choix d'antibiotique ou une durée de traitement inappropriée à la condition du patient. Par ailleurs, en présence de doutes à propos du diagnostic de maladie de Lyme, la décision d'une conduite thérapeutique devrait être prise conjointement avec un ou des médecins spécialistes ou collègues expérimentés. La prise en charge de patients qui se présentent avec un stade disséminé précoce ou tardif, ou des symptômes persistants post-traitement qui ne peuvent s'expliquer par d'autres conditions cliniques, aurait aussi avantage à être faite par un ou des médecins spécialistes.

Conclusion

La maladie de Lyme peut poser un défi clinique lorsqu'elle se présente par des atteintes cutanées atypiques ou des symptômes multisystémiques, et elle peut se complexifier si le diagnostic et le traitement surviennent tardivement. À l'exception des régions à haut risque comme l'Estrie et la Montérégie, l'expérience des cliniciens québécois en ce qui a trait à cette maladie émergente est somme toute limitée. C'est pourquoi les recommandations et les outils d'aide à la décision clinique élaborés par l'INESSS sont une première étape qui pourrait amener des changements dans la pratique afin d'offrir une expérience de soins améliorée.

ACRONYMS AND ABBREVIATIONS

AACODS	Authority, accuracy, coverage, objectivity, date and significance
AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
AC	Advisory committee
ACP	American College of Physicians
AGREE	Appraisal of Guidelines for Research and Evaluation
AHPPC	Australian Health Protection Principal Committee
ALAT	Alanine aminotransferase
AMMI	Association of Medical Microbiology and Infectious Disease
AQML	Association québécoise de la maladie de Lyme
AR	Absolute risk
ARR	Absolute risk reduction
ASAT	Aspartate aminotransferase
ASC-PCP	Advisory subcommittee on the provincial medical protocol and collective prescription template
AU-ROC	Area under the ROC curve
BID	*Bis in die*: twice daily
CASP	Critical Appraisal Skills Programme
CDC	Centers for Disease Control and Prevention
CEC	Clinical Excellence Committee
CEC-OMU	Clinical Excellence Committee on Optimal Medication Use
CEPPP	Centre of Excellence on Partnership with Patients and the Public
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
CNS	Central nervous system

CPG	Clinical practice guideline
CPS	Canadian Paediatric Society
CRDS	Service Request Dispatch Centre
CSF	Cerebrospinal fluid
d	Day
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
DGKJ	German Society of Pediatrics and Adolescent Medicine
DGN	German Neurological Society
DGSHMSU	Direction générale des services hospitaliers, de la médecine spécialisée et universitaire
DSP	Direction de santé publique
EBM	Evidence-Based Medicine Reviews database
e-CPS	Online Compendium of Pharmaceuticals and Specialties
ELISA	Enzyme-linked immunosorbent assay
EM	Erythema migrans
FCFPC	Fellow in the College of Family Physicians of Canada
FDA	Food and Drug Administration
FMOQ	Fédération des médecins omnipraticiens du Québec
FMSQ	Fédération des médecins spécialistes du Québec
FOPQ	Fellow de l'Ordre des pharmaciens du Québec
GAPAH	German Academy for Pediatrics and Adolescent Health
GDS	German Dermatological Society
GKJR	German Society for Pediatric Rheumatology
GL	Guideline
GMF	Family medicine group
HAS	Haute Autorité de Santé
HTA	Health technology assessment
IDSA	Infectious Diseases Society of America
Ig	Immunoglobulin
ILADS	International Lyme and Associated Diseases Society

IM	Intramuscular
IMAGe	Info-médicaments en allaitement et grossesse
INESSS	Institut national d'excellence en santé et en services sociaux
INSPQ	Institut national de santé publique du Québec
IV	Intravenous
kg	Kilogram
LDDWG	Lyme Disease Diagnostic Working Group
LSPQ	Laboratoire de santé publique du Québec
MADO	Reportable diseases
MC	Monitoring committee
mg	Milligram
MSSS	Ministère de la Santé et des Services sociaux
MUHC	McGill University Health Centre
NCCID	National Collaborating Centre for Infectious Diseases
NICE	National Institute for Health and Care Excellence
NLR	Negative likelihood ratio
NML	National Microbiology Laboratory
NNT	Number needed to treat
NPV	Negative predictive value
NSAID	Non-steroidal anti-inflammatory drug
OIIQ	Ordre des infirmières et infirmiers du Québec
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
PLR	Positive likelihood ratio
PNS	Peripheral nervous system
PO	*Per os*: by mouth
PPV	Positive predictive value
PR	Prevalence ratio

PSEID	Polish Society of Epidemiology and Infectious Diseases
PTLDS	Post-treatment Lyme disease syndrome
QD	*Quaque die*: once daily
QID	*Quater in die*: four times daily
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
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
SF	Synovial fluid
SR	Systematic review
SSID	Swiss Society for Infectious Diseases
TID	*Ter in die*: three times daily
U	Unit
WHO	World Health Organization

GLOSSARY

This glossary's definitions regarding Lyme disease were developed during this project based on data and information from the scientific literature and on the experiential knowledge of the members of the advisory committee, within the context of Quebec practice. The other definitions come from specialized dictionaries and glossaries.

Bacterial strain

A strain is a part of a bacterial genospecies that is distinguished from other bacteria of the same genospecies by a minor but identifiable difference.

Clinical diagnosis

Diagnosis based on information from the patient's medical history and a physical examination. Laboratory test results are not required, but can provide further information.

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.

Diagnosis

The determination of the nature of a disease by means of its signs and symptoms and the results of investigations.

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. 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.

ELISA

Enzyme-linked immunosorbent assay. Qualitative or quantitative assay test of tagged molecules based on an antibody's ability to bond with a specific antigen.

Genospecies

The equivalent of a species for bacteria, constituting a collection of genetic variations which are more similar to each other than to another genospecies.

Immunoblotting

1. Immunological technique (western blot or immunoblot) used to identify proteins

2. Transfer of proteins separated by electrophoresis onto an appropriate medium, usually a nitrocellulose membrane.

Late disseminated stage

Stage of Lyme disease generally characterized by the progression of the early 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 within four weeks of the transmission of bacteria by an infested tick.

Lyme arthritis

Inflammation of one or more joints, beginning some months after the bacteria have disseminated. Lyme arthritis usually presents with significant swelling of major joints (primarily the knee). Inflammatory flare-ups can last for several weeks or even months, be interspersed with periods of remission when untreated, and migrate from one joint to another.

Lyme carditis

Cardiac impairment caused by bacterial dissemination. The primary manifestation is an atrioventricular block.

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 genospecies and the stage of the disease and may include cutaneous, neurological, musculoskeletal, cardiac and/or ocular manifestations.

Multiple erythema migrans

Erythematous skin lesions that appear after the bacteria have disseminated. While they may share certain characteristics with solitary erythema migrans, their presentation (number, colour, appearance and size) is highly variable.

Neuroborreliosis

Condition of the nervous system (peripheral or central) or meninges in response to bacterial dissemination. Neurological manifestations vary according to the location of inflammation and may present singly or in combination. Some occur as soon as the bacteria have disseminated, while others are rarer and occur months later.

Non-neurological Lyme-related ocular impairment

Infection of the anterior layer (cornea) and/or posterior layers (choroid and retina) of the eye after the bacteria have disseminated. Differs from optic nerve impairment.

Persistent symptoms after Lyme disease treatment

Persistence of symptoms several weeks or months after the appropriate treatment for a patient officially diagnosed with Lyme disease. These symptoms cannot be explained by any other cause. According to current medical thinking based on human studies, they may result from damage caused by the infection (for example, changes to the functioning of the immune system or nervous system) rather than a continuing active infection. Note: this definition is subject to change as medical knowledge advances and better diagnostic tests become available.

Post-exposure prophylaxis

Preventative 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.

Prevalence

The number of people in a population with a specific disease or condition at a given time, usually expressed as a proportion of the number of affected people to the total population.

Provincial medical protocol

Reference document that professionals and qualified 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.

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)].

Serology

The study of serum, particularly the antibodies found in it.

Seropositivity

The state of having the antibodies being tested for in a serodiagnosis.

Signatory physician

Signatory physician(s) are physicians who adhere to a collective prescription and, by doing so, give their approval and permission for a professional or qualified person to carry out certain forms of medical care with patients covered by the prescription.

Solitary erythema migrans

Isolated erythematous skin lesion that generally appears between 3 and 30 days after bacteria are transmitted from an infested tick and may persist and change over several days. An erythema migrans rash usually spreads concentrically outward from the site of the bite to a diameter of more than 5 cm and causes little or no pain or itching. However, its characteristics (size, shape and appearance) and duration vary considerably between individuals. While a bull's eye rash

(concentric red rings) may also be caused by other factors, this type of lesion is highly suggestive of Lyme disease infection when the affected individual has been in a high-risk area.

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)].

Typical solitary erythema migrans

Circular skin rash, generally progressive, that is at least 5 cm in diameter, lasts at least 48 hours and is associated with little or no pain or itching. The lesion may be homogenous or ring-shaped and does not always look like a bull's eye. It may also be very pale and have poorly defined margins.

Two-tier serology

Serologic testing that combines the results of two laboratory tests to increase their diagnostic value.

INTRODUCTION

Research topic

Lyme disease results from an infection by bacteria of the complex *Borrelia burgdorferi* sensu lato (which includes 21 bacterial genospecies) following the bite of a black-legged tick. Diagnosis is complicated by the facts that the majority of patients do not remember being bitten, that a non-negligible proportion of patients do not observe clinical manifestations of the disease until it's at an advanced stage, and that the serologic tests have significant limitations. Furthermore, other clinical conditions, including other tick-borne illnesses, can have similar signs and symptoms to Lyme disease, which adds another layer of difficulty to the diagnosis.

While the definition and characteristics of early-stage Lyme disease seem to be universally agreed upon in the medical and scientific community, the same is not true for the later stages. Indeed, the distinction between the disseminated stages, post-treatment Lyme disease syndrome and so-called chronic Lyme disease is not a clear one, neither in medical practice nor in the scientific literature. Chronic Lyme disease is also the subject of controversy, with many health professionals and researchers worldwide questioning whether it exists.

Lyme disease is poorly understood by the general public. Patients' associations are working to have the so-called chronic form of the disease recognized and are calling for better care. Believing that Quebec health professionals know little about Lyme disease, some patients have turned to private US laboratories for a Lyme disease diagnosis, and so gain recognition of their condition. However, not all of these laboratories follow the interpretation standards of the Centers for Disease Control (CDC) and their positive results are largely questionable, especially as regards the reliability and validity of the tests used in establishing a diagnosis [Gregson et al., 2015]. Many beliefs about Lyme disease are also passed around websites and social media, contributing to the confusion.

Context

Lyme disease is a growing concern in Quebec. It has been monitored through the registry of reportable diseases (MADO) since November 2003. While the cases in this registry do not represent all affected patients, they do demonstrate the progression of the disease. The first case of Lyme disease contracted in Quebec was declared in 2006, and since then the total number of cases in the MADO registry has increased each year. It doubled between 2013 (143 cases) and 2017 (329 cases).[1] Of the 301 cases registered in 2018, 219 contracted the disease inside Quebec.[2] The number of cases in the MADO registry varies by socio-sanitary region. Three regions had no cases of Lyme disease in 2018 (Nord-du-Québec, Nunavik and Terres-Cries-de-la-Baie-James), and five others had only cases where the disease had been contracted outside Quebec.

[1] Ministère de la Santé et des Services sociaux (MSSS). Maladie de Lyme. Tableau des cas humains - Archives 2013 à 2017 [website, French only]. Available at http://www.msss.gouv.qc.ca/professionnels/zoonoses/maladie-lyme/tableau-des-cas-humains-lyme-archives/ (consulted February 5, 2019).
[2] 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/ (consulted February 5, 2019).

Black-legged ticks are currently established in four of Quebec's socio-sanitary regions: Montérégie, Estrie, Outaouais and Centre-du-Québec [INSPQ, 2018]. The tick is said to be established in a given region when all three of its stages of maturity have been observed there. Once established, the tick is there to stay. Due to climate change and with the help of forest animals and migratory birds, black-legged ticks are predicted to continue establishing themselves in other parts of the province.

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 Institut national de santé publique du Québec (INSPQ) are responsible for monitoring Lyme disease through the MADO registry and monitoring ticks, but no public institution is officially tasked with addressing the clinical and therapeutic aspects of the disease.

In order to remedy the absence of clear guidelines on caring for patients with Lyme disease in Quebec, the DGAPSP, in concert with the MSSS's Direction de la biovigilance et de la biologie médicale (DBBM) and Direction des affaires pharmaceutiques et du médicament (DAPM), called on INESSS to issue recommendations and develop knowledge transfer tools on preventative post-exposure prophylaxis (PEP) and recognizing, diagnosing and treating patients with Lyme disease. The goal was to equip health care professionals, especially primary care providers, to deal with this emerging illness. With the requesting organizations, it was agreed that the work would be divided into two components, the first of which would address PEP and the localized and disseminated stages of Lyme disease and the second of which would address the controversial form of Lyme disease (sometimes referred to as "chronic") and tick-borne co-infections. The second component is expected to be published in 2020.

Deliverables

The first component of this project has produced five deliverables:

- a notice including observations and recommendations intended for decision makers and other targeted stakeholders
- a supporting report on knowledge transfer tools concerning PEP after a tick bite in a high-risk area. These include 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 doxycycline usage in Lyme disease prevention by those covered by Quebec's public prescription drug insurance plan (RPAM)
- a supporting report on knowledge transfer tools on overall care of patients with localized or disseminated Lyme disease, from diagnosis to treatment. These include a decision support tool for diagnosing Lyme disease at the localized and disseminated stages, two optimal use guides for antibiotic therapy depending on patient age, a follow-up sheet for patients and an information sheet on two-tier serology
- a state of knowledge report on the diagnostic value of laboratory analysis.

Objectives

This supporting report presents the information and arguments that were used in developing these clinical recommendations and knowledge transfer tools. Their objectives are to:

- ensure that Lyme disease terminology is consistent
- demystify Lyme disease's various clinical manifestations
- demystify laboratory analysis to optimize its use
- support clinicians in:
    - evaluating the risks of tick exposure
    - making decisions about requesting serologic tests for Lyme disease
    - diagnosing Lyme disease
    - choosing antibiotics based on clinical presentation
    - determining what indicates that a case should be discussed with one or more specialists or that a patient should be referred to specialized services
- improve overall patient care
- better inform patients on their condition.

Excluded Topics

The reasons for providing PEP in Quebec, eligibility criteria for PEP, the methodology for making a Lyme disease risk map, ways to prevent tick bites, and Lyme disease monitoring are all topics excluded from this analysis, since DGAPSP and INSPQ are handling those aspects. The controversial form of Lyme disease (sometimes referred to as "chronic") and other tick-borne co-infections (including *Borrelia miyamotoi* infection) will be addressed in a later report. Accordingly, specialized third- and fourth-line care of patients with persistent post-treatment symptoms has not been the subject of an exhaustive analysis in this first component of the project. The neurological and skin conditions of the late disseminated stage, such as borrelial lymphocytoma, acrodermatitis chronica atrophicans and encephalitis, have also been excluded due to their rarity and since they are more frequently observed in Europe.

1. METHODOLOGY

1.1 Decision-Making Question

What recommendations will allow us to optimize the process of diagnosis, treatment, and patient care for Quebec children and adults with early- or disseminated-stage Lyme disease by Quebec's first- and second-line heath care professionals?

1.2. Assessment Questions

The assessment questions were developed to answer this decision-making question, to contextualize Lyme disease and to provide the information necessary for making recommendations for clinicians, requesters and other stakeholders.

The questions below do not include ones concerning PEP, since those are addressed in another document published by INESSS as part of its work on Lyme disease [INESSS, 2019b]. The questions about the diagnostic value of signs and symptoms, about laboratory analysis and about the efficacy and safety of medication therapies were formulated based on the PICOTS framework (patient population, intervention, comparators, outcomes assessed, time frame, and health care setting). The questions about good clinical practice were formulated using elements of the PIPOH framework (population, intervention, professionals targeted, outcome expected from the interventions and health care setting). The assessment questions about patient, family caregiver and clinician perspectives were formulated using elements of the SPICE framework (setting, perspective, intervention, comparison and evaluation). The PICOTS and PIPOH tables are given in the section titled "Selected documents," and the SPICE tables were given in the state of knowledge report on patient, family caregiver and clinician perspectives [INESSS, 2019c].

Definitions and pathophysiological aspects
1. How are Lyme disease and its manifestations defined?
2. What bacteria of the genus *Borrelia* cause Lyme disease in Quebec, and what are the mechanisms associated with its pathophysiogenesis?

Epidemiological aspects
3. What are the geographical areas where people are at risk of contracting Lyme disease, and what factors influence tick exposure?
4. What is the prevalence of Lyme disease and its various manifestations in Quebec?
5. What is the risk of contracting Lyme disease after being bitten by *Ixodes scapularis* in a geographical area at high risk for Lyme disease, and what factors influence its transmission?

Clinical aspects – History taking

For a correct diagnosis and an optimal care experience:

6. What should a questionnaire to evaluate the risk of tick exposure include?
7. What are the signs and symptoms associated with various manifestations of Lyme disease including the ones that affect patients' quality of life?
8. What other clinical conditions should be ruled out based on clinical presentation?

Clinical and technological aspects – Diagnosis

9. To limit overdiagnosis and underdiagnosis, what should be the basis for diagnosing Lyme disease given its various clinical presentations? More specifically:
    - What are the signs and symptoms associated with the various manifestations of Lyme disease that have diagnostic value?
    - What is the diagnostic value of analyzing ticks and of requesting laboratory tests (including serologic tests and polymerase chain reaction [PCR]) for the various manifestations of Lyme disease, compared to clinical diagnosis or other methods of diagnosis recognized by learned societies?
10. To use laboratory tests as effectively as possible, what situations require:
    - Serologic tests (screening and confirmatory)?
    - A PCR?
    - Other tests?
11. How should clinicians interpret a negative result for a confirmatory test based on clinical presentation, in order to judiciously integrate test results into the diagnosis process?

Clinical and pharmacological aspects – Treatment

To promote optimal medication use:

12. Under what circumstances could an antibiotic be prescribed without laboratory test results?
13. Are some antibiotics more effective than others at treating various clinical manifestations of Lyme disease?
14. What are the adverse effects associated with studied antibiotics used for the prevention or treatment of Lyme disease caused by *Borrelia burgdorferi* sensu stricto in adults or children, as compared to a placebo, no treatment or another antibiotic?
15. What are the adverse effects associated with the use of oral doxycycline (for any indication) in infants in utero, breastfeeding infants or children under the age of eight, as compared to a placebo, no treatment or another antibiotic?
16. For patients for whom doxycycline is contraindicated and who have a history of penicillin allergy, what are the preferred antibiotics for safely treating Lyme disease, depending on the severity of the prior allergic reaction(s) and the risk of cross reaction?

Clinical and pharmacological aspects – Treatment
17. How should antibiotics prescribed by a health care professional be used to treat the various stages of Lyme disease (e.g., type, route of administration, dosage, duration, contraindications, precautions) for patients diagnosed with Lyme disease? 18. What are the impacts on care experience and cost of using an intravenous antibiotic prescribed in an outpatient setting to a patient diagnosed with Lyme disease? 19. Are there medications that could be prescribed in conjunction with antibiotic treatment to relieve symptoms? 20. Are there drug classes that should be avoided or carefully considered when a patient diagnosed with Lyme disease is undergoing antibiotic therapy? 21. To encourage treatment success, what information and instructions should be given to patients with a prescription for antibiotics to treat Lyme disease?

Clinical aspects – Follow up
22. To optimize overall care and patients' care experience: • Under what circumstances should a primary care health professional (such as a specialized nurse practitioner, general practitioner or emergency physician) 1) consult one or more specialists and/or 2) refer a patient to a specialist? • What would be the optimal follow-up for patients who have been diagnosed and prescribed treatment?

The methods used to examine the assessment questions uphold the INESSS 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 gathered is described in detail below. This does not include the methodology used for the systematic review of scientific data regarding the perspectives of patients, family caregivers and clinicians, which will be addressed in detail in an upcoming INESSS state of knowledge report [INESSS, 2019c], or the methodology used in examining the diagnostic value of the laboratory tests studied in the context of Lyme disease in its localized and disseminated stages, which will be part of a different state of knowledge report [INESSS, 2019d].

1.3 Research and Synthesis Methods for Scientific Data and Published Clinical Information and Recommendations

For the assessment questions related to pathophysiology and epidemiology, non-systematic literature reviews were carried out with qualitative syntheses of the results. For the assessment questions related to the diagnostic value of signs and symptoms, serologic tests and polymerase chain reaction (PCR) tests, and for the assessment questions related to the efficacy and safety of the studied antibiotics for treating patients diagnosed with localized or disseminated Lyme disease, an update of recent systematic reviews in the scientific literature

was carried out, along with a new analysis of more recent primary studies, with a qualitative synthesis of the results. For the assessment questions related to clinical aspects and antibiotic use, a systematic review of documents providing information and recommendations was carried out, with a qualitative synthesis. To glean the perspectives of patients, family caregivers and clinicians from the scientific literature, systematic reviews were carried out with a thematic synthesis. For the aspects regarding users, professionals and organizations, see the section on the research and synthesis methods for contextual information and experiential knowledge.

For more details on the methodology of gathering and analyzing scientific data and clinical information and recommendations, see this report's supplementary appendices document as well as the details of information gathered in the supporting report on PEP tools or the state of knowledge reports on the diagnostic value of laboratory tests and on patient, family caregiver and clinician perspectives (forthcoming from INESSS [2019c]).

1.3.1 Identification of scientific data and published clinical information and recommendations

Our information-gathering strategy for all the assessment questions and the overall Lyme disease project was developed in collaboration with a science information specialist. To lessen publication bias, research was carried out using multiple databases, including PubMed, Embase, *Evidence-Based Medical Reviews* (EBM Reviews), Cochrane, the *NHS Economic Evaluation* database (only for economic aspects) and the *Cumulative Index to Nursing and Allied Health Literature* database (CINAHL, only for patients' perspectives) and in a register of ongoing clinical studies, in English and French. The objective was to carry out a systematic review of sufficient methodological quality to update it. When applicable, primary studies published during the time period not covered by a systematic review were also gathered. The details of the various research strategies used are available in the supplementary appendices documents of this report (Appendix A), the supporting report for PEP tools and the state of knowledge reports on the diagnostic value of laboratory tests and on patient, family caregiver and clinician perspectives.

To collect documents on clinical information and recommendations, a science professional carried out a survey of grey literature (in English, French and German) through December 2018. This included the websites of public health agencies; health care technology assessment agencies; learned societies in the fields of infectious disease, dermatology, rheumatology and neurology; and other organizations. A full list is given in Appendix A of this report's supplementary appendices document as well as in the supporting report for PEP tools.

A science professional also used the Google search engine to index documents not published in peer-reviewed periodicals and to gather documents from North American regulatory bodies, including the Food and Drug Administration (FDA) and Health Canada.

The product monographs officially registered with Health Canada for antibiotics used to treat Lyme disease were consulted using the *Electronic Compendium of Pharmaceuticals and Specialties* (e-CPS). Documents published by INESSS on histories of penicillin allergies were also consulted.

The bibliographies of selected publications were examined to identify other relevant documents.

The literature search for the pathophysiological aspects was carried out in the PubMed database by a science professional (GM) using key words such as *Lyme disease, incidence, Borrelia, tick, risk factor* and *endemic areas*. However, the only journals examined were those that dealt primarily with the study's subject and were published between January 1, 2015 and April 10, 2018. A science professional gathered data regarding the regions where the black-legged tick is endemic and the prevalence and incidence of Lyme disease using the websites of the Laboratoire de santé publique du Québec (LSPQ), the INSPQ, the Public Health Agency of Canada and CDC. Manual research on epidemiological data was carried out through February 2019.

1.3.2 Selection of documents

Documents on the pathophysiological aspects were selected by a science professional (GM) using the criteria that they be specialized reviews related to this topic and published in a peer-reviewed journal. Expert opinions, editorials and primary studies were excluded. Only reviews presenting theories founded on human validation were selected.

To carry out systematic reviews regarding the diagnostic value of signs and symptoms, regarding laboratory tests and regarding the efficacy and safety of antibiotics (as prevention or cure), two science professionals (FK, GG, GM or PH) independently reviewed the scientific literature and made an initial selection based on titles and abstracts, and according to the inclusion and exclusion criteria given in Tables 1 and 2 and in the supporting report for PEP tools [INESSS, 2019b]. The second round of selections was independently done by reading the publications in their entirety. All differences of opinion were resolved by consensus, without the need for a third party's opinion. If a text was published multiple times, only the most recent version was analyzed. Flow charts based on the PRISMA model (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [Moher et al., 2009] illustrating the study selection process and the reasons for exclusion are provided in the supplementary appendices documents of this report (Appendix B), the supporting report for PEP tools and the state of knowledge reports on the diagnostic value of laboratory tests and on patient, family caregiver and clinician perspectives.

Table 1 Inclusion and exclusion criteria for documents during systematic reviews of scientific data

Inclusion Criteria	
Question: The diagnostic value of signs and symptoms	
Population	Children and adults suspected of having Lyme disease
Intervention	Signs and symptoms suggestive of Lyme disease: • Solitary erythema migrans • Cardiac arrhythmia or heart block • Facial palsy or lymphocytic meningitis or radiculoneuritis • Oligoarticular, monoarticular or migratory arthritis • Conjunctivitis, uveitis, keratitis, iritis or scleritis • General systemic symptoms

Comparator	• Clinical diagnosis • Serologic testing • Pleocytosis and antibodies in the CSF for neurological conditions
Outcomes	• Diagnostic value of signs alone, in combination or combined with a diagnostic test: sensitivity, specificity, PPV, NPV, OR, PLR, NLR and AU-ROC • Analytic validity (agreement with the comparator)
Time frame	Localized stage Early disseminated stage Late disseminated stage
Study model	SR and observational studies
Publication year	2000–2018 SR: after January 1, 2012 Primary studies: depending on the literature search for an SR update, and after January 1, 2000 for an SR de novo.
Question: The diagnostic value of serologic tests and PCR	
Population	Samples from children and adults suspected of having Lyme disease (serum, blood, SF or CSF)
Intervention	• Two-tier serologic testing (ELISA with a synthetic VIsE peptide or the whole protein as antigen and immunoblotting) • PCR
Comparator	Other laboratory analyses Clinical diagnosis
Outcomes	• Diagnostic value: sensitivity, specificity, PPV, NPV, OR, PLR, NLR and AU-ROC • Analytic validity (agreement with the comparator)
Time frame	Localized stage Early disseminated stage Late disseminated stage
Study model	SR, observational studies
Publication year	2007–2018 SR: after January 1, 2012 Primary studies: depending on the literature search for an SR update, and after January 1, 2007 for an SR de novo.
Question: Efficacy and safety of antibiotics	
Population	Children and adults diagnosed with Lyme disease
Intervention	Antibiotics (dosage, route of administration and duration)
Comparator	Antibiotics other than the intervention, placebo
Outcomes	Efficacy: • Lack of Lyme disease signs and symptoms • Reduction or resolution of signs and symptoms (at the early, late, and post-Lyme disease stages) • Recurrence of signs and symptoms Safety (adverse effects and deaths)
Time frame	SR, randomized controlled trial (RCT), cohort studies
Study model	No year limit SR: after January 1, 2012 Primary studies: depending on the literature search for an SR update, and no time limit for an SR de novo.

Exclusion Criteria	
Population	Those not diagnosed with localized or disseminated Lyme disease
Intervention	Interventions other than the included ones; house tests, European commercial tests or commercial tests that have not been the subject of any indexed study since 2009
Type of Publication	Analytic primary studies other than RCTs, cohort and case-control studies; case-control studies with < 10 cases Descriptive studies; editorials, master's or doctoral theses, conference proceedings without a methodology that clarifies limitations and biases

Acronyms and abbreviations: RCT: randomized controlled trial; CSF: cerebrospinal fluid; SF: synovial fluid; SR: systematic review.

Table 2 Inclusion and exclusion criteria for documents during the systematic review of documents containing published clinical information and recommendations

Inclusion Criteria	
Questions regarding current practice, laboratory test use and medication use	
Population	Lyme disease at the localized or disseminated stages, contracted in North America or Europe
Intervention	Clinical information and recommendations for good practice
Professionals	First-, second- and third-line
Outcome	Optimal care of patients with Lyme disease
Health care setting	Inpatient and outpatient
Publication year	2012–2018
Exclusion Criterion	
Publication year	Before 2012, unless there is a lack of literature on the target population

1.3.3 Assessment of methodological quality

The quality of the documents selected during the systematic reviews was assessed independently by two science professionals (FK, GM, SOD, PH, PLB or HG) using the following assessment grids and tools:

- AGREE II (Appraisal of Guidelines for Research and Evaluation II) [Brouwers et al., 2010] to assess the quality of documents with clinical recommendations
- R-AMSTAR (Revised Assessment of Multiple Systematic Reviews) [Kung et al., 2010] to assess the quality of systematic reviews
- QUADAS-2 (revised Quality Assessment of Diagnostic Accuracy Studies) [Whiting et al., 2011] for diagnostic studies
- the AACODS checklist (authority, accuracy, coverage, objectivity, date and significance) [Tyndall, 2008] for narrative reviews and grey literature

- the Critical Appraisal Skills Programme (CASP) list [2018] for randomized controlled trials (RCTs).

1.3.4 Extracting scientific information and clinical information and recommendations

Clinical information and recommendations were extracted from clinical practice guidelines (CPG) and other guidelines by a science professional using pre-established extraction forms that included the organization, author(s), publication year, recommendations, strength, supporting evidence, and the authors' argument and conclusions. These forms were tested on some publications to ensure their validity. The information extracted was validated by a second science professional.

For the data from systematic reviews or primary studies, tables were created for the characteristics of reviews or studies and for the results organized by assessment parameters (outcomes). These tables were tested on some publications to ensure their validity. The data were extracted by a science professional and validated by a second science professional. If relevant data were absent from the published version, the publication's authors were contacted.

A single science professional extracted the data from other types of documents that contained useful information for the assessment questions and were the subject of a non-systematic review of the scientific literature.

1.3.5 Analysis and synthesis of scientific data

Raw data, efficacy indications calculated by the authors and conclusions were extracted from systematic reviews, RCTs and cohort studies, then analyzed and presented according to outcomes of interest, clinical manifestations, laboratory analysis (if relevant), antibiotics (if relevant) and continent where the primary studies took place.

1.3.5.1 Evaluation of the level of scientific evidence

The level of scientific evidence for each statement related to the assessment questions is based on the examination of all available data for a given outcome and is evaluated using four criteria. For statements regarding the diagnostic value of signs and symptoms or laboratory analysis, the criteria were the scientific and methodological limitations of the study, its consistency/reliability, its precision and its generalizability. The same criteria were applied to statements regarding the efficacy and safety of antibiotics, except that precision was replaced by clinical impact. These data quality assessment criteria are described in Appendix C of this report's supplementary appendices document. The scientific statements were subsequently ranked by their overall level of scientific evidence on a four-tier scale: high, moderate, low or insufficient (Table 3). The overall level of scientific evidence is based on the results of the four criteria for ranking scientific evidence, in order to measure our confidence in the results of the scientific data. The science professionals who performed the systematic review of the literature were the ones to rank the quality of scientific data.

Table 3 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 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 into 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 documents intended for clinicians and published in Quebec or Canada

A science professional (GM, FK or GG) 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 science professional participated in meetings of the Canadian Lyme Disease Diagnostic Working Group (LDDWG). The stakeholders consulted were asked to share information or documents relevant to the assessment questions. The Notices to the Minister from the INESSS evaluation of drugs for listing purposes and the lists of medications (Inpatient list and Public Prescription Drug Insurance Plan, both published by the Régie de l'assurance maladie du Québec [RAMQ]) were also consulted. MSSS documents on priority access to specialized services were examined as well as the websites and documents of the federal and provincial governments, including public health agencies, regarding Lyme disease (e.g., action plan and federal framework). A science professional also used the Google search engine to index brochures for the diagnostic kits assessed in this project.

1.4.1.1 Extraction

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

1.4.1.2 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.

1.4.2 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 obtained primarily through consultations with stakeholders: working groups put together specifically for the project, existing INESSS committees, patient associations, patients and key informants.

1.4.2.1 INESSS committees

To help guide its work on Lyme disease, INESSS formed an advisory committee of health care 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 (see the notice's supplementary appendices document). To identify potential candidates, INESSS solicited assistance from the CEPPP and from microbiology / infectious diseases specialists practising in high-risk regions 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 interest in participating in this project. The CEPPP 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 (see the notice's supplementary appendices document).

The advisory committee's 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 committee members 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 scientific rigour and professional and social acceptability of INESSS publications related to medication use.

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

1.4.2.2 MSSS Committee

Lastly, the DAPM governance committee of the MSSS, whose mandate relates to strategy, was consulted in order to address the project's challenges and promote the effective implementation of preferred recommendations and measures among those proposed by INESSS.

1.4.2.3 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. The questions asked to them can be found in the notice's supplementary appendices document.

Where the observations from these discussions relate to the assessment questions, they have been synthesized into the corresponding sections of this report. A second meeting with the representatives was held on March 12, 2019, to share the results of the first component of this project.

1.4.2.4 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 localized or disseminated stage who had been diagnosed in Quebec (see notice's supplementary appendices document). 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 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 (see notice's supplementary appendices document). 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 into the appropriate sections of this report.

1.4.2.5 Key informants

The heads of laboratories designated as responsible for screening tests were consulted at the beginning of the project in order to gather contextual data on laboratory analysis.

The Centre Info-Médicaments en Allaitement et Grossesse (IMAGe) at the Sainte-Justine university hospital centre (CHU) was consulted regarding data on doxycycline use in pregnant women.

1.4.2.6 Confidentiality and ethical considerations

Any personal or medical information provided by the stakeholders consulted was anonymized in order to protect the identity of the participants. Members of the project team and all stakeholders consulted 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.

1.4.2.7 Preventing, declaring and handling conflicts of roles and interests

All individuals who collaborated on this project were 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 standard 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. No specific handling method was required.

All conflicts of interest and role conflicts are publicly disclosed in the front matter of this report, of the notice [INESSS, 2019a] and of the supporting report for PEP decision support tools [INESSS, 2019b].

1.4.3 Analysis and synthesis of contextual information and experiential knowledge

Stakeholder contributions were documented using editable sheets and meeting minutes recorded in shared documents. Group consultations were recorded with participant consent. 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

Table 4 gives an overview of the sources of information used in documenting information on the various aspects of the assessment questions. For each assessment questions, all the data gathered were collated in a separate evidence table. These tables contained the table summarizing the statement of scientific data as well as the level of evidence associated with it when adequate, in addition to other relevant scientific and clinical data, contextual information and experiential knowledge related to each assessment questions on clinical practice, use of laboratory analysis and use of antibiotics. Each evidence table was also accompanied by a narrative synthesis of the points of convergence and divergence.

In developing clinical recommendations, the body of evidence was evaluated according to the following criteria (see Appendix D of this report's supplementary appendices document):

- Statement of scientific evidence and level of scientific evidence if relevant
- Pathophysiological aspects
- Epidemiological aspects
- Clinical aspects
- Pharmacological aspects
- Professional and organizational aspects and patients' perspectives
- Applicability of the intervention
- Acceptability of the intervention
- Potential impacts of implementation

Table 4 Summary of sources of information organized by aspects to be documented

Aspects	SOURCES OF INFORMATION		
	Scientific literature	**Grey literature**	**Consultations with stakeholders**
Pathophysiological	Primary studies, systematic and non-systematic reviews	CPGs, GLs, public health agencies	AC
Epidemiological	Primary studies, systematic and non-systematic reviews	INSPQ, LSPQ, PHAC, CDC, DSP Montérégie	AC
Clinical	Primary studies, systematic reviews	CPGs, GLs, public health agencies, laboratory analysis kit brochures	AC, ASC-PCP, MC, CEC-OMU, LDDWG, AQML, patients
Pharmacological	Primary studies, systematic reviews	CPGs, GLs, product monographs via e-CPS, regulatory agencies (Health Canada and FDA)	AC, ASC-PCP, CEC-OMU, AQML, patients, IMAGe centre

Professional and organizational, patient perspective	Primary studies	CPGs, GLs, public health agencies	AC, MC, CEC-OMU, AQML, patients, designated laboratories

Acronyms and abbreviations: PHAC: Public Health Agency of Canada; AC: advisory committee; CEC-OMU: Clinical Excellence Committee on Optimal Medication Use; CDC: Centers for Disease Control and Prevention; MC: monitoring committee; 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; ASC-PCP: advisory subcommittee on the provincial medical protocol and CP template; n/a: not applicable.

1.6 Deliberative Process and Formulation of Recommendations

For each research question related to diagnosis, treatment and patient care, a table containing the following information was presented to the advisory committee: 1) the scientific data, 2) the contextual data, 3) the experiential data and 4) the preliminary observations made by the project team. The committee members then discussed the evidence in an informal deliberation process in order to formulate initial recommendations and judge their “strength” which was translated by the choice of verb tense and the level of consensus (see Appendix D in this report’s supplementary appendices document). The committee members were required to give their opinions again on the final recommendations, either in deliberation or by email, depending on the degree of divergence of initial opinions. Recommendations were kept if approved by a majority of members of the advisory committee. Approval by all participants was considered unanimous, approval by at least 80% of participants was considered consensus, and approval of 51% to 79% was considered a divided opinion.

After advisory committee meetings, a version of the recommendations was emailed to the members of the monitoring committee so that they could comment on it, and then the recommendations were presented to the members of the CEC on Optimal Medication Use.

1.7 Method for Developing 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 care professionals. Afterward, the main elements of the clinical tools and their content including the definitions were determined, taking into account the aspects documented during consultations. Tables that laid out clinical information and definitions extracted from websites dedicated to Lyme disease as well as data extracted from CPGs, guidelines and endorsed reviews in addition to proposals were discussed with the members of the advisory committee. The project team then incorporated all comments in drafting new definitions and clinical information, and the advisory committee gave their opinions of the new versions.

Preliminary versions of the knowledge transfer tools were drafted based on the definitions, information and clinical recommendations developed in collaboration with the members. These members were then asked to comment on the preliminary versions and suggest changes based on their expertise and experience. Once comments were received, another version of the tools was developed, and the members asked to comment again. After at least 80% of the members approved of the tools, they were presented to other stakeholders.

Eight main knowledge transfer tools were developed to support clinicians in their practice:

- the *Decision Support* tool to guide and support practising health care professionals in prescribing PEP for Lyme disease
- 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 provincial medical protocol on PEP and a collective prescription template
- the *Diagnostic Support* tool to guide and support practising health care professionals in diagnosing Lyme disease in its localized and disseminated stages
- the *Optimal Use Guide* for antibiotics in adults to guide health care professionals in choosing treatment options
- the *Optimal Use Guide* for antibiotics in children to guide health care professionals in choosing treatment options
- the *Follow-up Sheet* to inform patients on their condition and what to do as it changes
- the *Information Sheet* on two-tier serology to guide clinicians in the optimal use of serologic tests and in interpreting the results.

Photos of erythema migrans were gathered from various sources: documents from the systematic literature review, the royalty-free image bank Shutterstock® and the specialists on the advisory committee. The microbiology / infectious diseases specialists and dermatologists on the committee then commented on the quality, relevance and usefulness of these photos in supporting future users of the knowledge transfer tools. For the photos from scientific articles or reference works, the authors were contacted to request permission to use them. The sources of all photos are given in Appendix E of this report's supplementary appendices document.

In order to ensure that these knowledge transfer tools will 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 April 2019 to collect their comments on the tools. The respondents for the surveys on the diagnostic support tool and the optimal use guides are listed in the front matter of this report, and the survey questions are given in Appendix F of this report's supplementary appendices document. The project team analyzed these future users' comments and, as appropriate, integrated them into the tools.

1.8 Validation

The supporting report for knowledge transfer tools was sent to three external readers, who assessed its relevance and overall scientific quality. The external readers were chosen based on their expertise or involvement in their field. The names and affiliations of the external readers appear in the front matter of this report. The project team analyzed their comments and integrated them into the final report as appropriate. They are reproduced in summary tables in Appendix G in this report's supplementary appendices document.

1.9 Update

The need to update INESSS's work on clinical care from Lyme disease diagnosis to treatment will be assessed at regular intervals based on future published clinical practice guidelines or other guidelines and on advances in scientific data.

2. DESCRIPTION OF DOCUMENTS

2.1. Scientific Data and Published Clinical Information and Recommendations

Our scientific information retrieval efforts to answer the assessment questions yielded 15,653 indexed references (excluding duplicates) from databases and 22 references from the scientific grey literature (see the flow chart in appendix B of this report's supplementary appendices document).

2.1.1. Clinical practice guidelines and other guidelines

Fifteen CPGs, guidelines and endorsed reviews that contained definitions of the various manifestations of Lyme disease, risk factors for contracting the disease and best clinical practices in caring for adults and children were selected:

- Six North American CPGs, guidelines or endorsed reviews, developed by:
    - the Infectious Diseases Society of America (IDSA) [Wormser et al., 2006]
    - the International Lyme and Associated Diseases Society (ILADS) [Cameron et al., 2014]
    - the American Academy of Family Physicians (AAFP) [Wright et al., 2012]
    - the Canadian Paediatric Society (CPS) [Onyett, 2014]
    - the American College of Physicians (ACP) [Hu, 2016]
    - the National Collaborating Centre for Infectious Diseases (NCCID) [Habegger, 2014].
- Eight European CPGs, guidelines or endorsed reviews, developed by:
    - the German Dermatological Society (GDS) [Hofmann et al., 2017]
    - the Haute Autorité de Santé (HAS) [HAS, 2018a]
    - the National Institute for Health and Care Excellence (NICE) [NICE, 2018a]
    - the German Academy for Pediatrics and Adolescent Health (GAPAH) [Huppertz et al., 2012]
    - the German Neurological Society (DGN) [Rauer et al., 2018]
    - the Polish Society of Epidemiology and Infectious Diseases (PSEID) [Pancewicz et al., 2015]
    - the Swiss Society of Infectious Diseases (SSID) [Nemeth et al., 2016];
    - the German Society for Pediatric Rheumatology (GKJR) and the German Society of Pediatrics and Adolescent Medicine (DGKJ) [Huppertz and Tzaribachev, 2013].
- One Australian guideline, developed by:
    - the Australian Health Protection Principal Committee (AHPPC) [Lum et al., 2015].

After subjectively assessing them with AGREE II [Brouwers et al., 2010], developed by the international team of researchers and guideline designers of the same name, the methodological quality was judged to be:

- very low for the document endorsed by PSEID [Pancewicz et al., 2015]
- low for the IDSA [Wormser et al., 2006], GAPAH [Huppertz et al., 2012] and AAFP [Wright et al., 2012] documents
- moderate for the ILADS [Cameron et al., 2014], GDS [Hofmann et al., 2017] and HAS [2018a] documents
- excellent for the NICE CPG [2018a].

The CPS [Onyett, 2014], ACP [Hu, 2016], NCCID [Habegger, 2014] and SSID [Nemeth et al., 2016] documents were consulted and assessed using the AACODS checklist. However, since these documents did not match the definition of a CPG as set out by the AGREE team, their methodological quality was not assessed. The DGN and GKJR/DGKJ documents were not assessed, since they were written in German. The results of the assessment of methodological quality for these documents are presented in Appendix H of this report's supplementary appendices document.

2.1.2. Clinical reference works

Three specialized works on medication use during pregnancy and breastfeeding were consulted [Briggs et al., 2017; Taketomo et al., 2014; Ferreira et al., 2013]. Their methodological quality was not assessed.

2.1.3. Systematic reviews

2.1.3.1. Diagnostic value of signs and symptoms

The NICE systematic review regarding the diagnostic value of signs and symptoms of Lyme disease [NICE, 2018b] was retained and its methodological quality judged to be moderate according to R-AMSTAR (Appendix I of this report's supplementary appendices document). A total of 12 cohort studies, 2 case-control studies and 2 mixed-design studies (cohort and case-control) were included in this systematic review: 7 with adult subjects [Tjernberg et al., 2011; Aucott et al., 2009; Ogrinc et al., 2008; Lipsker et al., 2001; Sangha et al., 1998; Engervall et al., 1995; Nadelman et al., 1990] and 9 with children subjects [Skogman et al., 2015; Sundin et al., 2012; Tveitnes et al., 2012; Waespe et al., 2010; Skogman et al., 2008; Avery et al., 2005; Shah et al., 2005; Pikelj-Pečnik et al., 2002; Peltomaa et al., 1998]. The sensitivity and specificity of various signs and symptoms was presented, and in some cases, a meta-analysis based on two or three studies was carried out. These results, along with the characteristics of the systematic review, are presented in Appendix I of this report's supplementary appendices document.

No systematic reviews were found on the diagnostic value for Lyme disease of general systemic symptoms, non-neurological ocular impairment or monoarticular, oligoarticular or migratory arthritis.

2.1.3.2. Diagnostic value of laboratory analysis

Five systematic reviews regarding the diagnostic value of laboratory analysis at various stages of Lyme disease were identified [NICE, 2018c; HAS, 2018b; Cook and Puri, 2016; Leeflang et al., 2016; Waddell et al., 2016] and one systematic review on levels of CXCL13 in cerebrospinal fluid [Yang et al., 2017]. INESSS evaluated the methodological quality of these six documents and judged them all to be moderate according to R-AMSTAR (Appendix J of this report's supplementary appendices document). The majority of studies included in these systematic reviews concerned enzyme-linked immunosorbent assays (ELISA), immunoblotting and two-tier serologic testing. The number of studies included in each systematic review ranged from 7 to 123 [NICE, 2018c]. The details of the included studies are given in *Valeur diagnostique des analyses de laboratoire pour la maladie de Lyme [Diagnostic value of laboratory analysis for Lyme disease]* [INESSS, 2019d]. The systematic reviews generally give data on sensitivity and specificity and, in some cases, also meta-analysis results. These results, along with the characteristics of the systematic reviews, are presented in Appendix J of this report's supplementary appendices document.

The conclusions of the systematic reviews by NICE [2018c], HAS [2018b], Cook and Puri [2016] and Yang et al. [2017] were not used to substantiate the scientific evidence, since the source of patients and the type of reference standard used were not inclusion criteria for studies. However, the studies included in the systematic reviews that met the INESSS selection criteria were used to make a table of scientific evidence statements. The conclusions of Leeflang's systematic review [2016] were not retained because they concern European commercial serologic tests, which are different from those used in North America. The conclusions of Waddel's systematic review [2016] were not retained, as its literature search dates from 2013. However, the studies included in it were considered and an update of the literature published in or before May 2018 was completed.

The literature search covered all laboratory tests that could potentially be used to diagnose Lyme disease, but in-house made serologic tests and tests not addressed in any scientific publication since 2009 (e.g., PCR on synovial biopsies) were excluded, as they are unlikely to be used in Quebec laboratories. The results from this systematic review are presented in *Valeur diagnostique des analyses de laboratoire pour la maladie de Lyme [Diagnostic value of laboratory analysis for Lyme disease]* [INESSS, 2019d]. This report will only address the diagnostic value of polymerase chain reaction (PCR) and two-tier serologic testing, for which the studied methods are the same as those used in Quebec.

2.1.3.3. Efficacy and safety of antibiotics

2.1.3.3.1. Erythema migrans associated with Lyme disease

NICE's systematic review on antibiotic therapy in the treatment of erythema migrans was retained and its methodological quality judged to be high according to R-AMSTAR [NICE, 2018d]. A total of 18 RCTs and 2 non-randomized studies were included in this systematic review: 15 with adult subjects [Stupica et al., 2012; Cerar et al., 2010; Wormser et al., 2003; Barsic et al., 2000; Dattwyler et al., 1997; Breier et al., 1996; Luft et al., 1996; Luger et al., 1995; Weber et al., 1993; Massarotti et al., 1992; Nadelman et al., 1992; Strle et al., 1992; Dattwyler et al., 1990; Weber et al., 1990; Steere et al., 1983] and 5 with children subjects [Arnež and Ružić-Sabljić, 2015; Nizič et al., 2012; Arnež et al., 2002; Eppes and Childs, 2002;

Arnež et al., 1999]. An efficacy index was calculated for each comparison, and in some cases a meta-analysis based on two or three studies was carried out. These results, along with the parameters of the systematic analysis, are given in Appendix K of this report's supplementary appendices document. Also, an HAS systematic review was published a few months after the NICE review, and the included studies were compared [HAS, 2018b]. The HAS review included 19 studies, 15 of which were also in the NICE review. The four studies that HAS examined but NICE did not were excluded for reasons relating to the issues studied, study model or an intervention deemed inappropriate under the NICE criteria. HAS did not calculate any efficacy indexes.

Considering that NICE combined heterogenous study results to arrive at levels of scientific evidence that support its recommendation, that it excluded some studies included by HAS, that two additional studies were published after the date limit of NICE's bibliography search and that it is important to understand what populations were included in the studies, the project team decided to individually analyze the primary studies of these two systematic reviews.

2.1.3.3.2. Neuroborreliosis

NICE's systematic review on antibiotic therapy for neuroborreliosis was retained and its methodological quality judged to be high according to R-AMSTAR [NICE, 2018f]. No additional primary studies published after the NICE review's period of literature search and meeting our review's set inclusion criteria were identified in the systematic literature search. In their clinical practice guideline published some months after NICE's, HAS presented a systematic review that addressed only late-stage neurological conditions, although the publications used in it included both early and late-stage forms. Furthermore, HAS included studies in which there was only a suspicion of neurological manifestations from neuroborreliosis (or a possible form thereof), since these manifestations were defined based only on the clinical description of early forms [Feder et al., 2007]. In the NICE review, no distinction was made between these two forms and the studies included in the review needed to include patients presenting clinical manifestations compatible with neuroborreliosis. It was therefore judged unnecessary to compare the studies used by the two institutions. NICE's systematic review included five RCTs on exclusively adult populations [Ljøstad and Mygland, 2010; Ljøstad et al., 2008; Karlsson et al., 1994; Pfister et al., 1991; Kohlhepp et al., 1989; Pfister et al., 1989] and one cohort study that included children and adults [Jowett et al., 2017]. An efficacy index was calculated for each comparison, but no meta-analysis could be carried out because the comparisons were based on a single study. Since several characteristics of primary studies were not included in NICE's tables, the project team decided to individually analyze the primary studies. The characteristics and results of each study are presented in Appendix L of this report's supplementary appendices document.

2.1.3.3.3. Lyme carditis

No systematic review on the efficacy of antibiotics in the context of Lyme carditis was found.

2.1.3.3.4. Non-neurological Lyme-related ocular impairment

No systematic review on the efficacy of antibiotics in the context of non-neurological Lyme-related ocular impairment was found.

2.1.3.3.5. Lyme arthritis

NICE's systematic review on antibiotic therapy for Lyme arthritis was retained and its methodological quality judged to be high according to R-AMSTAR [NICE, 2018g].

No additional primary studies published after the NICE review's period of literature search and meeting the review's set inclusion criteria were identified in the systematic literature search. However, an HAS systematic review was published a few months after the NICE review, and the included studies were compared.

Three RCTs were included in NICE's systematic review, one of them only with adult subjects [Caperton et al., 2010]. The other two included adolescents [Steere et al., 1994] and one of them included children eight years and older [Steere et al., 1985]. An efficacy index was calculated for each comparison, but no meta-analysis could be carried out because the comparison was based on a single trial. These results, along with the characteristics of the systematic review, are given in Appendix M of this report's supplementary appendices document.

The HAS systematic review included five more clinical studies than the NICE review, four of which were excluded by NICE due to a population or comparison that did not fit their criteria. HAS did not calculate any efficacy indexes.

Since some studies included by HAS were excluded and several characteristics of primary studies were not included in NICE's tables, the project team decided to individually analyze the primary studies of these two systematic reviews. Of the eight primary studies, four were retained based on this review's inclusion criteria. Three of those four were in the NICE review and one in the HAS review [Dattwyler et al., 1988]. The characteristics and results of each study, along with tables showing the differences between the published systematic reviews and the INESSS systematic reviews, are presented in Appendix M of this report's supplementary appendices document.

The included studies were all done in the United States and are of low methodological quality (bias, small number of patients, etc.). They are heterogenous, with some including patients with other late-stage manifestations such as neurological or cardiac manifestations. No included study was specifically interested in antibiotic efficacy in terms of choice of molecule, route or duration of administration for individuals who present with persistent symptoms after two antibiotic treatments for diagnosed Lyme arthritis but do not show signs of an active infection.

2.1.3.3.6. Persistent post-treatment symptoms

NICE's systematic review on antibiotic therapy for persistent symptoms was retained and its methodological quality judged to be high according to R-AMSTAR [NICE, 2018e]. Five primary studies, all from NICE's systematic review, were retained to assess the efficacy of antibiotics for persistent post-treatment symptoms. Four were carried out in the United States and one in the Netherlands. They were generally of low methodological quality, except the European one,

which was of good quality. The characteristics and results of each study are presented in Appendix N of this report's supplementary appendices document.

2.1.4. Primary studies

2.1.4.1. Diagnostic value of signs and symptoms

2.1.4.1.1. Solitary erythema migrans

Four studies included in NICE's systematic review [2018b] on the diagnostic value of signs and symptoms were retained to assess the diagnostic value of erythema migrans in the context of Lyme disease [Tveitnes et al., 2012; Aucott et al., 2009; Avery et al., 2005; Peltomaa et al., 1998]. A literature review was carried out to identify studies on Lyme disease diagnosis published between 2017 and 2018, with the aim of updating NICE's systematic review [2018b], but no additional primary studies were found.

The studies retained were assessed with the revised QUADAS-2 tool for quality assessment of diagnostic studies, and all were found to have a high risk of bias and low concerns regarding applicability.

The characteristics and results of each study are presented in Appendix I of this report's supplementary appendices document.

2.1.4.1.2. General systemic symptoms

The literature search on the diagnostic value of signs and symptoms covering the period of 2000 to 2018 identified nine primary studies on the diagnostic value of one or more general systemic symptoms in the context of Lyme disease. The methodological quality of the studies retained was assessed using QUADAS-2, and is as follows:

- Three studies had a moderate risk of bias and low concerns regarding applicability [Zomer et al., 2018; Barstad et al., 2017; Sundin et al., 2012].
- Four studies had a high risk of bias and low concerns regarding applicability [Remy et al., 2017; Picha et al., 2016; Aucott et al., 2009; Shah et al., 2005].
- One study had a very high risk of bias and low concerns regarding applicability [Skogman et al., 2008].
- One study had a high risk of bias and moderate concerns regarding applicability [Ogrinc et al., 2008].

The characteristics and results of these studies are presented in Appendix I of this report's supplementary appendices document.

2.1.4.1.3. Arrhythmia and heart block

Two studies included in NICE's systematic review on signs and symptoms [NICE, 2018b] were retained to assess the diagnostic value of arrhythmia and heart block in the context of Lyme disease [Ogrinc et al., 2008; Pikelj-Pečnik et al., 2002]. A literature review was carried out to

identify studies on Lyme disease diagnosis published between 2017 and 2018, with the aim of updating NICE's systematic review [2018b], but no additional primary studies were found.

The studies retained were assessed with QUADAS-2. The Ogrinc et al. study [2008] was found to have a high risk of bias and moderate concerns regarding applicability, and the Pikelj-Pečnik et al. study [2002] was found to have a moderate risk of bias and low concerns regarding applicability.

The characteristics and results of these studies are presented in Appendix I of this report's supplementary appendices document.

2.1.4.1.4. Facial palsy, lymphocytic meningitis and radiculoneuritis

Three studies included in NICE's systematic review on signs and symptoms [NICE, 2018b] were retained to assess the diagnostic value of facial palsy in the context of Lyme disease [Sundin et al., 2012; Tjernberg et al., 2011; Skogman et al., 2008]. Our literature search on the diagnostic value of signs and symptoms covering the period of 2000 to 2018 identified seven additional primary studies on the diagnostic value of facial palsy (update of the systematic review), lymphocytic meningitis and radiculoneuritis, some of which were included in NICE's review for other signs and symptoms [Barstad et al., 2017; Gyllemark et al., 2017; Remy et al., 2017; Picha et al., 2016; Cohn et al., 2012; Ogrinc et al., 2008; Shah et al., 2005].

The methodological quality of the studies retained was assessed using QUADAS-2, and is as follows:

- Two studies had a moderate risk of bias and low concerns regarding applicability [Barstad et al., 2017; Sundin et al., 2012].
- Four studies had a high risk of bias and low concerns regarding applicability [Remy et al., 2017; Picha et al., 2016; Tjernberg et al., 2011; Shah et al., 2005].
- Two studies had a high risk of bias and moderate concerns regarding applicability [Cohn et al., 2012; Ogrinc et al., 2008].
- Two studies had a very high risk of bias and low concerns regarding applicability [Gyllemark et al., 2017; Skogman et al., 2008].

The characteristics and results of these studies are presented in Appendix I of this report's supplementary appendices document.

2.1.4.1.5. Conjunctivitis, uveitis, keratitis, iritis and scleritis

No primary studies on the diagnostic value of non-neurological ocular impairment in the context of Lyme disease were retained after a literature search covering the period of 2000 to 2018.

2.1.4.1.6. Monoarticular, oligoarticular and migratory arthritis

No primary studies on the diagnostic value of monoarticular, oligoarticular or migratory arthritis in the context of Lyme disease were retained after a literature search covering the period of 2000 to 2018.

2.1.4.2. Diagnostic value of laboratory analysis based on clinical presentation

As stated above, this report will only address the diagnostic value of PCR and two-tier serologic testing, for which the studied methods are the same as those used in Quebec (ELISA with a synthetic VIsE peptide or the whole VIsE protein as antigen and immunoblotting). The diagnostic value of the tests that are available and could potentially be used in Quebec laboratories is presented in the state of knowledge report on the diagnostic value of laboratory analysis [INESSS, 2019d].

Twenty-one primary studies included in the systematic reviews by NICE, HAS or Waddell et al. were retained to assess the diagnostic value of PCR [Moniuszko et al., 2015; De Leeuw et al., 2014; Molins et al., 2014; O'Rourke et al., 2013; Eshoo et al., 2012; Liveris et al., 2012; Cerar et al., 2008; Schnarr et al., 2001; Lebech et al., 2000; Van der Heijden et al., 1999; Brettschneider et al., 1998; Lebech et al., 1998; Vasiliu et al., 1998; Picken et al., 1997; Priem et al., 1997; Rijpkema et al., 1997; Jaulhac et al., 1996; Von Stedingk et al., 1995; Moter et al., 1994; Nocton et al., 1994; Lebech and Hansen, 1992], as were five studies on the diagnostic value of two-tier serologic testing with the same methods used in Quebec [Molins et al., 2016; Lahey et al., 2015; Molins et al., 2014; Branda et al., 2013; Wormser et al., 2013]. The literature search on the diagnostic value of laboratory analysis covering the period of 2007 to 2018 identified three additional primary studies on PCR [Barstad et al., 2018; Forselv et al., 2018; Deanehan et al., 2013] and three additional studies on two-tier serologic testing [Eckman et al., 2018; Branda et al., 2017; Wormser et al., 2014].

The methodological quality of the studies retained was assessed using QUADAS-2, and is as follows:

- Two studies had a low risk of bias and low concerns regarding applicability [Deanehan et al., 2013; Picken et al., 1997].
- Two studies had a moderate risk of bias and low concerns regarding applicability [De Leeuw et al., 2014; Liveris et al., 2012].
- Twelve studies had a high risk of bias and low concerns regarding applicability [Eckman et al., 2018; Forselv et al., 2018; Molins et al., 2016; Moniuszko et al., 2015; Molins et al., 2014; Branda et al., 2013; O'Rourke et al., 2013; Eshoo et al., 2012; Van der Heijden et al., 1999; Brettschneider et al., 1998; Rijpkema et al., 1997; Von Stedingk et al., 1995].
- Ten studies had a very high risk of bias and low concerns regarding applicability [Lahey et al., 2015; Wormser et al., 2013; Cerar et al., 2008; Schnarr et al., 2001; Lebech et al., 2000; Vasiliu et al., 1998; Priem et al., 1997; Jaulhac et al., 1996; Moter et al., 1994; Lebech and Hansen, 1992].
- One study had a high risk of bias and moderate concerns regarding applicability [Barstad et al., 2018].
- One study had a high risk of bias and high concerns regarding applicability [Nocton et al., 1994].
- Three studies had a very high risk of bias and high concerns regarding applicability [Branda et al., 2017; Wormser et al., 2014; Lebech et al., 1998].

The characteristics and results of these studies are presented in Appendix J of this report's supplementary appendices document.

2.1.4.3. Efficacy and safety of antibiotics

2.1.4.3.1. Erythema migrans associated with Lyme disease

Since NICE's bibliography search had a July 2017 cut-off, INESSS conducted an update, and the systematic research identified two additional primary studies [Eliassen et al., 2018; Stupica et al., 2018]. Stupica's study [2018] focused only on people with multiple erythema migrans, unlike NICE's systematic review, for which populations studied could present with solitary or multiple erythema migrans. This study was deemed to be of low methodological quality using the CASP-RCT checklist. The characteristics and results of this study are presented in Appendix O of this report's supplementary appendices document. Since its results do not differ from the conclusions of NICE's systematic review, Eliassen's study's [2018] data were not extracted and its methodological quality was not assessed.

2.1.4.3.2. Neuroborreliosis

No primary studies were added to those included in NICE's systematic review in this context [NICE, 2018f].

2.1.4.3.3. Lyme carditis

No primary studies on the efficacy of antibiotics in the context of Lyme carditis were found.

2.1.4.3.4. Non-neurological Lyme-related ocular impairment

No primary studies on the efficacy of antibiotics in this context were found.

2.1.4.3.5. Lyme arthritis

No primary studies were added to those included in the NICE and HAS systematic reviews in this context [NICE, 2018g; HAS, 2018b].

2.1.4.3.6 Persistent post-treatment symptoms

No primary studies were added to those included in NICE's systematic review in this context [NICE, 2018e].

2.1.4.4. Safety of doxycycline during pregnancy and breastfeeding and for children under eight years of age

The primary studies are described in the supporting report on clinical tools for PEP [INESSS, 2019b].

3. LYME DISEASE

Assessment question
What bacteria of the genus *Borrelia* cause Lyme disease in Quebec, and what are the mechanisms associated with its pathophysiogenesis?

3.1. Enzootic Cycle of Lyme Disease-Causing Bacteria

The genospecies of bacteria that cause Lyme disease (*Borrelia burgdorferi* sensu lato *[B. burgdorferi* s.l.] complex) are motile, spiral-shaped bacteria of the spirochete class, distinguished by their dependence on arthropods for their transmission and maintenance in susceptible vertebrate hosts [Cutler et al., 2017; Hodzic, 2015].

Until recently, four species of ticks of the genus *Ixodes* were known to shed bacteria of the *B. burgdorferi* s.l. complex into the environment: *I. scapularis* in northeastern America, *I. pacificus* in northwestern America, *I. ricinus* in Europe and *I. persulcatus* in Asia [Kilpatrick et al., 2017]. However, a recent study showed that five species of ticks (including *I. scapularis* and *I. pacificus*) may contribute to the dissemination of bacteria of the *B. burgdorferi* s.l. complex in Canada [Scott et al., 2018].

The life cycle of ticks consists of three stages, with a single blood meal before each metamorphosis (larva and nymph) and before reproducing [Kilpatrick et al., 2017] (figure 1). The larvae feed on a wide variety of animals (e.g., mice, squirrels and birds) and acquire bacteria of the *B. burgdorferi* s.l. complex from an infested host. After metamorphosis, the nymph transmits these bacteria to a host, generally a small mammal, during the blood meal. The adults primarily feed on larger animals (such as deer), which are not competent hosts for the multiplication of bacteria of the *B. burgdorferi* s.l. complex [Kilpatrick et al., 2017; Hodzic, 2015].

Although ticks can feed on human blood at all three stages of their life cycle, the majority of human infections are caused by nymphs. Indeed, larvae are not generally infested with bacteria of the *B. burgdorferi* s.l. complex (vertical transmission is essentially nonexistent for these bacteria, although it is possible for other *Borrelia* not belonging to this complex [Rollend et al., 2013]), and adults are more easily noticed than nymphs and are often removed before they have attached for long enough to transmit the bacteria [Kilpatrick et al., 2017; Hodzic, 2015].

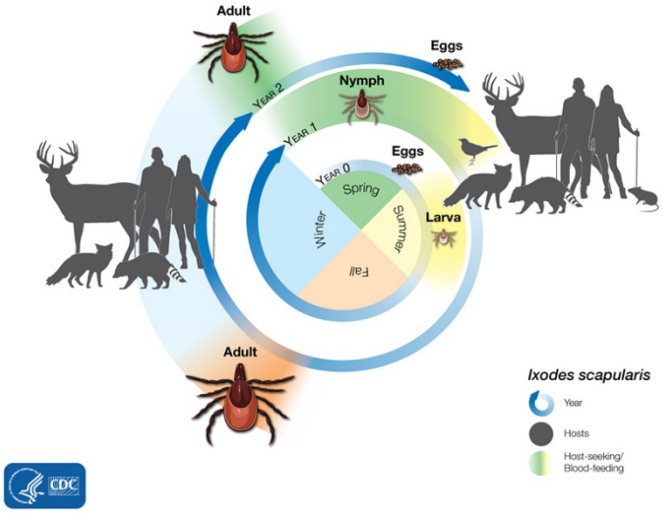

Figure 1 The life cycle of the black-legged tick

Centers for Disease Control and Prevention (CDC). Ticks. How ticks spread disease [website]. Available at https://www.cdc.gov/ticks/life_cycle_and_hosts.html.

3.2. Genospecies of the *Borrelia burgdorferi* sensu lato Complex

The *B. burgdorferi* s.l. complex includes 21 genospecies [Cutler et al., 2017]. It has recently been suggested that the genus *Borreliella* be used to distinguish these bacteria from other *Borrelia*, including those that cause relapsing fever. However, this new nomenclature is controversial, and thus will not be used in this report or the other documents published by INESSS [Stevenson et al., 2019; Adeolu and Gupta, 2014].

The various genospecies can be distinguished not only by their primary reservoir, vector and geographical location, but also by their pathogenicity in humans, which depends primarily on differences in their DNA (see Appendix A). While the genospecies of the *B. burgdorferi* s.l. complex have a highly conserved linear chromosome, they also have several linear and circular plasmids whose sequence and number vary between genospecies and between bacterial strains [Steere et al., 2016; Petzke and Schwartz, 2015]. This heterogeneity contributes to the clinical variability of Lyme disease [Hyde, 2017; Caine and Coburn, 2016; Kraiczy, 2016; Oosting et al., 2016; Steere et al., 2016; Petzke and Schwartz, 2015] (see Appendix A of this document).

3.3. Overview of the Clinical Evolution of Lyme Disease

The immune system is generally able to respond both innately and adaptively to bacteria of the *B. burgdorferi* s.l. complex to contain and stop the infection. The presence of specific antibodies in the serum is a reflection of that response. Individuals who nevertheless develop Lyme disease usually recover quickly and completely if antibiotic therapy is administered in the early stages of the disease [CDC, 2018b].

At the localized stage, Lyme disease is an acute condition characterized by the presence of an erythema migrans at the site of the bite. Without treatment, the disease can progress to the

disseminated stages. The early disseminated stage may include general systemic symptoms (fever, joint pain, myalgia and/or headache), cutaneous manifestations (multiple erythema migrans), neurological manifestations (neuroborreliosis) and/or cardiac manifestations (Lyme carditis), while the late disseminated stage is characterized by articular manifestations (Lyme arthritis).

4. DEFINITIONS

Assessment question
How are Lyme disease and its manifestations defined?

The review of the literature and websites showed that terms related to Lyme disease are heterogeneously defined. In order to avoid confusion and standardize the terminology in Quebec, INESSS has developed definitions, in partnership with the advisory committee, after systematically reviewing documents containing clinical recommendations. These definitions will be used throughout INESSS documents and clinical tools.

For each term, the team extracted and analyzed information from North American websites on Lyme disease, the World Health Organization (WHO) website, CPGs, guidelines and literature reviews endorsed by learned societies. The extraction tables are available in Appendix P of this report's supplementary appendices document. The definitions reflect the opinions of the advisory committee members, based on their experiential knowledge and the information summarized below. For some terms, a definition specifically intended for patients and their family caregivers has been elaborated to aid in comprehension. Definitions related to the controversial form of Lyme disease (sometimes referred to as "chronic") and to co-infections will be given in the documents of the second component of this work.

4.1. Lyme Disease

4.1.1. Grey literature and websites

Lyme disease is caused by *Borrelia burgdorferi* bacteria. While some organizations only speak of *B. burgdorferi,* others refer more precisely to the genospecies of the *B. burgdorferi* sensu lato complex. The Australian Health Protection Principal Committee (AHPPC) noted that these genospecies are distinguished by their organotropism and pathogenic potential [Lum et al., 2015].

The bacteria that cause Lyme disease are transmitted to humans by infested ticks. Some documents specify the tick species in question (*Ixodes scapularis* and *I. pacificus* in North America and *I. ricinus* in Europe) while others use their common names (black-legged tick or deer tick). The animals that act as reservoirs (such as rodents, birds and small mammals) are mentioned several times in the definitions found.

Several groups define Lyme disease as a systemic illness involving cutaneous, neurological, rheumatological and cardiac manifestations. According to the IDSA, extracutaneous manifestations are less common than previously [Wormser et al., 2006]. The AHPPC, the German Academy for Pediatrics and Adolescent Health (GAPAH), the WHO, NICE and the German Dermatological Society (GDS) describe the progressive appearance of symptoms: skin inflammation followed by flu-like symptoms and the progressive appearance of manifestations in other organs, such as the nervous system and the joints. However, the progression varies between individuals [NICE, 2018a; Hofmann et al., 2017; Lum et al., 2015; Huppertz et al., 2012]. NICE adds that the disease is easily treatable with antibiotic therapy if

treated in time, but that without treatment the infection spreads to the joints, heart and nervous system and causes complex disorders that are more difficult to treat later [NICE, 2018a]. The International Lyme and Associated Diseases Society (ILADS) states that symptoms may be acute and persistent [Cameron et al., 2014].

CDC describes erythema migrans as a clinical marker. However, the GDS states that skin inflammation may go unnoticed or remain invisible [Hofmann et al., 2017].

4.1.2. Contextual and experiential data

The members of the advisory committee felt that the definition should emphasize the progressive nature of Lyme disease and the fact that the clinical picture varies depending on the bacterial genospecies involved.

While it's common to describe ticks carrying bacteria of the *B. burgdorferi* s.l. complex as infected, the advisory committee members chose not to use this term in INESSS documents, since the ticks themselves are not ill. The terms infested and carrier were deemed to be more suitable for the documents intended for clinicians and patients, respectively.

4.1.3. Definitions

The definition of Lyme disease developed for the notice and tools intended for clinicians is:

- 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 genospecies and the stage of the disease and may include cutaneous, neurological, musculoskeletal, cardiac and/or ocular manifestations.

The definition developed for tools intended for patients and family caregivers is:

- 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 genospecies in question and the stage of the disease and may include skin, neurological, joint-related, cardiac and/or eye-related manifestations.

4.2. Localized Stage

4.2.1. Grey literature and websites

Minor variations on the name of this stage are used in the documents and websites consulted: early localized stage, localized early stage, early stage, acute form, stage I or acute skin infection. The time interval for this stage is not always clearly defined; some works refer to an interval of 3 to 30 days after a bite from an infested tick (ILADS: 2 to 30 days), while others simply state that this stage corresponds to the first few days after the bite. The American Academy of Family Physicians (AAFP) and NICE specify that symptoms usually appear one to two weeks after the bite [NICE, 2018a; Wright et al., 2012]. The AHPPC refers to an interval of up to four months after the bite [Lum et al., 2015].

Depending on the author, erythema migrans is characterized as the most common symptom, the characteristic symptom of this stage or the earliest symptom. The CPS and NICE point out that this symptom is not always present, and NICE adds that it may take an atypical form [NICE, 2018a; Onyett, 2014].

According to CPGs, other symptoms of the early localized stage include fever and chills, fatigue, headaches, cervical stiffness and muscle and joint pain. These symptoms are sometimes described as systemic. Some also mention swelling of the lymph glands and skin rashes distinct from erythema migrans (such as borrelial lymphocytoma and raised skin rashes that disappear and reappear). GAPAH adds lymphocytic meningitis, facial palsy, myopericarditis and atrioventricular block [Huppertz et al., 2012]. NICE and the AHPPC point out that some people may be asymptomatic at this stage [NICE, 2018a; Lum et al., 2015].

4.2.2. Contextual and experiential data

The members of the advisory committee were of the opinion that the localized stage should refer only to the presence of erythema migrans and that the other signs and symptoms such as general systemic symptoms occur during bacterial dissemination. They also felt that the definition should emphasize the fact that erythema migrans does not always look like a bull's eye.

4.2.3. Definitions

The definition of the localized stage developed for the notice and tools intended for clinicians is:

- 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 within four weeks of the transmission of bacteria by an infested tick.

The definition developed for tools intended for patients and family caregivers is:

- Stage of Lyme disease (sometimes called early stage) at the beginning of the infection, before the dissemination of bacteria. An isolated red patch that usually increases in size, known as erythema migrans, is the primary manifestation observed on the skin, but it is not always present or noticed. When present, it appears within four weeks of the transmission of bacteria by an infested tick.

4.3. Disseminated Stages

4.3.1. Grey literature and websites

While the majority of extracted definitions distinguish the early disseminated stage from the late disseminated stage, others speak of the disseminated stage in general. The names for the stages encountered most often are early disseminated stage and late disseminated stage. However, other terms are used:

- Early disseminated stage: early disseminated infection, early disseminated illness, stage II and acute disseminated Lyme disease.

- Late disseminated stage: persistent late infection, late illness, stage III and late stage.
- Disseminated stage: disseminated stage, late stage, advanced stage, chronic stage.

The time interval for each of these stages is never clearly defined, and there is overlap between the early and late disseminated stages.

- Early disseminated stage: the majority of extracted data refer to a time interval of a number of weeks to months after the bite. The American College of Physicians (ACP) begins this interval a few days after erythema migrans appears and NICE counts it as the first three months after the infection [NICE, 2018a; Hu, 2016].
- Late disseminated stage: all extracted data report a time interval of several months to years after the bite.
- Disseminated stage: the majority of extracted data refer to weeks, months or years after the bite. CDC begins their interval a few days after the bite.

Some emphasize that the disseminated stage occurs when the disease is not treated. Depending on the time interval considered, the description of manifestations varies between organizations.

- Early disseminated stage: the majority of extracted data mention the following manifestations: cutaneous (e.g., multiple erythema migrans), neurological (e.g., facial palsy, meningitis), cardiac (e.g., heart block). NCCID, ACP, NICE and the GDS also include monoarticular or oligoarticular arthritis manifestations that they call brief, intermittent or acute [NICE, 2018a; Hofmann et al., 2017; Hu, 2016; Habegger, 2014]. The AAFP, ACP and the GDS mention systemic symptoms resembling those of the early localized stage [Hofmann et al., 2017; Hu, 2016; Wright et al., 2012]. Wright et al. is the only study to include ocular manifestations and myositis.
- Late disseminated stage: the majority of extracted data mention intermittent or chronic arthritic manifestations (e.g., oligoarticular or monoarticular arthritis) and neurological symptoms (e.g., encephalomyelitis and peripheral neuropathy). The CPS points out that peripheral neuropathies and central nervous system manifestations are rare in children [Onyett, 2014]. ACP adds that at this stage, systemic symptoms are generally absent, and NCCID suggests that myalgia, arthralgia, weakness, cognitive impairment, numbness and tingling are possible [Hu, 2016; Habegger, 2014]. In addition to neurological and rheumatological conditions, the GDS includes acrodermatitis chronica atrophicans and the AHPPC mentions that chronic fatigue is also commonly reported [Hofmann et al., 2017; Lum et al., 2015].
- Disseminated stage: websites about Lyme disease rarely make a distinction between the early and late disseminated stages. The manifestations mentioned are systemic, cutaneous, neurological, rheumatological and cardiac. ILADS states that Lyme disease can cause pain and inflammatory symptoms in any of the body's organs or systems [Cameron et al., 2014]. IDSA and GAPAH state that late manifestations include arthritis (episodic or chronic), encephalomyelitis, peripheral neuropathy and acrodermatitis

chronica atrophicans [Huppertz et al., 2012; Wormser et al., 2006]. GAPAH mentions ocular manifestations as well [Huppertz et al., 2012].

4.3.2. Contextual and experiential data

It was agreed that two definitions would be provided for the notice and tools intended for clinicians (early disseminated stage and late disseminated stage) and only one definition for the tools intended for patients and family caregivers. The members of the advisory committee felt it was important for the definition to mention that these stages occur when the disease is not treated and that it is possible to observe erythema migrans simultaneously with manifestations of the early disseminated stage.

4.3.3. Definitions

The definitions of the disseminated stages developed for the notice and tools intended for clinicians are:

- 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 symptoms. Erythema migrans may or may not be present.
- Late disseminated stage: Stage of Lyme disease generally characterized by the progression of the early 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.

The definition developed for tools intended for patients and family caregivers is:

- Disseminated stage: Stage of Lyme disease that generally occurs when a localized infection has not been detected or effectively treated, and that is characterized by the dissemination of bacteria through the bloodstream. It generally develops a few weeks after the transmission of bacteria by an infested tick, but it can also occur months later. From the beginning of the disseminated stage, systemic symptoms as well as skin, neurological, musculoskeletal, cardiac and eye-related symptoms may occur, with or without a red patch that usually increases in size, known as erythema migrans. Over time, Lyme arthritis may occur.

4.4. Persistent Symptoms After Lyme Disease Treatment

4.4.1. Grey literature and websites

Post-treatment Lyme disease syndrome (PTLDS) is also called: post-Lyme disease syndrome, post-Lyme syndrome, chronic post-treatment Lyme disease and late post-treatment Lyme disease.

There is no generally accepted definition. The majority of extracted data define post-Lyme disease syndrome as the persistence of symptoms after appropriate antibiotic therapy in

patients who have been diagnosed with Lyme disease. Symptoms may persist for several weeks. For the condition recognized as PTLDS, some scholarly associations specify that the symptoms should not have any other etiology and that they should persist for at least six months. According to the IDSA, objective evidence of *B. burgdorferi* s.l. infection is a condition sine qua non [Wormser et al., 2006]. IDSA and SSID submitted a list of inclusion and exclusion criteria to define the syndrome [Nemeth et al., 2016; Wormser et al., 2006].

The symptoms mentioned in the majority of documents are non-specific. The ones described most often are fatigue, muscle and joint pain and cognitive impairment. IDSA states that objective clinical manifestations are uncommon [Wormser et al., 2006]. However, ACP specifies that there is disagreement on this subject and that arthritis, neuropathies and radiculopathies may persist after antibiotic therapy and be objectively documented by physicians [Hu, 2016]. At least two learned societies reported that the prevalence of symptoms is identical in the general population. In March 2019, the Association of Medical Microbiology and Infectious Disease Canada (AMMI) published a position statement on the treatment of people with persistent symptoms that have been attributed to Lyme disease [AMMI Canada, 2019]. The authors recognize that the persistent symptoms that have been attributed to Lyme disease are real and may be debilitating for the patients who suffer from them.

The cause of PTLDS is unknown. However, human studies suggest that PTLDS may be attributable to residual involvement of the tissues and immune system (autoimmune and inflammatory response). The majority of scholarly associations emphasize that PTLDS is not caused by an active or persistent *Borrelia* infection. Also, the Swiss Society for Infectious Diseases (SSID) states that a causal relationship has not been established between co-infections and PTLDS [Nemeth et al., 2016].

The patient associations do not address PTLDS on their websites, because they don't distinguish between PTLDS and chronic Lyme disease. However, the scholarly associations hold that the distinction between the two conditions is an important one.

According to the NCCID, the utility of this category is challenged by the fact that many of its symptoms are common in clinical practice and may be due to a large number of illnesses [Habegger, 2014]. NICE feels that PTLDS is poorly defined and controversial, and does not address it in its guideline [NICE, 2018a]. The committee that worked on recommendations noted that the available evidence was of low quality.

4.4.2. Contextual and experiential data

The members of the advisory committee acknowledge the presence of persistent symptoms post-treatment. The experience of some consulted patients who have had or who still have persistent symptoms after treatment of a disseminated stage demonstrates that these symptoms affect patients' ability to lead a normal life (e.g., limitations on certain daily activities). However, according to clinicians, this persistence of symptoms can occur following various types of infections and does not generally have a distinct name. The current state of knowledge is not sufficient to confirm or reject the idea that these symptoms are caused by an active infection. It was agreed that a different terminology than PTLDS would be used to define the persistence of symptoms post-treatment in order to avoid including the controversial form

of Lyme disease (sometimes referred to as "chronic"), which will be addressed in the second component of this work.

4.4.3. Definition

The terminology chosen was “persistent symptoms after Lyme disease treatment.”

The definition of these symptoms developed for the notice and tools intended for clinicians and for tools intended for patients and family caregivers is:

- Persistence of symptoms several weeks or months after the appropriate treatment for a patient officially diagnosed with Lyme disease. These symptoms cannot be explained by any other cause. According to current medical thinking based on human studies, they may result from damage caused by the infection (for example, changes to the functioning of the immune system or nervous system) rather than a continuing active infection. Note: this definition is subject to change as medical knowledge advances and better diagnostic tests become available.

4.5. Solitary Erythema Migrans

4.5.1. Grey literature and websites

The majority of definitions describe erythema migrans as an expanding erythematous skin lesion. The expansion occurs over a period of a few days to a few weeks, but the GDS and the AHPPC specify that some erythemas do not enlarge [Hofmann et al., 2017; Lum et al., 2015].

The size of the lesion varies significantly between individuals. The diameter is at least 5 cm and may be as much as 70 cm (median is 16 cm). Generally, an erythema migrans is a solitary lesion that appears at the site of the bite. However, it can also appear elsewhere and be accompanied by secondary lesions.

An erythema migrans is generally round or oval, with the tick bite visible at the centre. The appearance of the lesions varies; some are uniformly erythematous while others have central clearing or a distinctive ring shape. Erythema migrans is generally coloured and may be pale to dark pink according to ILADS, red to bluish red according to NCCID, and sometimes dark purple according to the GDS [Hofmann et al., 2017; Cameron et al., 2014; Habegger, 2014]. NCCID states that the central clearing is dependent on duration, and is absent in early erythema migrans [Habegger, 2014]. The GDS, the AHPPC and the Polish Society of Epidemiology and Infectious Diseases (PSEID) state that, less commonly, an erythema migrans may have an irregular shape or a blotchy appearance, contain vesicles (blisters) or be hemorrhagic [Hofmann et al., 2017; Lum et al., 2015; Pancewicz et al., 2015]. An erythema migrans may be warm to the touch but is not generally associated with other local symptoms such as itching or pain.

The majority of groups mention that erythema migrans appears one or two weeks after infection: between 3 and 30 days, and 7 days on average. However, NICE states that it may appear beginning on the first day of infection, while the AHPPC gives an interval of 3 days to 16 weeks after the tick bite [NICE, 2018a; Lum et al., 2015]. The GDS states that the duration of the lesion varies considerably between individuals [Hofmann et al., 2017]. The Canadian government and NICE mention that it may last several weeks and the AHPPC adds that the

duration is dependent on the genospecies of the *B. burgdorferi* s.l. complex involved and varies from 4 to 14 days [NICE, 2018a; Lum et al., 2015]. Erythema migrans generally disappears on its own after a few days to a few months (on average, four weeks).

NCCID states that the distinctiveness of erythema migrans is overestimated [Habegger, 2014]. Erythema migrans is a common clinical manifestation of Lyme disease, but is not always present. NCCID, GAPAH and the AHPPC point out that erythema migrans is pathognomonic in patients exposed to a tick bite in an endemic area [Lum et al., 2015; Habegger, 2014; Huppertz et al., 2012]. NICE specifies that it is the bull's-eye-shaped erythema migrans that is characteristic of *B. burgdorferi* infection.

4.5.2. Contextual and experiential data

The advisory committee considered it important that the definition emphasize the changing nature of erythema migrans while including the fact that it is not always observed. They also wanted to highlight that a bull's eye lesion may be due to micro-organisms other than the genospecies of the *B. burgdorferi* s.l. complex, but that it is highly suggestive of Lyme disease in the context of exposure in a high-risk area.

4.5.3. Definitions

The definition of solitary erythema migrans developed for the notice and tools intended for clinicians is:

- Isolated erythematous skin lesion that generally appears between 3 and 30 days after bacteria are transmitted from an infested tick and may persist and change over several days. An erythema migrans rash usually spreads concentrically outward from the site of the bite to a diameter of more than 5 cm, and causes little or no pain or itching. However, its characteristics (size, shape and appearance) and duration vary considerably between individuals. While a bull's eye rash (concentric red rings) may also be caused by other factors, this type of lesion is highly suggestive of Lyme disease infection when the affected individual has been in a high-risk area.

The definition developed for tools intended for patients and family caregivers is:

- Isolated reddish skin lesion that generally appears between 3 and 30 days after bacteria are transmitted from an infested tick and may persist and change over several days. An erythema migrans rash usually spreads concentrically outward from the site of the bite to a diameter of more than 5 cm, and causes little or no pain or itching. However, its characteristics (size, shape and appearance) and duration vary considerably between individuals. While a bull's eye rash (concentric red rings) may also be caused by other factors, this type of lesion is highly suggestive of Lyme disease infection when the affected individual has been in a high-risk area.

4.6. Typical Solitary Erythema Migrans

4.6.1. Contextual and experiential data

The members of the advisory committee felt it was important to develop a definition of the typical erythema migrans for the tools intended for clinicians. Generally, a typical erythema

migrans presents as a round or oval rash with a diameter of over 5 cm that lasts at least 48 hours. The expanding nature of an erythema migrans is not always observable, especially when the patient presents with a lesion greater than 5 cm in diameter. The members of the advisory committee felt it was important for the definition to emphasize that the lesion may be pale and with poorly defined margins. It may also be homogenous or ring-shaped and does not always resemble a bull's eye.

4.6.2. Definition

The definition of the typical solitary erythema migrans developed for the notice and tools intended for clinicians is:

- Circular skin rash, generally progressive, that is at least 5 cm in diameter, lasts at least 48 hours and is associated with little or no pain or itching. The lesion may be homogenous or ring-shaped and does not always look like a bull's eye. It may also be very pale and have poorly defined margins.

4.7. Multiple Erythema Migrans

4.7.1. Grey literature and websites

After the bacteria have disseminated, some people may have erythema migrans-like lesions in multiple locations. This is called multiple erythema migrans. This type of lesion generally appears several weeks after the tick bite. The lesions may be smaller than 5 cm, and the GDS states that children often have symmetrical erythemas on their face [Hofmann et al., 2017]. The AHPPC points out that certain genospecies of the *B. burgdorferi* s.l. complex cause multiple erythema migrans more commonly than others [Lum et al., 2015].

4.7.2. Contextual and experiential data

The members of the advisory committee considered it important that the definition emphasize that the presentation of multiple erythema migrans is very atypical and highly variable.

4.7.3. Definitions

The definition of multiple erythema migrans developed for the notice and tools intended for clinicians is:

- Erythematous skin lesions that appear after the bacteria have disseminated. While they may share certain characteristics with the solitary erythema migrans, their presentation (number, colour, appearance and size) is highly variable.

The definition developed for tools intended for patients and family caregivers is:

- Reddish skin lesions that appear after the bacteria have disseminated. While they may share certain characteristics with the solitary reddish skin lesion (erythema migrans), their presentation (number, colour, appearance and size) is highly variable.

4.8. Lyme Carditis

4.8.1. Grey literature and websites

Lyme carditis refers to the cardiac manifestations caused by the bacterial genospecies of the *B. burgdorferi* s.l. complex. It is less common than neuroborreliosis and Lyme arthritis. It may occur from one week to seven months after the tick bite, but usually occurs within the first two months. It may occur simultaneously with erythema migrans and neuroborreliosis.

The main manifestation reported is a sudden and intermittent atrioventricular block that resolves over the following days or weeks. Some groups specify that it is a second- or third-degree block, while others speak of a high-grade block.

ACP and PSEID mention a range between a first-degree block and a complete block [Hu, 2016; Pancewicz et al., 2015]. The atrioventricular block often occurs at the atrioventricular node and is sometimes associated with myopericarditis or myocarditis. SSID points out that an atrioventricular block is potentially fatal [Nemeth et al., 2016]. The AAFP and PSEID state that other manifestations of Lyme carditis are bundle-branch block, a block of electrical conduction system bundles, heart failure and chronic congestive cardiomyopathy [Pancewicz et al., 2015; Wright et al., 2012]. However, PSEID specifies that myocarditis, pericarditis, heart failure and chronic congestive cardiomyopathy are rare manifestations [Pancewicz et al., 2015].

IDSA states that severe or fulminant congestive heart failure or development of valvular heart disease is not associated with Lyme disease and that there is no convincing evidence that Lyme disease is a cause of chronic cardiomyopathy [Wormser et al., 2006]. The CPS states that Lyme carditis is rare in children [Onyett, 2014].

4.8.2. Contextual and experiential data

The members of the advisory committee emphasized that the presentation of Lyme carditis is highly variable. They were of the opinion that the definition should be kept simple. The specialist physicians on the committee had seen few cases of Lyme carditis.

4.8.3. Definitions

The definition of Lyme carditis developed for the notice and tools intended for clinicians is:

- Cardiac impairment caused by bacterial dissemination. The primary manifestation is an atrioventricular block.

The definition developed for tools intended for patients and family caregivers is:

- Cardiac impairment caused by bacterial dissemination. The primary manifestation is a cardiac conduction disorder.

4.9. Neuroborreliosis

4.9.1. Grey literature and websites

Neuroborreliosis is associated with the nervous system manifestations of Lyme disease. The majority of works consulted mentioned that both the central and peripheral nervous systems could be affected. However, NICE only specifies manifestations of the central nervous system in its definition [NICE, 2018a]. PSEID and SSID state that neuroborreliosis is the most common manifestation of Lyme disease in Europe (*B. garinii* is the main etiological agent)

[Nemeth et al., 2016; Pancewicz et al., 2015]. Neuroborreliosis is less common in North America.

Neuroborreliosis appears after the infection has disseminated. The AHPCC states that it develops 1 to 12 weeks (usually 4 to 6 weeks) after the tick bite [Lum et al., 2015]. The manifestations of neuroborreliosis may occur singly or in combination. They are sometimes presented in order of appearance and sometimes more generally.

4.9.2. Contextual and experiential data

The members of the advisory committee felt that the early manifestations of neuroborreliosis should be distinguished from the late manifestations, which are much rarer.

4.9.3. Definitions

The definition of neuroborreliosis developed for the notice and tools intended for clinicians is:

- Condition of the nervous system (peripheral or central) or meninges in response to bacterial dissemination. Neurological manifestations vary according to the location of inflammation and may present singly or in combination. Some occur as soon as the bacteria have disseminated, while others are rarer and occur months later.

The definition developed for tools intended for patients and family caregivers is:

- Condition affecting the peripheral or central nervous system in response to bacterial dissemination. Neurological manifestations are variable, may present singly or in combination, and are the cause of symptoms such as facial palsy. Some manifestations occur as soon as the bacteria have disseminated, while others are rarer and begin months later.

4.10. Lyme Arthritis

4.10.1. Grey literature and websites

Lyme arthritis may manifest a few weeks or a few months after the tick bite (usually between four and six months after, but it may be as little as four days or as much as two years). The GDS mentions that it may be concomitant with erythema migrans [Hofmann et al., 2017]. Musculoskeletal symptoms are the most common extracutaneous manifestations of the disseminated stage in North America, and are less common in Europe.

Lyme arthritis involves intermittent or persistent attacks of swelling and pain in one or more large joints. Inflammatory flare-ups can last for weeks or months. Significant effusions out of proportion to the pain are characteristic. The GDS states that the joint near the erythema migrans is frequently affected [Hofmann et al., 2017].

ACP, the AAFP and CDC state that the arthritis may become chronic in some cases [Hu, 2016; Wright et al., 2012]. The AAFP specifies that, in these cases, the affected joints are primarily the knee and the hip [Wright et al., 2012]. The knee joint is the most typically affected, and the GDS specifies that a Baker’s cyst may develop [Hofmann et al., 2017]. The ankles, elbows, shoulders, hips and wrists are less often affected, while the temporomandibular joint and the joints of the feet and hands are only very rarely affected. PSEID notes that Lyme arthritis is

rarely symmetrical [Pancewicz et al., 2015]. The AHPPC states that myositis and regional lymphadenopathies are other musculoskeletal manifestations that may be observed [Lum et al., 2015].

4.10.1. Contextual and experiential data

The members of the advisory committee emphasized that Lyme arthritis is a manifestation of the late disseminated stage of Lyme disease and stated that the definition should not mention the musculoskeletal manifestations that appear during the early disseminated stage (e.g., polyarthralgia and polymyalgia) and that may occur at the same time as erythema migrans. They also considered it important that the definition mention that Lyme arthritis may migrate from one joint to another, that flare-ups may be interspersed with periods of remission and that small joints may also be affected.

4.10.2. Definition

The definition of Lyme arthritis developed for the notice and tools intended for clinicians and for tools intended for patients and family caregivers is:

- Inflammation of one or more joints, beginning some months after the bacteria have disseminated. Lyme arthritis usually presents with significant swelling of large joints (primarily the knee). Inflammatory flare-ups can last for several weeks or even months, be interspersed with periods of remission when untreated, and migrate from one joint to another.

5. HISTORY TAKING

Assessment Questions
What are the geographical areas where people are at risk of contracting Lyme disease, and what factors influence tick exposure? What is the prevalence of Lyme disease and its various manifestations in Quebec? What is the risk of contracting Lyme disease after being bitten by *Ixodes scapularis* in a geographical area at high risk for Lyme disease, and what factors influence its transmission? For a correct diagnosis and an optimal care experience: • What should a questionnaire to evaluate the risk of tick exposure include? • What are the signs and symptoms associated with various manifestations of Lyme disease, and which of them affect patients' quality of life? • What other clinical conditions should be ruled out based on clinical presentation?

5.1. Geographical Areas Where There is a Risk of Tick Exposure

5.1.1. Clinical practice guidelines and other guidelines

Of the CPGs retained, only NICE's addresses areas with a risk of tick exposure [NICE, 2018a]. It states that the risk of Lyme disease is very high in southern England, in the Scottish Highlands and in various areas of Europe (including Scandinavia), Asia, the United States and Canada.

5.1.2. Contextual and experiential data

INSPQ's mapping of Lyme disease risk helps classify cases reported by public health branches and supports authorities in their risk management. According to this map, as of July 2018 the risk of Lyme disease was significant[3] in some areas of Montérégie, Estrie, Centre-du-Québec and Outaouais, and risk was present[4] in other areas of these regions as well as areas of Montréal, Laurentides, Lanaudière, Mauricie, Chaudière-Appalaches and Saguenay–Lac-Saint-Jean. However, INSPQ states that there is a possible risk of contracting Lyme disease

[3] At least three cases of Lyme disease contracted locally over the past five years (municipalities < 100,000 inhabitants), OR at least 23 submissions of *Ixodes scapularis* ticks found on humans over the past five years, obtained by passive surveillance (municipalities < 100,000 inhabitants), OR three stages of the *Ixodes scapularis* tick (larva, nymph, adult) collected in one year during active surveillance activities, including at least one nymph that tests positive for *Borrelia burgdorferi*.

[4] Two cases of Lyme disease contracted locally over the past five years (municipalities < 100,000 inhabitants), OR between 11 and 22 submissions of *Ixodes scapularis* ticks found on humans over the past five years, obtained by passive surveillance (municipalities < 100,000 inhabitants), OR at least one *Ixodes scapularis* tick collected during active surveillance activities.

throughout all of Quebec's regions due to the presence of ticks transported by migratory birds (adventitious ticks).

The risk of Lyme disease is present in other Canadian provinces (including Ontario, New Brunswick and Nova Scotia) [PHAC, 2018] and in the United States (primarily in the northeast, including all states bordering Quebec) [CDC, 2018a], Europe,[5] Asia and northern Africa.

The members of the advisory committee felt that the INSPQ's map could be useful to health care professionals in that it identifies areas of high Lyme disease risk. However, since its objective is not to support clinical decisions, it should not be used to rule out Lyme disease. In other words, exposure in a non-high-risk area lowers the probability of a Lyme disease diagnosis but does not rule it out.

Key Takeaways

The risk of contracting Lyme disease is present in Quebec, other Canadian provinces (including Ontario, New Brunswick and Nova Scotia), the United States (primarily in the northeast, including all states bordering Quebec), Europe, northern Africa and Asia.

Lyme disease could potentially be contracted in any region of Quebec, but the risk is higher in Montérégie, Estrie, Centre-du-Québec and Outaouais.

The objective of INSPQ's risk mapping is to identify regions where people have a high risk of contracting Lyme disease in order to support public health authorities. While it is useful to health care professionals, its objective is not clinical, so it should not be used to rule out Lyme disease. Exposure in a non-high-risk area lowers the probability of the diagnosis but does not rule it out.

5.2. Risk Factors for Tick Exposure

The risk factors for tick exposure are documented in the notice [INESSS, 2019a].

Ticks prefer damp places and are mainly found in forests, wooded areas and fields. They may also be found in places where the microclimate is conducive to their survival, such as gardens, landscaped spaces and leaf piles. Therefore, outdoors enthusiasts, gardeners and workers who come into contact with any of these types of environments are all at risk of tick exposure.

Pets are another risk factor for Lyme disease, since they can carry ticks that have not yet attached into proximity with human beings. An American study has also shown that owners of pets who have access to the outdoors (mainly cats or dogs) have 1.83 times the risk of finding a tick crawling on and 1.49 times the risk of finding a tick attached to a member of the household, compared to people who do not own pets [Jones et al., 2018].

[5] European Centre for Disease Prevention and Control (ECDC). Tick maps [website]. Available at https://ecdc.europa.eu/en/disease-vectors/surveillance-and-disease-data/tick-maps (consulted February 27, 2019).

A tick attached to a person or animal does not represent a significant risk for nearby individuals to contract Lyme disease, since ticks take only one blood meal per developmental stage [Kilpatrick et al., 2017] and since they do not survive well in the microclimate of houses [Sonenshine, 2005]. Nonetheless, there may be a low risk of infection through an existing wound if someone removes a tick attached to another person or an animal and the tick's body is damaged during the process of removal [Day, 2011].

Nymph and adult ticks are the developmental stages responsible for transmitting bacteria of the *B. burgdorferi* s.l. complex to humans. Nymphs are present in spring and summer, while adults are present in fall and winter. Since nymphs are primarily responsible for human infections, the risk of contracting Lyme disease is highest in summer when the nymphs are seeking their blood meal before metamorphosing [INESSS, 2019a].

5.2.1. Clinical practice guidelines and other guidelines

The CPGs retained do not directly address risk factors for contracting Lyme disease. NICE states that ticks prefer damp places and are mainly found in forests, wooded areas and fields. They may also be found in places where the microclimate is conducive to their survival, such as parks and urban gardens [NICE, 2018a].

5.2.2. Contextual and experiential data

While 12 species of ticks have been identified in Quebec [Gasmi et al., 2018], not all of them are capable of carrying bacteria of the *B. burgdorferi* s.l. complex. In a Canada-wide study, Scott et al. [2018] identified four tick species infested with bacteria of this complex in Quebec. Although three of these species are known to bite humans, according to the current state of knowledge, only *I. scapularis* ticks can transmit Lyme disease.

Of the 2,010 Lyme disease cases included in a Canadian study, 96% began to have symptoms between May and November, with the greatest incidence in July [Gasmi et al., 2017]. The data collected on MADO cases in Montérégie are similar: symptoms appear between April and November, but primarily between June and September [DSP Montérégie, 2018; DSP Montérégie, 2017b; DSP Montérégie, 2017a; DSP Montérégie, 2016; DSP Montérégie, 2015; DSP Montérégie, 2014]. Furthermore, data on doxycycline use for Lyme disease prevention show two usage peaks, between April and August and between October and November [INESSS, 2019b].

In the Canadian study cited above, there were slightly more Lyme disease cases among male individuals (56% of cases) and among two age groups, children aged 5 to 9 and adults aged 40 to 75 [Gasmi et al., 2017]. These two trends were also observed in the Montérégie MADO cases [DSP Montérégie, 2018; DSP Montérégie, 2017b; DSP Montérégie, 2017a; DSP Montérégie, 2016; DSP Montérégie, 2015; DSP Montérégie, 2014]. Work type and outdoor activities may explain these differences.

The members of the advisory committee reminded the team that ticks are transported by small animals and may therefore be present around houses in high-risk areas in any setting, even in cities. According to the public health members, the risk associated with domestic animals is very low, given that black-legged ticks are sensitive to desiccation and do not survive well

inside homes. Additionally, once a tick has attached to an animal, it poses no danger to humans, because once attached it has no need of another blood meal.

Some members of the advisory committee and AQML mentioned that, while tick exposure in winter is minimal compared to other seasons, ticks are active year-round and the risk of Lyme disease is therefore always present. Some clinicians added that people travelling to high-risk areas with warmer climates than Quebec's are at risk of Lyme disease regardless of the season.

Key Takeaways

Ticks are mainly found in forests, wooded areas and fields, but they may also be found in places where the microclimate is conducive to their survival, such as gardens, landscaped spaces or leaf piles.

The primary risk factors for contracting Lyme disease are associated with tick exposure. They are therefore linked to lifestyle habits, hobbies, outdoor activities and type of work.

The risk of contracting Lyme disease after a tick bite is present year-round, and is highest in summer and low in winter in Quebec. However, people travelling to high-risk areas with warmer climates are at risk of Lyme disease regardless of the season.

Proximity to pets that go outdoors is a risk factor for Lyme disease. However, since black-legged ticks are sensitive to desiccation, they do not survive well in the microclimate of houses.

A tick attached to a person or animal does not represent a significant risk factor for nearby individuals. However, there is a low risk of infection through an existing wound for a person removing an attached tick if the tick's body is damaged during the process of removal.

5.3. Assessing the Risk of Tick Exposure

5.3.1. Clinical practice guidelines and other guidelines

IDSA [Wormser et al., 2006] and the GSD [Hofmann et al., 2017] do not address the issue of what elements to consider when taking a history. While GAPAH [Huppertz et al., 2012] mentions that the patient's history should be compatible with Lyme disease, it gives no specifics. NICE [2018a] states that it is important to ask about how long ago the exposure was, as well as about the patient's activities and places they've travelled. However, it is recommended that Lyme disease not be ruled out in patients with symptoms suggestive of Lyme disease whose history of tick exposure is unclear.

5.3.2. Contextual and experiential data

The members of the advisory committee and monitoring committee and the public health physicians consulted agreed on the importance of assessing the risk of tick exposure by questioning the patient on their lifestyle habits, outdoor activities and work-related activities and those of others who live with the patient, as well as asking about the patient's place of residence and places (regions and countries) that they or their household members have

visited. According to the public health members, although friends and family can carry ticks, this risk is very low, given that black-legged ticks are sensitive to desiccation and do not survive well inside homes. The clinicians emphasized that when taking history, documenting the possibility of tick exposure is more important than documenting which geographical areas the patient visited.

According to the clinicians consulted, only a quarter of patients say they were bitten by a tick. This matches the data from the Montérégie investigation of MADO cases, in which between 23% and 33% of patients remember having been bitten by a tick [DSP Montérégie, 2018; DSP Montérégie, 2017b; DSP Montérégie, 2017a; DSP Montérégie, 2016; DSP Montérégie, 2015; DSP Montérégie, 2014]. A Quebec study reported that 32% of the included patients (N = 720) remember the bite [Charbonneau et al., 2018]. The same is true for 51% of the respondents to an AQML survey of its members (N = 188) [AQML, 2018]. As for the patients consulted, the two patients who were diagnosed at the localized stage (presence of a solitary erythema migrans) remember having been bitten, while those who were diagnosed in one of the disseminated stages were not aware that they had been bitten by a tick. According to the members of the advisory committee, the absence of a documented tick bite should not be used to rule out Lyme disease.

The clinicians consulted emphasized that a documented bite is a sign of tick exposure and suggests that other bites may have gone unnoticed. They were of the opinion that the tools should specify that documentation of a bite does not mean that that bite is the origin of the infection. The discussions on the relationship between the risk of Lyme disease transmission and the duration of tick attachment are recorded in the supporting report on PEP tools [INESSS, 2019b]. According to the clinicians, patients' estimates of duration of attachment are not always accurate and therefore not always reliable.

Clinicians must examine the information collected as a unified whole to determine whether or not the clinical picture is compatible with Lyme disease. For example, a patient whose risk of tick exposure seems very low in terms of their lifestyle may still have a compatible clinical picture if they live in an area with a high risk of Lyme disease.

Key Takeaways

It is important to assess the risk of tick exposure by asking the patient about their life habits and those of the people they live with and by learning about their outdoor activities (hobbies and work), the geographic area they live in and where they've travelled, as well as the proximity of pets that go outside.

A documented tick bite confirms a tick exposure, but the absence of one should not be considered sufficient reason to rule out Lyme disease.

Lyme disease should not be ruled out for patients whose history of tick exposure is unclear if the rest of the clinical picture is compatible with it.

5.4. Manifestations Suggestive of Lyme Disease

5.4.1. Clinical practice guidelines and other guidelines

Generally speaking, a solitary erythema migrans is the most common sign of Lyme disease. However, it is not present in all patients nor always noticed when present. According to the CPGs retained in the literature search, the prevalence of general systemic symptoms varies greatly from one study to another; neurological involvement is more common in Europe and musculoskeletal involvement in North America (Table 5). The prevalence of cardiac involvement varies, but is lower than that of neurological and musculoskeletal involvement; the prevalence of non-neurological ocular involvement, however, is very low [NICE, 2018a; HAS, 2018a; Huppertz et al., 2012; Wormser et al., 2006].

Table 5 Prevalence of Lyme disease conditions

INVOLVEMENT	PREVALENCE (%)			
	CPG	CANADIAN CASES (N = 1,657)[1]	QUEBEC CASES	
			MADO MONTÉRÉGIE (N = 358)[2]	CHARBONNEAU ET AL. (N = 38)[3]
SOLITARY EM	unavail.	74.2	56 to 83[4]	39 (95% CI: 24.0% to 56.6%)
GENERAL SYSTEMIC SYMPTOMS[5]	5 to 35[6]	unavail.	33 to 69	32 to 53
MULTIPLE EM	5 to 6[6]	5.9	27 to 56	unavail.
NERVOUS SYSTEM	5[6]	22.7	11 to 36	10[7] (95% CI: 2.9% to 24.8%)
CARDIAC SYSTEM	0 to 10[8]	3.6	2 to 5	rare
ARTHRITIS	5 to 20[8]	35.7	14 to 45	unavail.
OCULAR SYSTEM (NON-NEUROLOGICAL)	1[6]	unavail.	unavail.	rare

Sources: NICE, 2018a; Charbonneau et al., 2018; DSP Montérégie, 2018; HAS, 2018a; DSP Montérégie, 2017b; DSP Montérégie, 2017a; Gasmi et al., 2017; Hofmann et al., 2017; DSP Montérégie, 2016; DSP Montérégie, 2015; DSP Montérégie, 2014; Wormser et al., 2006

Acronyms and abbreviations: EM: erythema migrans; CPG: clinical practice guideline; HAS: Haute Autorité de Santé; IDSA: Infectious Diseases Society of America; MADO: reportable diseases; GDS: German Dermatological Society

[1] Cases reported from 2009 to 2015

[2] This number is the total number of MADO cases reported in Montérégie from 2013 to 2017

[3] Cases reported from 2012 to 2015

[4] N = 213

[5] Fever, headache, myalgia, arthralgia and/or fatigue

[6] HAS

[7] Facial palsy only

[8] IDSA, HAS, GDS

The CPGs describe various manifestations of Lyme disease that may occur in patients (Table 6) and state that more than one system may be affected at one time. While several

CPGs mention a timeframe for the appearance of a solitary erythema migrans after a tick bite, only HAS gives timeframes for other manifestations.

Table 6 Manifestations of Lyme disease according to CPGs

INVOLVEMENT	SYMPTOMS	PRESENTATION AND SIGNS	TIME FROM TICK BITE TO APPEARANCE[1]
CUTANEOUS	Little pain Little itching May be accompanied by systemic symptoms	One or more expanding rashes	Solitary EM: • 3 to 30 days[2] • 3 days to 3 months[3] Multiple EM: • Less than 6 months
GENERAL	Myalgia Arthralgia Fever and chills Headache Influenza-like illness Isolated adenopathies Discomfort Fatigue Neck pain or stiffness Cognitive impairment Paresthesia	n/a	unavail.
NERVOUS SYSTEM	Headaches Paresthesia Hypoesthesia Loss of deep tendon reflexes Photophobia Nausea Vomiting Fatigue Emotional instability Slight or no neck pain	Radiculopathy Cranial neuropathy (primarily facial palsy) Mononeuritis multiplex Lymphocytic meningitis	Less than 6 months
CARDIAC	Chest pains Heart palpitations Dyspnea Syncopes	Atrioventricular block Myopericarditis Pancarditis	4 days to 7 months
MUSCULOSKELETAL	Significant joint swelling Joint pain	Monoarticular arthritis Oligoarticular arthritis Migratory arthritis	4 days to several years
OCULAR (NON-NEUROLOGICAL)	Decreased visual acuity Eye pain Impaired accommodation	Uveitis Keratitis Conjunctivitis Episcleritis Iridocyclitis	unavail.

Sources: NICE, 2018a; HAS, 2018a; Rauer et al., 2018; Hofmann et al., 2017; Huppertz et al., 2012; Wormser et al., 2006.
Acronyms: EM: erythema migrans; HAS: Haute Autorité de Santé; IDSA: Infectious Diseases Society of America; NICE: National Institute for Health and Care Excellence; GDS: German Dermatological Society
[1] The timeline for EM appearance is mentioned by several CPGs, but only HAS mentions timelines for the appearance of other manifestations.
[2] IDSA, HAS and GDS
[3] NICE

5.4.2. Contextual and experiential data

As with the CPGs, the data collected in Quebec from people with Lyme disease also show the variable prevalence of various conditions (Table 5). General systemic symptoms and multiple erythema migrans were observed in less than a third of MADO cases in Montérégie. Neurological conditions affected between 11% and 36% of patients, while joint conditions affected between 14% and 45% of patients [DSP Montérégie, 2018; DSP Montérégie, 2017b; DSP Montérégie, 2017a; DSP Montérégie, 2016; DSP Montérégie, 2015; DSP Montérégie,

2014]. While the MADO cases do not fully represent patients with Lyme disease, these data help illustrate the disease's presentation in the Quebec context.

The experiential knowledge collected from clinicians and their representatives suggests that general systemic symptoms and multiple erythema migrans are common in Quebec's population. Cardiac involvement is much less common than musculoskeletal or neurological involvement. According to the specialist physicians consulted, the low prevalence of cardiac involvement is not attributable to a relative lack of vigilance from doctors. No health care professionals consulted had treated a patient presenting with non-neurological ocular involvement. The patients consulted reported a variety of symptoms including incapacitating fatigue, severe headaches and joint pain. Some patients had solitary erythema migrans and several had multiple erythema migrans. In 2018, AQML surveyed 170 of its members, and 42% of respondents reported that they had had solitary or multiple erythema migrans, 24% reported other rashes and 34% no rashes. The survey did not research the prevalence of other involvement [AQML, 2018]. The clinicians emphasized that solitary erythema migrans is not always present or detected.

The clinicians consulted stated that borrelial lymphocytoma, acrodermatitis chronica atrophicans and encephalitis are very rare conditions that are observed primarily in Europe. These manifestations are known to specialists and will therefore not be addressed in the tools intended for primary care providers.

The AQML representatives consulted and the members of the advisory committee stressed that Lyme disease's speed of progression, presentation and intensity of symptoms varies between individuals. Different systems may be affected, simultaneously or otherwise.

A list of the main manifestations suggestive of Lyme disease (Table 7) was developed based on the information presented in the CPGs and the experience of the advisory committee's members. While several CPGs consider general systemic symptoms, the clinicians felt that general systemic symptoms should not be considered as suggestive to the same degree as the other conditions, because of their non-specific nature. Since no member of the advisory committee had had a patient present with non-neurological ocular involvement, AMOQ was contacted to define the conditions in question. That information is presented in the table, but it was decided to not include it in the diagnostic algorithm since ocular involvement is rare.

According to the microbiology / infectious diseases specialists consulted, it is difficult to associate symptoms with the moment of the tick bite, because the bite often goes unnoticed, may be repeated and does not always result in an infection. Also, it is relatively rare for prolonged symptoms other than arthritis to be due to Lyme disease. Still, clinical cases may occur nearly year-round. Some manifestations may present in any season, even winter (e.g., arthritis) since the incubation period is long.

Regarding musculoskeletal manifestations, the members of the advisory committee felt that only joint conditions should be included among the main conditions suggestive of Lyme disease. Arthralgia and myalgia are considered to be general systemic symptoms, and their presence alone is less suggestive of Lyme disease.

According to pediatrics experts, cardiac involvement is rarer in children.

Table 7 Main manifestations suggestive of Lyme disease according to the members of the advisory committee

INVOLVEMENT	SYMPTOMS[1]	PRESENTATION AND SIGNS	TIME FROM TICK BITE TO APPEARANCE
CUTANEOUS	▪ Little or no pain or itching	▪ Isolated, expanding reddish cutaneous lesion that is present for over 48 hours	▪ Usually 3 to 30 days (up to 3 months is possible)
	▪ Little or no pain or itching	▪ Multiple, expanding reddish cutaneous lesions that are present for over 48 hours	▪ A few days to a few weeks after the solitary EM (usually up to 6 months)
NERVOUS SYSTEM	▪ Facial palsy (sometimes bilateral) ▪ Facial numbness ▪ Deafness ▪ Diplopia	▪ Cranial neuritis (particularly facial palsy, but other conditions are possible)	▪ A few days to a few weeks after the solitary EM (usually up to 6 months)
	▪ Weakness of the lower motor neuron type, affecting one or more nerve or radicular territories ▪ Paresthesia or hypoesthesia affecting one or more nerve or radicular territories ▪ Loss of one or more deep tendon reflexes	▪ Mononeuropathy ▪ Mononeuritis multiplex ▪ Radiculopathy without other cause ▪ Plexopathy	
	▪ Headache ▪ Nuchal pain or stiffness ▪ Photophobia ▪ Nausea ▪ Vomiting	▪ Aseptic meningitis	
CARDIAC	▪ Heart palpitations ▪ Dizziness ▪ Syncope ▪ Chest pains ▪ Dyspnea	▪ Non-specific arrhythmia (SVES/PVC) ▪ Atrioventricular block (1st to 3rd degree) ▪ Pericardial syndrome (with or without block) ▪ Heart failure (rare) ▪ Sudden death (rare)	▪ A few days to a few weeks after the solitary EM (usually up to 6 months)
OCULAR (NON-NEUROLOGICAL)	▪ Decreased visual acuity ▪ Eye pain ▪ Pain with eye movement ▪ Redness ▪ Photophobia ▪ Seeing vitreous floaters	▪ Uveitis ▪ Keratitis ▪ Conjunctivitis ▪ Episcleritis ▪ Retinitis ▪ Choroiditis	▪ Unavailable

MUSCULOSKELETAL (JOINT CONDITIONS)	▪ Joint swelling, often disproportionate to associated symptoms (e.g., pain) ▪ Knee involvement is most common.	▪ Swelling of one or more joints (mainly the knee, but smaller joints may be affected) ▪ Possible flare-ups of arthritis interspersed with remission periods when untreated	▪ A few weeks to a few months after the infection (usually up to a year after the bite)

Acronym: EM: erythema migrans

[1] General systemic symptoms may also be present. A non-exhaustive list: fever and chills, discomfort, fatigue, myalgia, arthralgia, slight cognitive impairment, headache, isolated adenopathies, influenza-like illness, mononucleosis-like illness, asthenia, lethargy, anorexia.

In order to better inform people who have been bitten by a tick, who are under observation for potential Lyme disease or who are undergoing antibiotic therapy to treat Lyme disease (see the section “Information and instructions to give to patients”), a list of the main symptoms a patient should look for has also been created (Table 8).

Table 8 Main symptoms a patient should look for after a tick bite, if their clinician has chosen to place them under observation or if they are receiving antibiotic therapy for Lyme disease

INVOLVEMENT	SYMPTOMS	OBSERVATION PERIOD
SKIN	Isolated expanding rash that is present for at least 48 hours and has little or no associated pain or itching	At least 3 months
	Multiple expanding rashes that are present for at least 48 hours and have little or no associated pain or itching	
GENERAL	Fatigue, headache, fever, muscle and joint pain **after a tick bite**	2 months at most
NERVOUS SYSTEM	Facial palsy, numbness or localized weakness in a single limb, neck pain without other explanations, serious headache	At least 6 months
CARDIAC	Chest pains, heart palpitations and dizziness	At least 6 months
MUSCULOSKELETAL	Joint swelling, generally with little pain, primarily of the knee	At least 1 year

Key Takeaways

Lyme disease’s speed of progression, presentation and intensity of symptoms varies between individuals. Different systems may be affected, simultaneously or otherwise.

Erythema migrans is not always present or noticed.

The main manifestations suggestive of Lyme disease are:

- isolated or multiple expanding cutaneous lesion(s) present for over 48 hours

- neurological manifestations such as cranial neuritis (particularly facial palsy), mononeuropathy, mononeuritis multiplex, radiculopathy without other cause, plexopathy or aseptic meningitis
- cardiac manifestations such as episodes of arrhythmia, conduction disturbances, pericarditis or myocarditis
- joint manifestations such as swelling of one or more joints (mainly the knee) and flare-ups of arthritis interspersed with remission periods when untreated.

The main symptoms that a patient should look out for after a tick bite or if a health care professional has chosen to place them under observation or administer antibiotic therapy to treat Lyme disease are:

- isolated or multiple expanding skin rashes, present for at least 48 hours and with little or no associated pain or itching
- joint swelling (mainly the knee), generally with little pain
- facial palsy, numbness or localized weakness in a single limb, neck pain without other explanations, serious headache
- chest pains, heart palpitations and dizziness
- fatigue, headache, fever, muscle and joint pain within four to eight weeks after the bite.

5.5. Other Aspects to Consider when Assessing a Patient

5.5.1. Clinical practice guidelines and other guidelines

NICE recommends taking into account the fact that people with Lyme disease may have difficulty explaining their symptoms due to cognitive impairment [NICE, 2018a].

GAPAH mentions giving the patient a physical examination [Huppertz et al., 2012].

5.5.2. Contextual and experiential data

The clinicians emphasized the importance of giving the patient a physical examination in order to be able to capture a full clinical picture. The physical examination should include a neurological examination. The physician or primary care nurse practitioner (PCNP) should look for a skin lesion that could correspond to an erythema migrans and for other signs of the dissemination of bacteria of the *B. burgdorferi* s.l. complex. They mentioned looking for symptoms like those of meningitis, such as severe headache and neck stiffness. It was pointed out that solitary erythema migrans is often located in places where a tick can go unnoticed and remain attached for a long time (e.g. the trunk, axilla, groin, popliteal fossa, lower buttocks or lower back).

According to the AQML representatives consulted, the symptoms of Lyme disease are difficult to explain, and particular attention should be paid to young children and people with neurocognitive impairment. However, the clinicians did not judge that this observation was

important to include in the tools developed, since it is well known to clinicians and not specific to Lyme disease.

Key Takeaways

It is important to include a neurological examination in the physical examination and to look for a lesion which might correspond to an erythema migrans or to other manifestations suggestive of disseminated stage Lyme disease.

Solitary erythema migrans is often located in places where a tick can go unnoticed and remain attached for a long time.

5.6. Excluding Other Clinical Conditions

5.6.1. Clinical practice guidelines and other guidelines

IDSA [Wormser et al., 2006], NICE [2018a] and HAS [2018a] state that a skin lesion may be caused by a hypersensitive reaction. In addition to that possibility, the GDS lists the following options [Hofmann et al., 2017]: moderate erysipelas (bacterial infection), an allergic reaction to a medication, hypodermitis due to venous insufficiency, atrophoderma of Pasini and Pierini (rare dermatosis with a controversial etiology), cutaneous herpes, solitary morphea, circumscribed scleroderma, granuloma annulare and tinea corporis (ringworm).

Only the GDS addresses what other conditions should be considered when multiple lesions are observed [Hofmann et al., 2017]. The conditions listed are as follows: persistent urticaria, multiple granuloma annulare, erythema annulare centrifugum, multilocular eruption reactions to a drug and fifth disease (erythema infectiosum).

IDSA stated that anaplasmosis and babesiosis should be considered for general systemic symptoms in geographical areas where people are at risk of contracting them [Wormser et al., 2006].

For neurological involvement, IDSA [Wormser et al., 2006], the DGN [Rauer et al., 2018] and GAPAH [Huppertz et al., 2012] suggest taking viral meningitis and aseptic meningitis into account. The DGN also adds the following possibilities [Rauer et al., 2018]: idiopathic facial palsy, herpes zoster oticus (Ramsay Hunt syndrome), polyradiculitis cranialis (Miller Fisher syndrome), traumatic facial palsy, facial palsy secondary to a tumour, mastoiditis (otitis media), tuberculous meningitis, sarcoidosis (Heerfordt syndrome), Melkersson Rosenthal syndrome, mono/polyradiculopathy caused by another pathogenic agent (including HIV or syphilis), spinal cord compression from a herniated disk, facet syndrome, sacroiliac joint syndrome, piriformis syndrome, a spinal tumour (e.g., neurinoma, ependymoma), carcinomatous meningitis, spondylodiscitis, spinal/epidural abscess, chronic myelitis and myelitis caused by another pathogenic agent.

No CPG addresses other conditions to consider for cardiac, musculoskeletal or non-neurological ocular symptoms.

5.6.2. Contextual and experiential data

According to the clinicians consulted, what other conditions a health care professional should consider depend on the patient's clinical picture and will vary from one patient to another, since the presentation of Lyme disease is highly variable.

A non-exhaustive list of other conditions a health care professional should consider has been developed using the CPGs and the experiential data of the clinician and public health members of the advisory committee (Table 9). Some of the patients consulted had also received one of these diagnoses before being diagnosed with Lyme disease, including zoster, infectious cellulitis, viral infection, rheumatoid arthritis and gout.

According to the public health members, differential diagnoses should be prioritized according to the risk level in the geographical area of the exposure. For example, the order of differential diagnoses for manifestations suggestive of Lyme disease other than the typical solitary erythema migrans should be different for an individual living in Abitibi than for an individual living in southern Quebec. The clinicians, however, stated that in prioritizing differential diagnoses, professionals should take into account the patient's entire clinical picture, including the possibility of tick exposure, but that the risk level of areas the patient has been in is less important. Nonetheless, both public health and clinician members agreed that Lyme disease should be prioritized in differential diagnoses when there has been exposure in a high-risk area, regardless of the possibility of tick exposure, since ticks can be carried by small animals and thus may be present anywhere around houses, even in cities. Incidentally, in those areas, Lyme disease would be a condition to rule out during the diagnostic process of some other clinical conditions.

Primary care clinicians are not always well equipped to rule out other probable clinical conditions when the clinical presentation goes beyond cutaneous involvement. Furthermore, in summer there are viral infectious agents that should be considered in differential diagnoses of general systemic symptoms (adenovirus, enterovirus).

It may be difficult to tell in practice whether a rash at the site of a bite corresponds to the beginning of a typical solitary erythema migrans or to a local hypersensitive reaction. The characteristics of each lesion that can help distinguish between them are discussed in the supporting report on PEP tools [INESSS, 2019b].

It may also be difficult to distinguish between infectious cellulitis and erythema migrans; members observed that cellulitis is not generally round in shape and that it spreads proximally. Furthermore, erythema migrans has little or no associated pain, itching and warmth. In cases of doubt, a course of treatment adequate for treating both types of lesion might be adopted (see the section "Antibiotic treatment indications").

Lastly, distinguishing between contact dermatitis and erythema migrans can also be problematic for some health care professionals. According to the dermatologists consulted, the pruriginous nature of contact dermatitis is its most distinctive element. Contact dermatitis may take much more varied forms than erythema migrans, and may also include a burning sensation. Contact dermatitis is more probable if the lesion presents with papules, vesicles or squames, while erythema migrans is more probable if the lesion is smooth and lacks squames.

In cases of doubt regarding the cause of reddened skin, the recommendation is to discuss the case with a specialist or an experienced colleague.

Key Takeaways

The other conditions that a health care professional should consider depend on the patient's clinical picture and will vary from one patient to another, since the presentation of Lyme disease is highly variable.

In prioritizing differential diagnoses, professionals should take into account the patient's clinical picture, including the possibility of tick exposure and the possible geographic area of the exposure.

Table 9 Non-exhaustive list of other conditions to consider depending on the patient's clinical picture

Cutaneous system	*Solitary lesion*	▪ Local hypersensitivity reaction ▪ Nummular eczema ▪ Tinea corporis ▪ Infectious cellulitis ▪ Pityriasis rosea Gibert	▪ Granuloma annulare ▪ Erythema nodosa ▪ Fixed pigmented erythema (fixed drug eruption) ▪ Contact dermatitis ▪ Herpes (cutaneous or zoster)	▪ Southern tick-associated rash illness (STARI) **Late-phase** ▪ Solitary morphea ▪ Stasis dermatitis
	Multiple lesions	▪ Local hypersensitivity reaction ▪ Urticaria ▪ Erythema multiforme ▪ Pityriasis rosea Gibert ▪ Sweet's neutrophilic dermatosis	▪ Fixed pigmented erythema (fixed drug eruption) ▪ Granuloma annulare ▪ Erythema nodosa	▪ Erythema annulare centrifugum ▪ Subacute cutaneous lupus erythematosus ▪ Urticarial vasculitis ▪ Sarcoidosis
Musculoskeletal system ▪ Arthritis (most common)		▪ Spondyloarthropathies (other than reactive), psoriatic arthritis and arthritis associated with inflammatory bowel diseases ▪ Juvenile idiopathic arthritis	▪ Reactive arthritis ▪ Septic arthritis ▪ Rheumatoid polyarthritis ▪ Parvovirus B19 infection (fifth disease) ▪ Post-infectious arthritis	▪ Collagenosis or vasculitis ▪ Microcrystalline arthritis ▪ Gout
Nervous system	*Facial palsy (most common, sometimes bilateral) or other cranial nerve conditions*	▪ Idiopathic facial palsy (Bell palsy) ▪ Herpes zoster oticus (Ramsay Hunt syndrome) ▪ Mastoiditis, otitis media	▪ Guillain-Barré syndrome ▪ Facial palsy secondary to other infectious processes (e.g., HIV, syphilis) ▪ Sarcoidosis (Heerfordt syndrome) ▪ Sjögren's syndrome	▪ Facial palsy secondary to a tumour ▪ Meningitis at the cranial base
	Aseptic meningitis	▪ Viral meningitis ▪ Syphilitic meningitis ▪ Tuberculous meningitis	▪ Fungal meningitis (cryptococcosis, coccidioidomycosis) ▪ Leptomeningeal carcinomatosis	▪ Drug-induced meningitis
	Peripheral neurological conditions: mononeuritis multiplex, polyradiculopathy, plexopathy	▪ Secondary radicular compression (mechanical impairment, e.g., foraminal stenosis, disk herniation) ▪ Mono/polyradiculopathy caused by other pathogenic agent (e.g., HIV, syphilis)	▪ Vasculitis and collagenosis ▪ Idiopathic brachial plexopathy (Parsonage-Turner syndrome) ▪ Diabetic lumbosacral plexopathy (Bruns-Garland syndrome)	▪ Spondylodiscitis, epidural abscess ▪ Leptomeningeal carcinomatosis
Cardiac system ▪ Atrioventricular block (most common) ▪ Myo/Pericarditis ▪ Arrhythmia		▪ CAD ▪ Medication (e.g., β-blockers) ▪ Viral infection (e.g., Coxsackie) ▪ Collagenosis ▪ Kawasaki disease	▪ ARA ▪ Bacterial infection (e.g., *Y. enterocolitica*) ▪ Parasitic infection ▪ Rocky Mountain spotted fever	▪ Congenital/acquired cardiac malformation ▪ Sarcoidosis
Other tick-borne illnesses/Co-infections		▪ Anaplasmosis ▪ Babesiosis	▪ Infection by *Borrelia miyamotoi* ▪ STARI	▪ Viral arbovirus (e.g., Powassan encephalitis)

Abbreviations: CAD: coronary artery disease; ARA: acute rheumatic arthritis; STARI: Southern tick-associated rash illness; HIV: human immunodeficiency virus.

6. ESTABLISHING A DIAGNOSIS

Assessment Questions
To limit overdiagnosis and underdiagnosis, what should be the basis for diagnosing Lyme disease given its various clinical presentations? More specifically: • What are the signs and symptoms associated with the various manifestations of Lyme disease that have diagnostic value? • What is the diagnostic value of analyzing ticks and of requesting laboratory tests (including serologic tests and polymerase chain reaction [PCR]) for the various manifestations of Lyme disease, compared to clinical diagnosis or other methods of diagnosis recognized by learned societies? To use laboratory tests as effectively as possible, what situations require: • Serologic tests (screening and confirmatory)? • A PCR? • Other tests? How should clinicians interpret a negative result for a confirmatory test based on clinical presentation, in order to judiciously integrate test results into the diagnosis process?

6.1. Diagnostic Value of Signs and Symptoms

6.1.1. Clinical practice guidelines and other guidelines

The CPGs retained all recognized the diagnostic value of the typical solitary erythema migrans, i.e., an expanding rash that reaches a diameter of over 5 cm. The CPGs mention various characteristics associated with the typical form (e.g., appearing at the site of the bite, round or oval shape), but central clearing is not always included [NICE, 2018a; HAS, 2018a; Hofmann et al., 2017; Huppertz et al., 2012; Wormser et al., 2006]. NICE, however, states that the data supporting the diagnostic value of erythema migrans are limited [NICE, 2018a].

When a typical solitary erythema migrans is present, only IDSA requires a clinical and epidemiological history compatible with Lyme disease [Wormser et al., 2006]. HAS points out that mention of a recent tick bite when a patient's history is taken can facilitate the diagnosis of erythema migrans, but its absence should not lead clinicians to dismiss that diagnosis [HAS, 2018a]. However, NICE, the GDS and GAPAH do not specify other aspects of the clinical picture that must be documented [NICE, 2018a; Hofmann et al., 2017; Huppertz et al., 2012].

Three CPGs addressed the diagnostic value of atypical solitary erythema migrans and gave different recommendations. HAS and GAPAH recommend measuring the lesion and seeing the patient again in 18 to 72 hours. They also mention that progressive growth of the lesion is sufficient to confirm the diagnosis [HAS, 2018a; Huppertz et al., 2012]. The GDS does not recommend a diagnosis based only on the presence of an atypical erythema migrans and recommends laboratory analysis [Hofmann et al., 2017].

Only two CPGs retained addressed diagnosing Lyme disease when multiple erythema migrans are present. While HAS recommends a clinical diagnosis based on the appearance of the lesions and above all on their progressive, centrifugal expansion [HAS, 2018a], the GDS recommends laboratory analysis [Hofmann et al., 2017].

According to the CPGs, no other sign or symptom can be used to establish a diagnosis without confirmation from the clinical picture and laboratory tests [NICE, 2018a; HAS, 2018a; Rauer et al., 2018; Hofmann et al., 2017; Huppertz et al., 2012].

6.1.2. Scientific data

A systematic review of the scientific literature was carried out in order to assess the diagnostic value of the following manifestations:

- Erythema migrans
- General systemic symptoms
- Arrhythmia or heart block
- Facial palsy, lymphocytic meningitis or radiculoneuritis
- Oligoarticular, monoarticular or migratory arthritis
- Conjunctivitis, uveitis, keratitis, iritis or scleritis

6.1.2.1. Solitary erythema migrans

6.1.2.1.1. Results from systematic reviews

Of the sixteen studies in NICE's systematic review on the diagnostic value of signs and symptoms [NICE, 2018b], seven cohort studies and one case-control study were retained for our examination of the diagnostic value of solitary erythema migrans. The authors emphasized that the majority of studies included did not have the objective of determining the diagnostic precision of these signs and symptoms. The aggregate results show that erythema migrans has a low sensitivity in adults (67%) and children (40%) (Table 10), but a high specificity: 88% in adults and 99% in children. Note, however, that the authors do not include the place where Lyme disease was contracted, the choice of reference used or the context of the disease. As previously mentioned, it is well known that the Borrelia genospecies are differently distributed in North America and in Europe, and that they cause different clinical manifestations (see the section "Genospecies of the *Borrelia burgdorferi* sensu lato complex"). Also, the choice of reference test could have an effect on the sensitivity and specificity data, since the commonly used tests (e.g., bacterial culture, serologic tests and clinical diagnosis) have different diagnostic values at various stages of the disease (see the section "Diagnostic value of laboratory analysis" and the state of knowledge report [INESSS, 2019d]). Lastly, all studies on the pediatric population were done in the context of suspected neuroborreliosis, and patient inclusion entailed a cerebrospinal fluid tap.

The authors judged the evidence to be of very low quality because of the high risk of bias and the lack of diagnostic precision. They also expressed reservations about how the signs and symptoms were described and evaluated in the included studies, given the absence of an adequate reference standard. According to the authors, it is the evidence demonstrating the

high specificity of erythema migrans that supports its diagnostic use in clinical practice (Appendix I of this report's supplementary appendices document).

Table 10 Diagnostic value of erythema migrans in the context of Lyme disease

Participants	Studies included	Reference test and context	Sensitivity,[1] % (95% CI)	Specificity,[1] % (95% CI)
Adults N: 310	**N:** 3 **Design**: cohort **Years**: 1990, 2001 and 2009 **Countries**: 2 United States and 1 France	**Reference**: CDC criteria, culture or PCR **Context**: symptoms compatible with LD for 12 weeks or less	67 (21 to 94)	88 (52 to 99)
Children N: 537	**N**: 4 **Design**: cohort **Years**: 1998, 2005, 2005 and 2012 **Countries**: 2 United States, 1 Norway and 1 Finland	**Reference**: CDC criteria or various criteria related to diagnosing neuroborreliosis **Context**: suspicion of NB	40 (15 to 71)	99 (96 to 1.00)

Source: NICE, 2018b.
Acronyms and abbreviations: CDC: Centers for Disease Control and Prevention; 95% CI: confidence interval of 95%; LD: Lyme disease; NB: neuroborreliosis; PCR: polymerase chain reaction

[1] No heterogeneous data were calculated.

6.1.2.1.2. Results from primary studies

The objective of the studies retained for examining the diagnostic value of solitary erythema migrans was not to determine its diagnostic precision.

As stated in the previous section, NICE's systematic review does not include the place where Lyme disease was contracted, the choice of reference test or the context of the disease. It was therefore decided that INESSS would assess the level of scientific evidence for the diagnostic value of erythema migrans by separating the data based on the place where the disease was contracted and its context. Four studies included in NICE's systematic review [2018b] met the inclusion and exclusion criteria (see the section "Selection of documents") and were retained. No other studies were found in our literature search. The limitations of these studies were discussed in the section "Description of documents."

A single study was retained to assess the diagnostic value of erythema migrans in the context of Lyme disease contracted in North America [Aucott et al., 2009]. In this study of 165 patients, the sensitivity of solitary erythema migrans was 87% (95% CI: 79% to 93%) and its specificity was 100% (95% CI: 94% to 100%). Based on the assessment criteria, the level of

scientific evidence was rated as low (Appendix Q of this report's supplementary appendices document).

One study was retained to assess the diagnostic value of erythema migrans in the context of neuroborreliosis contracted in North America [Avery et al., 2005]. In this study of 108 patients, the sensitivity of solitary erythema migrans was 60% (95% CI: 36% to 81%) and its specificity was 100% (95% CI: 96% to 100%). The sensitivity is different from that of Aucott's study [2009] because patients were included if they had documented meningitis and not because of suspected Lyme disease based on a skin lesion or systemic symptoms. Based on the assessment criteria, the level of scientific evidence was rated as low (Appendix Q of this report's supplementary appendices document).

No studies were retained to assess the diagnostic value of erythema migrans in the context of Lyme disease contracted in Europe. However, two studies were retained to assess its diagnostic value in the context of neuroborreliosis [Tveitnes et al., 2012; Peltomaa et al., 1998]. In all, 254 patients were included in these studies. The sensitivity of erythema migrans was 59% (95% CI: 33% to 82%) in one study and 23% (95% CI: 17% to 31%) in the other. This difference is possibly due to the cohorts' inclusion criteria and the generation of the tests used to support the diagnosis. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Key Takeaways

Very few studies were retained to assess the diagnostic value of erythema migrans.

The diagnostic value of erythema migrans is higher in the context of Lyme disease contracted in North America than in the context of Lyme disease contracted in Europe.

The level of scientific evidence for the statements is low or insufficient. In summary:

- Erythema migrans has a sensitivity of 87% (95% CI: 79% to 93%) and a specificity of 100% (95% CI: 94% to 100%) in the context of Lyme disease contracted in North America (1 study, N = 165, low level of evidence).
- Erythema migrans has a sensitivity of 60% (95% CI: 36% to 81%) and a specificity of 100% (95% CI: 96% to 100%) in the context of neuroborreliosis contracted in North America (1 study, N = 108, low level of evidence).
- Erythema migrans has a sensitivity of 59% (95% CI: 33% to 82%) and a specificity of 23% (95% CI: 17% to 31%) in the context of neuroborreliosis contracted in Europe (2 studies, N = 254, insufficient level of evidence).

6.1.2.2. General systemic symptoms

6.1.2.2.1. Results from systematic reviews

No systematic review on the diagnostic value of general systemic symptoms was found in the literature search.

6.1.2.2.2. Results from primary studies

Fourteen primary studies addressing the diagnostic value of one or more general systemic symptoms were found in the literature search [Zomer et al., 2018; Barstad et al., 2017; Gyllemark et al., 2017; Remy et al., 2017; Roaldsnes et al., 2017; Picha et al., 2016; Sundin et al., 2012; Fine et al., 2011; Tjernberg et al., 2011; Aucott et al., 2009; Nigrovic et al., 2008; Ogrinc et al., 2008; Skogman et al., 2008; Shah et al., 2005].

Note that the objective of the studies retained to assess the diagnostic value of general systemic symptoms was not to determine their diagnostic precision.

Arthralgia, myalgia, fatigue, headache and mental impairment

No studies addressing the diagnostic value of general systemic symptoms (arthralgia, myalgia, fatigue, headache and mental impairment) in the context of neuroborreliosis contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of general systemic symptoms (arthralgia, myalgia, fatigue, headache and mental impairment) in the context of neuroborreliosis contracted in Europe [Picha et al., 2016]. The general systemic symptoms had a sensitivity of 0% in the 74 patients with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index), a sensitivity of 33% in the 36 patients with possible neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity of 75% in the 134 controls who were healthy or presented with other conditions. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Viral-like illness

One study was retained to assess the diagnostic value of viral-like illness without evidence of another infection in the context of Lyme disease contracted in North America [Aucott et al., 2009]. Viral-like illness had a sensitivity of 7% and a specificity of 34% in the 165 study subjects suspected of having Lyme disease. Based on the assessment criteria, the level of scientific evidence was rated as low (Appendix Q of this report's supplementary appendices document).

No studies addressing the diagnostic value of viral-like illness without evidence of another infection in the context of Lyme disease contracted in Europe were found in the literature search.

Headache

Two studies addressing the diagnostic value of headache in the context of Lyme disease or neuroborreliosis contracted in North America were found, but neither was retained because they did not fit the inclusion criteria.

Two studies were retained to assess the diagnostic value of headache in the context of Lyme disease contracted in Europe [Zomer et al., 2018; Ogrinc et al., 2008]. Headache had a sensitivity of 15% and 29% in the 284 people with Lyme disease included and a specificity of

71% and 72% in the 685 controls presenting with other conditions. Based on the assessment criteria, the level of scientific evidence was rated as low (Appendix Q of this report's supplementary appendices document).

Four studies were retained to assess the diagnostic value of headache in the context of neuroborreliosis contracted in Europe [Barstad et al., 2017; Remy et al., 2017; Sundin et al., 2012; Skogman et al., 2008]. Headache has a sensitivity ranging from 37% to 70% in the 247 people with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity ranging from 26% to 64% in the 306 controls who were healthy or presented with other conditions. The reason for the difference in sensitivity is not clear; it may possibly be due to patient characteristics. The difference in specificity is due to one study, that of Remy et al. [2017]. If that study is omitted, headache has a specificity ranging from 26% to 28% (N = 273). Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Fever

Two studies addressing the diagnostic value of fever in the context of Lyme disease or neuroborreliosis contracted in North America were found, but neither was retained because they did not fit the inclusion criteria.

One study was retained to assess the diagnostic value of fever in the context of Lyme disease contracted in Europe [Ogrinc et al., 2008]. Fever had a sensitivity of 3% in the 72 people with Lyme disease and a specificity of 96% in the 206 controls presenting with other conditions. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Three studies were retained to assess the diagnostic value of fever in the context of neuroborreliosis contracted in Europe [Barstad et al., 2017; Sundin et al., 2012; Skogman et al., 2008]. Fever had a sensitivity ranging from 5% to 44% in the 213 people with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity ranging from 78% to 88% in the 273 controls presenting with other conditions. The explanation for the difference in sensitivity among these studies has not been determined. Based on the assessment criteria, the level of scientific evidence was rated as low (Appendix Q of this report's supplementary appendices document).

Fatigue or generally impaired condition

No studies addressing the diagnostic value of fatigue or of generally impaired condition in the context of Lyme disease or neuroborreliosis contracted in North America were found in the literature search.

Two studies were retained to assess the diagnostic value of fatigue or generally impaired condition in the context of Lyme disease contracted in Europe [Zomer et al., 2018; Ogrinc et al., 2008]. Fatigue or generally impaired condition had a sensitivity of 20% and 52% for the 284 people with Lyme disease, and a specificity of 32% and 85% for the 685 controls

presenting with other conditions. The difference in sensitivity between these studies may be attributable to the fact that one study allowed for clinical diagnosis while the other required a positive serologic test. The difference in specificity may be due to patient characteristics. Based on the assessment criteria, the level of scientific evidence was rated as low (Appendix Q of this report's supplementary appendices document).

Three studies were retained to assess the diagnostic value of fatigue or generally impaired condition in the context of neuroborreliosis contracted in Europe [Barstad et al., 2017; Sundin et al., 2012; Skogman et al., 2008]. Fatigue or generally impaired condition had a sensitivity ranging from 10% to 77% in the 191 people with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity of 44% to 73% in the 217 controls who were healthy or presented with other conditions. The difference in sensitivity between these studies may be attributable to the criteria for neuroborreliosis used by Sundin et al. [2012] (the diagnostic criteria are not well defined) and to the small number of individuals in the cohort (N = 21). If this study is omitted, the sensitivity of fatigue or generally impaired condition ranges from 45% and 77% (2 studies, N = 162). Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Arthralgia

No studies addressing the diagnostic value of arthralgia in the context of Lyme disease contracted in North America were found in our literature search.

Two studies were retained to assess the diagnostic value of arthralgia in the context of Lyme disease contracted in Europe [Zomer et al., 2018; Ogrinc et al., 2008]. Arthralgia had a sensitivity of 40% and 64% in the 284 people with Lyme disease and a specificity of 40% and 48% in the 685 controls who presented with other conditions. The difference in sensitivity between the two studies may be attributable to the fact that one study allowed clinical diagnosis while the other required a positive serology. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Myalgia

Two studies addressing the diagnostic value of myalgia in the context of Lyme disease or neuroborreliosis contracted in North America were found, but neither was retained because they did not fit the inclusion criteria.

Two studies were used to assess the diagnostic value of myalgia in the context of Lyme disease contracted in Europe [Zomer et al., 2018; Ogrinc et al., 2008]. Myalgia had a sensitivity of 22% and 36% in the 284 people with Lyme disease and a specificity of 42% and 75% in the 685 controls who presented with other conditions. The difference in sensitivity between the two studies may be attributable to the fact that one study allowed clinical diagnosis while the other required a positive serology. The difference in specificity may be due

to patient characteristics. Based on the assessment criteria, the level of scientific evidence was rated as low (Appendix Q of this report's supplementary appendices document).

Two studies were retained to assess the diagnostic value of myalgia in the context of neuroborreliosis contracted in Europe [Sundin et al., 2012; Skogman et al., 2008]. Myalgia had a sensitivity of 19% and 25% in the 147 people with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity of 78% and 88% in the 162 controls who were healthy or presented with other conditions. Based on the assessment criteria, the level of scientific evidence was rated as low (Appendix Q of this report's supplementary appendices document).

Neck pain and stiffness

No studies addressing the diagnostic value of neck pain and stiffness in the context of Lyme disease contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of neck pain and stiffness in the context of neuroborreliosis contracted in North America [Shah et al., 2005]. Neck pain and stiffness had a sensitivity of 71% in the 24 patients with neuroborreliosis (pleocytosis and positive serology) and a specificity of 25% in the 83 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

One study was retained to assess the diagnostic value of neck pain or stiffness in the context of Lyme disease contracted in Europe [Zomer et al., 2018]. Stiffness or neck pain had a sensitivity of 45% in the 212 patients with Lyme disease and a specificity of 43% in the 479 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Three studies were retained to assess the diagnostic value of neck pain or stiffness in the context of neuroborreliosis contracted in Europe [Barstad et al., 2017; Sundin et al., 2012; Skogman et al., 2008]. Neck pain or stiffness had a sensitivity ranging from 0% to 43% in the 330 people with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity ranging from 64% to 97% in the 334 controls who presented with other conditions. The difference in sensitivity between these studies may be attributable to the criteria regarding neuroborreliosis used in Sundin's study [2012] (the diagnostic criteria were not well defined) and to the small number of individuals included in the cohort (N = 21). When this study is omitted, the sensitivity instead ranges between 27% and 43% (2 studies, N = 309) and the specificity ranges between 64% and 91% (N = 231). The difference in specificity may be due to patient characteristics. Based on the assessment criteria, the level of scientific evidence was rated as low (Appendix Q of this report's supplementary appendices document).

Convulsions

One study was retained to assess the diagnostic value of convulsions in the context of neuroborreliosis contracted in North America [Shah et al., 2005]. Convulsions had a sensitivity of 0% in the 24 patients with neuroborreliosis (pleocytosis and positive serology) and a specificity of 95% in the 151 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

One study was retained to assess the diagnostic value of convulsions in the context of neuroborreliosis contracted in Europe [Sundin et al., 2012]. Convulsions had a sensitivity of 0% in the 21 people with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity of 91% in the 103 controls who presented with other conditions. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Photophobia and visual disorders

One study was retained to assess the diagnostic value of photophobia in the context of neuroborreliosis contracted in North America [Shah et al., 2005]. Photophobia had a sensitivity of 42% in the 12 patients with neuroborreliosis (pleocytosis and positive serology) and a specificity of 30% in the 74 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

One study was retained to assess the diagnostic value of visual disorders in the context of Lyme disease contracted in Europe [Zomer et al., 2018]. Visual disorders had a sensitivity of 10% in the 212 patients with Lyme disease and a specificity of 75% in the 479 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Dizziness

No studies addressing the diagnostic value of dizziness in the context of Lyme disease or neuroborreliosis contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of dizziness in the context of Lyme disease contracted in Europe [Zomer et al., 2018]. Dizziness had a sensitivity of 20% in the 212 patients with Lyme disease and a specificity of 63% in the 479 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

One study was retained to assess the diagnostic value of dizziness in the context of neuroborreliosis contracted in Europe [Barstad et al., 2017]. Dizziness had a sensitivity of 21% in the 56 patients with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity of 63% in the 101 controls who presented with another condition. Based

on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Vertigo

No studies addressing the diagnostic value of vertigo in the context of Lyme disease or neuroborreliosis contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of vertigo in the context of Lyme disease contracted in Europe [Ogrinc et al., 2008]. Vertigo had a sensitivity of 0% in the 72 patients with Lyme disease and a specificity of 90% in the 206 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Two studies were retained to assess the diagnostic value of vertigo in the context of neuroborreliosis contracted in Europe [Sundin et al., 2012; Skogman et al., 2008]. Vertigo had a sensitivity of 18% and 24% in the 139 people with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity of 63% and 74% in the 162 controls who presented with other conditions. Based on the assessment criteria, the level of scientific evidence was rated as low (Appendix Q of this report's supplementary appendices document).

Paresthesia

No studies addressing the diagnostic value of paresthesia in the context of Lyme disease or neuroborreliosis contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of paresthesia in the context of Lyme disease contracted in Europe [Ogrinc et al., 2008]. Paresthesia had a sensitivity of 1% in the 72 patients with Lyme disease and a specificity of 92% in the 206 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

One study was retained to assess the diagnostic value of paresthesia in the context of neuroborreliosis contracted in Europe [Skogman et al., 2008]. Paresthesia had a sensitivity of 3% in the 118 patients with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity of 97% in the 59 controls who presented with other conditions. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Anxiety

No studies addressing the diagnostic value of anxiety in the context of Lyme disease contracted in North America was found in the literature search.

One study was retained to assess the diagnostic value of anxiety in the context of Lyme disease contracted in Europe [Ogrinc et al., 2008]. Anxiety had a sensitivity of 3% in the 72 patients with Lyme disease and a specificity of 97% in the 206 controls who presented with

another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Memory disturbances

No studies addressing the diagnostic value of memory disturbances in the context of Lyme disease in North America were found in the literature search.

One study was retained to assess the diagnostic value of memory disturbances in the context of Lyme disease contracted in Europe [Ogrinc et al., 2008]. Memory disturbances had a sensitivity of 1% in the 72 patients with Lyme disease and a specificity of 99% in the 206 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Cognitive impairment

No studies addressing the diagnostic value of cognitive impairment in the context of Lyme disease contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of cognitive impairment in the context of Lyme disease contracted in Europe [Zomer et al., 2018]. Cognitive impairment had a sensitivity of 27% in the 212 patients with Lyme disease and a specificity of 56% in the 479 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Sleep disturbances

No studies addressing the diagnostic value of sleep disturbances in the context of Lyme disease contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of sleep disturbances in the context of Lyme disease contracted in Europe [Zomer et al., 2018]. Sleep disturbances had a sensitivity of 43% in the 212 patients with Lyme disease and a specificity of 36% in the 479 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Sensory disorders

No studies addressing the diagnostic value of sensory disorders in the context of Lyme disease or neuroborreliosis contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of sensory disorders in the context of Lyme disease contracted in Europe [Zomer et al., 2018]. Sensory disorders had a sensitivity of 35% in the 212 patients with Lyme disease and a specificity of 54% in the 479 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

One study was retained to assess the diagnostic value of sensory disorders in the context of neuroborreliosis contracted in Europe [Sundin et al., 2012]. Sensory disorders had a sensitivity of 0% in the 21 patients with neuroborreliosis and a specificity of 95% in the 103 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Motor disorders

No studies addressing the diagnostic value of motor disorders in the context of neuroborreliosis contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of motor disorders in the context of neuroborreliosis contracted in Europe [Sundin et al., 2012]. Motor disorders had a sensitivity of 0% in the 21 patients with neuroborreliosis and a specificity of 98% in the 103 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Mood disorders

No studies addressing the diagnostic value of mood disorders in the context of Lyme disease contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of mood disorders in the context of Lyme disease contracted in Europe [Zomer et al., 2018]. Mood disorders had a sensitivity of 24% in the 212 patients with Lyme disease and a specificity of 62% in the 479 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Shortness of breath or palpitations

No studies addressing the diagnostic value of shortness of breath or palpitations in the context of Lyme disease in North America were found in the literature search.

Two studies were retained to assess the diagnostic value of shortness of breath or palpitations in the context of Lyme disease contracted in Europe [Zomer et al., 2018; Ogrinc et al., 2008]. Shortness of breath or palpitations had a sensitivity of 1% and 15% in the 284 patients with Lyme disease and a specificity of 72% and 97% in the 685 controls who presented with another condition. The difference in specificity may be due to patient characteristics. Based on the assessment criteria, the level of scientific evidence was rated as low (Appendix Q of this report's supplementary appendices document).

Back pain

No studies addressing the diagnostic value of back pain in the context of neuroborreliosis contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of back pain in the context of neuroborreliosis contracted in Europe [Sundin et al., 2012]. Back pain had a sensitivity of 14% in the 21 patients with neuroborreliosis and a specificity of 90% in the 103 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Behavioural changes

No studies addressing the diagnostic value of behavioural changes in the context of neuroborreliosis contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of behavioural changes in the context of neuroborreliosis contracted in Europe [Sundin et al., 2012]. Behavioural changes had a sensitivity of 5% in the 21 patients with neuroborreliosis and a specificity of 26% in the 103 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Confusion

No studies addressing the diagnostic value of confusion in the context of neuroborreliosis contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of confusion in the context of neuroborreliosis cases contracted in Europe [Sundin et al., 2012]. Confusion had a sensitivity of 0% in the 21 patients with neuroborreliosis and a specificity of 98% in the 103 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Loss of appetite

No studies addressing the diagnostic value of loss of appetite in the context of neuroborreliosis contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of loss of appetite in the context of neuroborreliosis contracted in Europe [Skogman et al., 2008]. Loss of appetite had a sensitivity of 58% in the 118 patients with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity of 78% in the 59 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Nausea

No studies addressing the diagnostic value of nausea in the context of neuroborreliosis contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of nausea in the context of neuroborreliosis contracted in Europe [Skogman et al., 2008]. Nausea had a sensitivity of 26% in the 118 patients with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity of 66% in the 59 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Key Takeaways

The majority of studies retained evaluated the diagnostic value of general systemic symptoms in the context of Lyme disease contracted in Europe.

The majority of systemic symptoms had a sensitivity of less than 50% for both Lyme disease and neuroborreliosis.

The level of scientific evidence for the majority of the scientific statements is insufficient. In summary:

- Influenza-like illness has a sensitivity of 7% and a specificity of 34% in the context of Lyme disease contracted in North America (1 study, N = 165, low level of evidence).
- Convulsions and possible general systemic symptoms (arthralgia, myalgia, fatigue, headache, mental impairment) have a sensitivity of less than 50% in the context of neuroborreliosis contracted in North America. Their specificity is 95% and 75%, respectively, in controls who are healthy or present with other conditions (insufficient level of evidence).
- Neck pain or stiffness have a sensitivity of 71% in the context of neuroborreliosis contracted in North America and a specificity of 25% in controls who present with other conditions (1 study, N = 24 [sensitivity] and 183 [specificity], insufficient level of evidence).
- The following general systemic symptoms have a sensitivity of less than 50% in the context of Lyme disease contracted in Europe: headache, fever, fatigue or generally impaired condition, myalgia, neck pain and stiffness, vision problems, dizziness, vertigo, paresthesia, anxiety, memory disturbances, cognitive impairment, sleep disturbances, sensory disorders, mood disorders, shortness of breath and palpitations. The specificity of these symptoms varies a great deal. It is greater than 80% for fever, fatigue or generally impaired condition, vertigo, paresthesia, anxiety, memory disturbances, shortness of breath and palpitations (low or insufficient level of evidence).
- Arthralgia has a sensitivity of 40% and 64% in the context of Lyme disease contracted in Europe and a specificity of less than 50% in controls presenting with other conditions (2 studies, N = 284, insufficient level of evidence).
- The following general systemic symptoms have a sensitivity of less than 50% in the context of neuroborreliosis contracted in Europe: fever, myalgia, neck pain and stiffness, convulsions, photophobia, dizziness, vertigo, sensory disturbances, motor

disorders, back pain, behavioural changes, confusion and nausea. The specificity of these symptoms varies a great deal. It is greater than 80% for fever, myalgia, neck pain or stiffness, sensory disturbances, motor disorders, back pain and confusion (low level of evidence or insufficient).

- Headache has a sensitivity of 37% and 70% in the context of neuroborreliosis contracted in Europe and a specificity of 26% and 64% in controls who are healthy or present with other conditions (2 studies, N = 247 [sensitivity] and 306 [specificity], insufficient level of evidence).
- Fatigue or generally impaired condition has a sensitivity of 45% to 77% in the context of neuroborreliosis contracted in Europe and a specificity of 44% to 73% in controls who are healthy or present with other conditions (3 studies, N = 162 [sensitivity] and 217 [specificity], insufficient level of evidence).
- Loss of appetite has a sensitivity of 58% in the context of neuroborreliosis contracted in Europe and a specificity of 78% in controls who present with other conditions (1 study, N = 118 [sensitivity] and 59 [controls], insufficient level of evidence).

6.1.2.3. Arrhythmia or heart block

6.1.2.3.1. Results from systematic reviews

Of the 16 studies on the diagnostic value of signs and symptoms that are included in the NICE SR [NICE, 2018b], two case-control studies were retained to assess the diagnostic value of cardiac conditions. The authors emphasized that the studies included did not have the objective of determining the diagnostic precision of these signs and symptoms. Sangha's study [1998] shows a sensitivity less than or equal to 1% for the various types of arrhythmia (bradycardia, tachycardia and non-sinus rhythm) observed in adults and a specificity that ranges from 95% to 100%. In the same study, atrioventricular block has a sensitivity of 10% (95% CI: 6% to 15%) and a specificity of 95% (95% CI: 90% to 98%), while right bundle-branch block has a sensitivity of 16% (95% CI: 11% to 23%) and a specificity of 84% (95% CI: 78% to 90%). For arrhythmia (without distinction between types), Pikelj-Pečnik [2002] shows a sensitivity of 5% (95% CI: 2% to 10%) in children with Lyme disease and a specificity of 79% (95% CI: 72% to 85%).

The authors judged that the evidence was not strong enough to recommend diagnosing Lyme disease on the sole basis of arrhythmia or heart block. However, they took into consideration both the high specificity of these conditions and the adverse effects of an incorrect diagnosis if arrhythmia and heart block are not considered as possible symptoms of Lyme disease (Appendix I of this report's supplementary appendices document).

6.1.2.3.2. Results from primary studies

Other than those included in the NICE systematic review on signs and symptoms [NICE, 2018b], no studies examining the diagnostic value of arrhythmia and atrioventricular block were found [Pikelj-Pečnik et al., 2002; Sangha et al., 1998]. The study by Sangha et al. [1998]

was not retained, since it did not meet the INESSS inclusion criteria regarding its choice of reference test (see the section “Selection of documents”). Note that the objective of the study by Pikelj-Pečnik et al. [2002] was not to determine the diagnostic precision of cardiac signs and symptoms.

No studies addressing the diagnostic value of arrhythmia and heart block in the context of Lyme disease contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of atrioventricular block in the context of Lyme disease contracted in Europe [Pikelj-Pečnik et al., 2002]. Atrioventricular block had a sensitivity of 1% in the 220 patients with Lyme disease and a specificity of 100% in the 165 healthy controls. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report’s supplementary appendices document).

One study was retained to assess the diagnostic value of right bundle-branch block in the context of Lyme disease contracted in Europe [Pikelj-Pečnik et al., 2002]. Right bundle-branch block had a sensitivity of 5% in the 220 patients with Lyme disease and a specificity of 92% in the 165 healthy controls. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report’s supplementary appendices document).

Key Takeaways

No studies were retained that addressed this subject in the North American context. The level of scientific evidence for the scientific statements is insufficient.

The symptoms assessed all had a sensitivity of less than 50% in the context of Lyme disease.

In summary:

- Atrioventricular block has a sensitivity of 1% in the context of Lyme disease contracted in Europe and a specificity of 100% in healthy controls (1 study, N = 220 [sensitivity] and 165 [specificity], insufficient level of evidence).
- Right bundle-branch block has a sensitivity of 5% in the context of Lyme disease contracted in Europe and a specificity of 92% in healthy controls (1 study, N = 220 [sensitivity] and 165 [specificity], insufficient level of evidence).

6.1.2.4. Facial palsy, lymphocytic meningitis or radiculoneuritis

6.1.2.4.1. Results from systematic reviews

Of the 16 studies included in the NICE systematic review on the diagnostic value of signs and symptoms [NICE, 2018b], six studies were retained to assess the diagnostic value of facial palsy, cranial neuritis and the NeBoP score conditions. The authors emphasized that the studies included did not have the objective of determining the diagnostic precision of these signs and symptoms. The results show a low sensitivity (29% to 60%) and a high specificity (66% to 100% depending on the type of control used) for facial palsy in both children and adults. The authors emphasized the great variability in type and degree of facial palsy.

The authors were of the opinion that the evidence was not strong enough to recommend diagnosing Lyme disease on the sole basis of facial palsy. However, they took into consideration both the high specificity of these conditions and the adverse effects of an incorrect diagnosis if facial palsy is not considered as possible symptoms of Lyme disease (Appendix I of this report's supplementary appendices document).

6.1.2.4.2. Results from primary studies

Three studies included in the NICE systematic review on signs and symptoms [NICE, 2018b] were retained to assess the diagnostic value of facial palsy [Sundin et al., 2012; Tjernberg et al., 2011; Skogman et al., 2008]. The literature search found seven additional primary studies addressing the diagnostic value of facial palsy (systematic review update), lymphocytic meningitis and radiculoneuritis, some of which were included in NICE's review for other signs and symptoms [Barstad et al., 2017; Gyllemark et al., 2017; Remy et al., 2017; Picha et al., 2016; Cohn et al., 2012; Ogrinc et al., 2008; Shah et al., 2005].

Note that the objective of the studies retained to assess the diagnostic value of facial palsy, lymphocytic meningitis and radiculoneuritis was not to determine their diagnostic precision.

Facial palsy

No studies addressing the diagnostic value of facial palsy in the context of neuroborreliosis contracted in North America were found in the literature search.

Four studies were retained to assess the diagnostic value of facial palsy in the context of neuroborreliosis contracted in Europe [Barstad et al., 2017; Remy et al., 2017; Picha et al., 2016; Skogman et al., 2008]. Facial palsy had a sensitivity of 31% to 66% in the 312 patients with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity of 66% to 94% in the 332 controls who were healthy or presented with another condition. The difference in sensitivity may be attributable to differences in the criteria for definite or probable neuroborreliosis. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Cranial neuritis

Three studies were retained to assess the diagnostic value of cranial nerve palsy in the context of neuroborreliosis contracted in North America [Gyllemark et al., 2017; Cohn et al., 2012; Shah et al., 2005]. Cranial nerve palsy had a sensitivity of 49% to 71% in the 204 patients with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity of 77% to 100% in the 544 controls who presented with another condition. The difference in sensitivity may be attributable to the diagnosis criteria used. The study with the highest sensitivity is also the one which required the absence of a virus detectable by PCR or culture in the cerebrospinal fluid. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Two studies were retained to assess the diagnostic value of cranial nerve palsy in the context of neuroborreliosis contracted in Europe [Sundin et al., 2012; Tjernberg et al., 2011]. Cranial nerve palsy had a sensitivity of 43% and 54% in the 171 patients with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity of 86% and 91% in the 195 controls who were healthy or presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as low (Appendix Q of this report's supplementary appendices document).

Lymphocytic meningitis

No studies addressing the diagnostic value of lymphocytic meningitis in the context of neuroborreliosis contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of lymphocytic meningitis in the context of neuroborreliosis contracted in Europe [Picha et al., 2016]. Lymphocytic meningitis had a sensitivity of 89% in the 74 patients with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity of 62% in the 134 controls who were healthy or presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Radiculoneuritis

No studies addressing the diagnostic value of radiculoneuritis in the context of Lyme disease or neuroborreliosis contracted in North America were found in the literature search.

One study was retained to assess the diagnostic value of radiculoneuritis in the context of Lyme disease contracted in Europe [Ogrinc et al., 2008]. Radiculoneuritis had a sensitivity of 4% in the 72 patients with Lyme disease and a specificity of 100% in the 206 controls who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix Q of this report's supplementary appendices document).

Three studies were retained to assess the diagnostic value of radiculoneuritis in the context of neuroborreliosis contracted in Europe [Gyllemark et al., 2017; Picha et al., 2016; Tjernberg et al., 2011]. Radiculoneuritis had a sensitivity ranging from 20% to 41% in the 273 patients with confirmed neuroborreliosis (pleocytosis in the CSF and positive IgG antibody index) or probable neuroborreliosis (pleocytosis and anti-*Borrelia* antibodies in the CSF) and a specificity ranging from 89% to 100% in the 314 controls who were healthy or who presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as low (Appendix Q of this report's supplementary appendices document).

Key Takeaways

No studies were retained to assess the diagnostic value of facial palsy, meningitis and radiculoneuritis in the North American context. The only studies retained addressed the diagnostic value of cranial nerve palsy.

Radiculoneuritis has a sensitivity of less than 50%, while facial and cranial nerve palsy have a sensitivity of less than 71%. The sensitivity of meningitis is higher, but its specificity is lower.

The level of scientific evidence for the majority of scientific statements is insufficient.

In summary:

- Facial palsy has a sensitivity of 31% to 66% in the context of neuroborreliosis contracted in Europe and a specificity of 66% to 94% in controls who are healthy or present with other conditions (4 studies, N = 312 [sensitivity] and 332 [specificity], insufficient level of evidence).
- Cranial nerve palsy has a sensitivity of 49% to 71% in the context of neuroborreliosis contracted in North America and a specificity of 77% to 100% in controls who present with other conditions (3 studies, N = 204 [sensitivity] and 544 [specificity], insufficient level of evidence).
- Cranial nerve paralysis has a sensitivity of 43% and 54% in the context of neuroborreliosis contracted in Europe and a specificity of 86% and 91% in controls who present with other conditions (2 studies, N = 171 [sensitivity] and 195 [specificity], low level of evidence).
- Meningitis has a sensitivity of 89% in the context of neuroborreliosis contracted in Europe and a specificity of 62% in controls who are heathy or present with other conditions (1 study, N = 74 [sensitivity] and 134 [specificity], insufficient level of evidence).
- Radiculoneuritis has a sensitivity of 4% in the context of Lyme disease contracted in Europe and a specificity of 100% in controls who present with other conditions (1 study, N = 72 [sensitivity] and 206 [specificity], insufficient level of evidence).
- Radiculoneuritis has a sensitivity of 20% to 41% in the context of neuroborreliosis contracted in Europe and a specificity of 89% to 100% in controls who are healthy or present with other conditions (3 studies, N = 273 [sensitivity] and 314 [specificity], low level of evidence).

6.1.2.5. Oligoarticular arthritis, monoarticular arthritis or migratory arthritis

6.1.2.5.1. Results from systematic reviews

No systematic reviews addressing the diagnostic value of oligoarticular, monoarticular or migratory arthritis were found in the literature search.

6.1.2.5.2. Results from primary studies

No primary studies addressing the diagnostic value of oligoarticular, monoarticular or migratory arthritis were found in the literature search.

6.1.2.6. Conjunctivitis, uveitis, keratitis, iritis or scleritis

6.1.2.6.1. Results from systematic reviews

No systematic reviews addressing the diagnostic value of non-neurological ocular impairments were found in the literature search.

6.1.2.6.2. Results from primary studies

No primary studies addressing the diagnostic value of non-neurological ocular impairments were found in the literature search.

6.1.3. Contextual and experiential data

The members of the advisory committee recognize the diagnostic value of the typical solitary erythema migrans, the definition of which is given in the corresponding section. The clinicians consulted, however, were of the opinion that a solitary erythema migrans does not always match the proposed definition. They pointed out that a solitary erythema migrans can:

- Have a diameter of less than 5 cm
- Be hemorrhagic
- Present with vesicles, squames, crusts or petechia
- Have a shape other than circular, ring-like or oval

When the lesion's appearance is not that of a typical erythema migrans, a Lyme disease diagnosis can be established provided that its expanding nature is documented. Observation of a lesion should take the following points into account:

  - The outline of the rash or solitary erythema migrans should be traced and the diameter measured to document any potential expansion, by the patient or by a health care professional.
  - A photo with a measuring object should be taken and kept by the patient.
  - The patient should be asked to trace the outline of the rash or erythema migrans again and to take photos with a measuring object if they observe any expansion.
  - The patient should be informed of the signs and symptoms suggestive of Lyme disease to watch for, and of the importance of consulting a health care professional if they have any questions or concerns or notice that the rash or atypical lesion has expanded.

The clinicians consulted reiterated that the absence of erythema migrans should not be used to rule out Lyme disease, since erythema migrans is not always present or noticed.

The members of the advisory committee were given access to the results of the systematic review on the diagnostic value of signs and symptoms. Although they held that the presence of these conditions is not sufficient to establish a diagnosis, they stressed that it is important to document musculoskeletal, neurological and cardiac conditions when taking a patient's history.

None of the clinicians consulted had had a patient present with non-neurological ocular impairment. Since those conditions are so rare, it is less important to investigate them.

A number of clinicians mentioned that a patient rarely presents with a single general systemic symptom and that, therefore, examining the diagnostic value of each individual symptom does not reflect the clinical reality. Although the presence of a systemic symptom does not suggest Lyme disease, a constellation of several such symptoms may provide an indication of it, even if their diagnostic value is not high enough to allow for diagnosis.

Key Takeaways

The data from the scientific literature on the diagnostic value of signs and symptoms of Lyme disease have not yielded any manifestations that have adequate diagnostic value in the context of Lyme disease, other than a solitary erythema migrans. The examination of this symptom's diagnostic value, however, rests on a small number of studies, and their level of evidence is low.

The definition of the typical solitary erythema migrans is presented in the corresponding section. However, erythema migrans may have other, less typical characteristics, such as:

- Having a diameter of less than 5 cm
- Being hemorrhagic
- Presenting with vesicles, squames, crusts or petechia
- Having a shape other than circular, ring-like or oval

The presence of a typical solitary erythema migrans in a patient with a clinical picture (evaluation of the possibility of tick exposure, physical examination and other conditions taken into account) compatible with Lyme disease is sufficient for establishing a diagnosis.

Lyme disease may be diagnosed in a patient with a compatible clinical picture when the expanding nature of a lesion whose appearance is not typical of erythema migrans has been documented.

Observation of a lesion should take the following points into account:

- The outline of the rash or solitary erythema migrans should be traced and the diameter measured to document any potential expansion, by the patient or by a health care professional.
- A photo with a measuring object should be taken and kept by the patient.
- The patient should be asked to trace the outline of the rash or erythema migrans again and to take photos with a measuring object if they notice any expansion.
- The patient should be informed of the signs and symptoms suggestive of Lyme disease to watch for, and urged to consult a health care professional if they have any questions or concerns or if they notice that the rash or atypical lesion has expanded.

The absence of erythema migrans should not be used to rule out Lyme disease, since erythema migrans is not always present or noticed.

Neurological, cardiac and joint conditions are not sufficient for establishing a Lyme disease diagnosis, but it is important to document their presence and when they appear.

General systemic symptoms are not sufficient for establishing a diagnosis, but the presence of multiple systemic symptoms may be an indication in favour of diagnosis.

6.2. Diagnostic Value of Tick Analysis

6.2.1. Clinical practice guides and guidelines

IDSA, the GDS and the GAPAH recommend not testing ticks removed in order to detect the presence of bacteria from the *B. burgdorferi* s.l. complex for diagnostic purposes [Hofmann et al., 2017; Huppertz et al., 2012; Wormser et al., 2006]. The use of tests to detect microbial agents is not recommended by CDC [2019] as they are not subject to the same stringent quality standards as diagnostic tests. Furthermore, a positive result for the presence of bacteria from the *B. burgdorferi* s.l. complex does not necessarily mean that transmission of the pathogen has occurred and that the person is infected.

6.2.2. Contextual and experiential data

As of the fall of 2018, the results of PCR molecular analysis tests conducted to determine whether a tick is a carrier of microbial agents are no longer sent to clinicians by the LSPQ. Health care professionals can, however, submit the tick according to their institution's procedure if they wish to participate in the LSPQ's black-legged tick passive surveillance program. Over-the-counter tests to detect bacteria from the *B. burgdorferi* s.l. complex in ticks are now sold at pharmacies in Quebec. While it may seem like a good idea to use these tests to better target people who should receive PEP, the tests may, according to Sprong et al. [2013], result in false negatives and, as per information shared by the LSPQ, probably false positives as well. Use of such home tests is therefore not recommended to guide decisions about the medical care provided to people exposed to ticks. Moreover, a positive result does not mean that transmission of the pathogen has occurred: the overall risk of contracting Lyme disease following a black-legged tick bite (with no distinction made between engorgement stages and levels) in a high-risk geographic area (12% to 50% of black-legged ticks infested) is between 1% and 3% [INESSS, 2019b].

According to the AQML representatives consulted for this report, people bitten by a tick want to know if the tick is a carrier of bacteria from the *B. burgdorferi* s.l. complex and are willing to receive an antibiotic treatment to avoid developing Lyme disease, regardless of the theoretical risk of transmission.

Key Takeaways

According to published studies, the overall risk of contracting Lyme disease following a black-legged tick bite (with no distinction made between engorgement stages and levels) in a high-risk geographic area (12% to 50% of black-legged ticks infested) is between 1% and 3%.

Tick analysis results should not be used to establish a diagnosis because test kits are not subject to the same stringent quality standards as diagnostic tests, they may result in false

positives and false negatives, and a positive result does not mean that transmission of bacteria has occurred.

6.3. Diagnostic Value of Laboratory Analysis

A systematic review of the scientific literature on the diagnostic value of laboratory analysis with respect to Lyme disease was conducted. The literature search covered all laboratory tests that could potentially be used to diagnose Lyme disease, but in-house made serologic tests and tests not addressed in any scientific publication since 2009 were excluded, as they are unlikely to be used in Quebec laboratories. The results of this systematic review are presented in the state of knowledge report on the diagnostic value of laboratory analysis [INESSS, 2019d]. Analysis of the results did not identify a more effective test than two-tier serologic testing as a first-line analysis for patients who have contracted Lyme disease [INESSS, 2019d]. It should be noted that most of the designs of the studies included in the systematic review were inappropriate, and the quality of scientific evidence they produced was low or insufficient. For some analyses, such as the lymphocyte transformation test and the CD57+/CD3- NK cell count test, the number of studies was limited or nil. Various approaches to two-tier serologic testing are used in different types of tests, the most common one being ELISAs, followed by immunoblotting. The five approaches to two-tier serologic testing assessed in the review had similar diagnostic value [INESSS, 2019d].

Two-tier serologic testing is made up of a screening test (first tier) and a confirmation test (second tier). In Quebec, the screening test consists of an ELISA with the whole VIsE protein as well as the synthetic peptide pepC10 as antigens, and the confirmation test uses immunoblotting. The ELISA is performed at two designated laboratories in Quebec: the CHU de Sherbrooke and Hôpital Charles-Le Moyne. The LSPQ then sends samples for which results are positive or ambiguous to the National Microbiology Laboratory (NML) in Winnipeg for immunoblotting testing, which consists of an immunoglobin M (IgM) analysis and an immunoglobin G (IgG) analysis. Since IgMs have a lesser diagnostic value than IgGs (see the “Interpretation of serology results and information to transmit” section), the IgG analysis is done first, and an IgM analysis is performed if the first test results are negative (IgMs are the first antibodies produced, while IgGs typically appear four to six weeks later). The immunoblotting tests used by the NML are able to detect the presence of antibodies against the North American bacterial genospecies of the *B. burgdorferi* s.l. complex. In cases when the disease has been contracted on another continent, immunoblotting tests with different antigens are used. According to CDC criteria (which are used by the NML), for an IgM result to be positive, two out of three antigens must be detected, while five out of ten antigens must be detected for an IgG result to be positive [CDC, 1995].

This report presents only the diagnostic values of PCR and two-tier serologic testing whose approach is similar to the one used in Quebec, as both of these analyses are the subject of clinical recommendations. Most of the two-tier serology studies considered used a slightly different ELISA than the one used in Quebec (VIsE synthetic peptide rather than the whole protein). Moreover, the diagnostic value of the tests commercially available in Europe presented in the report is the value derived from Leeflang’s [2016] meta-analysis. Finally, as

per CDC's[6] algorithm, IgG and IgM results were taken into account in patients who had been presenting signs or symptoms for 30 days or less, while only IgG results were considered in patients whose symptoms had lasted longer than 30 days.

6.3.1. Erythema migrans

This section looks at both solitary and multiple erythema migrans, as primary studies sometimes fail to distinguish between the two.

6.3.1.1. Clinical practice guides and guidelines

The CPGs retained recommend not to conduct laboratory analysis in cases of typical solitary erythema migrans:

- IDSA emphasizes the lack of sensitivity of serologic tests in the first two weeks of infection [Wormser et al., 2006].
- NICE mentions that no testing is required because erythema migrans is very specific to Lyme disease [NICE, 2018a].
- HAS does not recommend serologic testing or PCR blood or urine tests due to their weak negative predictive value [HAS, 2018a].
- The GDS does not recommend laboratory analysis of any kind, including molecular biology techniques [Hofmann et al., 2017].
- The GAPAH underscores that serologic tests are often negative at this stage of the disease and that they should not be performed, adding that PCR biopsy is a reliable test to confirm an erythema migrans diagnosis, but that it is rarely warranted [Huppertz et al., 2012].

However, IDSA adds when there is uncertainty surrounding a diagnosis, it is recommended to perform two-tier serologic testing using CDC's algorithm, on samples taken in both the acute and convalescent phases [Wormser et al., 2006].

Three CPGs address the diagnosis of Lyme disease in patients presenting with atypical erythema migrans, and their recommendations differ:

- HAS and the GAPAH recommend documenting the expanding nature of the erythema and do not mention any laboratory analysis [HAS, 2018a; Huppertz et al., 2012].
- The GDS recommends serologic testing and adds that if any doubts persist despite a negative result, PCR and a biopsy culture should be considered to confirm the diagnosis. According to the GDS, histology is rarely useful when an erythema migrans is present, but it can help to clarify a differential diagnosis [Hofmann et al., 2017].

Only two CPGs address the diagnosis of Lyme disease in patients presenting with multiple erythema migrans. While HAS considers a multiple erythema migrans diagnosis to be clinical, since serologic tests are not always positive [HAS, 2018a], the GDS is of the opinion that

[6]Centers for Disease Control and Prevention (CDC). Lyme Disease. Two-step Laboratory Testing Process [website]. Available at https://www.cdc.gov/lyme/diagnosistesting/labtest/twostep/index.html (accessed February 17, 2019).

serologic testing must always be performed [Hofmann et al., 2017]. When the result is negative but doubt persists, PCR or culture analysis is necessary.

6.3.1.2. Scientific data

The majority of primary studies that address the diagnostic value of erythema migrans in the context of Lyme disease do not distinguish between solitary and multiple erythema migrans and do not exclude patients if they present with general systemic symptoms.

6.3.1.2.1. Results from systematic reviews

No systematic reviews addressing the diagnostic value of two-tier serology and PCR in the context of erythema migrans associated with Lyme disease contracted in North America were retained (see the “Description of documents” section). However, the studies included in the NICE systematic review [2018a] as well as those conducted by HAS [2018a], Cook and Puri [2016], and Waddell et al. [2016] were considered in the literature search.

One systematic review was retained to assess the diagnostic value of two-tier serology in the context of erythema migrans associated with Lyme disease contracted in Europe, but none were deemed adequate for use in assessing the diagnostic value of PCR. According to Leeflang’s [2016] meta-analysis, two-tier serology (all methods considered) carried out with tests commercially available in Europe had a sensitivity ranging from 12% to 64% in the 125 patients with erythema migrans associated with Lyme disease contracted in Europe, and a specificity ranging from 67% to 96% in the 190 controls (Appendix J of this report’s supplementary appendices document).

6.3.1.2.2. Results from primary studies – Two-tier serology

Five studies were retained to assess the diagnostic value of two-tier serology (tests commercially available in North America) in the context of Lyme disease contracted in North America [Branda et al., 2017; Molins et al., 2016; Lahey et al., 2015; Wormser et al., 2014; Wormser et al., 2013]. Two-tier serology had a sensitivity ranging from 27% to 57% in the 552 patients with erythema migrans associated with Lyme disease, a specificity of 100% in the 3,048 healthy controls and a specificity of 99% to 100% in the 1,845 controls who were healthy or presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as low (Appendix R of this report’s supplementary appendices document).

Two studies were retained to assess the diagnostic value of two-tier serology (tests commercially available in North America) in the context of Lyme disease contracted in Europe [Wormser et al., 2014; Branda et al., 2013]. Two-tier serology had a sensitivity of 10% and 20% in the 40 patients with erythema migrans associated with Lyme disease, and a specificity of 100% in the 100 healthy controls. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix R of this report’s supplementary appendices document).

6.3.1.2.3. Results from primary studies – PCR

Two studies were retained to assess the diagnostic value of PCR on a skin biopsy in the context of Lyme disease contracted in North America [Molins et al., 2014; Liveris et al., 2012]. PCR had a sensitivity of 46% and 66% in the 64 patients with erythema migrans associated

with Lyme disease. No data on the specificity of PCR were presented in the studies. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix R of this report's supplementary appendices document).

Eight studies were retained to assess the diagnostic value of PCR on a skin biopsy in the context of Lyme disease contracted in Europe [Moniuszko et al., 2015; O'Rourke et al., 2013; Lebech et al., 2000; Brettschneider et al., 1998; Picken et al., 1997; Rijpkema et al., 1997; Von Stedingk et al., 1995; Moter et al., 1994]. PCR had a sensitivity ranging from 25% to 88% in the 1,090 patients with erythema migrans associated with Lyme disease, while the specificity was 100% in the 14 healthy controls and 100% in the 109 controls who were healthy or presented with another condition. The variability in sensitivity levels may have been due to the criteria for inclusion of individuals (whether or not there was a risk of dissemination of the infection) and to the parameters of the PCR. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix R of this report's supplementary appendices document).

Three studies were retained to assess the diagnostic value of PCR on a blood sample in the context of Lyme disease contracted in North America [Molins et al., 2014; Eshoo et al., 2012; Liveris et al., 2012]. PCR had a sensitivity ranging from 31% to 62% in the 141 patients with erythema migrans associated with Lyme disease and a specificity of 100% in the 44 healthy controls. The result of 62% was recorded in the case of patients who presented with systemic symptoms. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix R of this report's supplementary appendices document).

One study was retained to assess the diagnostic value of PCR on a blood sample in the context of Lyme disease contracted in Europe [Moniuszko et al., 2015]. PCR had a sensitivity of 2% in the 93 patients with erythema migrans associated with Lyme disease; no data on specificity were presented. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix R of this report's supplementary appendices document).

Key Takeaways

When an erythema migrans is present:

- Two-tier serology has low sensitivity (less than 65%).
- PCR on skin biopsies has variable sensitivity (25% to 88%).
- PCR on blood samples has low sensitivity (less than 65%).

Tests commercially available in North America have low sensitivity for the detection of Lyme disease contracted in Europe.

The level of scientific evidence for the statements is generally insufficient.

In summary:

- When an erythema migrans is present, the sensitivity of two-tier serology (tests commercially available in North America) ranges from 27% to 57% in the context of Lyme disease contracted in North America (5 studies, N = 552, low level of evidence),

while sensitivity ranges from 10% to 20% in the context of Lyme disease contracted in Europe (2 studies, N = 40, insufficient level of evidence).

- When an erythema migrans is present, two-tier serology (tests commercially available in Europe) has a sensitivity ranging from 12% to 64% in the context of Lyme disease contracted in Europe.
- When an erythema migrans is present, PCR on a skin biopsy has a sensitivity ranging from 46% to 66% in the context of Lyme disease contracted in North America (2 studies, N = 64, insufficient level of evidence) and a sensitivity ranging from 25% to 88% in the context of Lyme disease contracted in Europe (8 studies, N = 1,090, insufficient level of evidence).
- When an erythema migrans is present, PCR on a blood sample has a sensitivity ranging from 31% to 62% in the context of Lyme disease contracted in North America (3 studies, N = 44, insufficient level of evidence), and a sensitivity of 2% in the context of Lyme disease contracted in Europe (1 study, N = 93, insufficient level of evidence).

6.3.1.3. Contextual and experiential data

6.3.1.3.1. Solitary erythema migrans

Members of the advisory committee acknowledged the low sensitivity of serologic tests when an erythema migrans is present. They were of the opinion that such tests are not appropriate for patients whose clinical picture is compatible with Lyme disease and who have a skin lesion consistent with typical solitary erythema migrans (whether or not there are symptoms characteristic of the early disseminated stage) or when the progressive nature of a skin lesion that is not typical of erythema migrans can be objectified in a patient who does not present with any other manifestations of the disseminated stage. Committee members acknowledged that serologic testing can be useful in some circumstances, but only when performed at later stages, once the body's immune response has been fully activated. Since, however, such delayed serology has little effect on the diagnosis, given the wait period for results (among other factors), it was decided not to include it in the diagnostic tool.

The clinicians consulted were of the opinion that serologic testing is appropriate for patients who have a lesion that is not consistent with typical solitary erythema migrans, who have other symptoms characteristic of the early disseminated stage and whose clinical picture is compatible with Lyme disease. However, they emphasized that the results would probably be negative and that a discussion with a specialist or an experienced colleague would be required in order to determine whether it was appropriate to begin treatment before getting results back.

Members of the advisory committee were of the opinion that PCR on biopsies should not be a first course of action for all patients, but that it may be necessary in some cases. A negative result, however, should be not be used to rule out the diagnosis, given the intrinsic limitations of such samples. It would be preferable for a specialist to be directly involved in deciding to do PCR and in interpreting the results. A number of the clinicians consulted explained that because PCR is conducted at the NML, the results are not readily available and therefore have little bearing on the diagnostic process.

Key Takeaways

When the clinical picture is compatible with Lyme disease, two-tier serology is not indicated for patients who present with typical solitary erythema migrans (whether or not there are symptoms characteristic of the early disseminated stage), nor for patients with a skin lesion that is not typical of erythema migrans and that is not accompanied by symptoms of the early disseminated phase, but whose progressive nature can be objectified. In some circumstances, serologic testing may be indicated, but the decision should be made jointly with a specialist, the test should be performed at a later stage (four to six weeks later) and it should not be considered a reason to delay treatment.

Two-tier serology is indicated for patients who have a lesion that is not consistent with typical solitary erythema migrans, who have other symptoms characteristic of the early disseminated stage and whose clinical picture is compatible with Lyme disease. However, it is likely that test results would be negative. A discussion with a specialist or an experienced colleague is therefore advised in order to determine whether it is appropriate to begin treatment before getting results back.

PCR on biopsies should not be a first course of action for all patients. A specialist should be directly involved in deciding to do PCR and in interpreting the results.

6.3.1.3.2. Multiple erythema migrans

In the experience of the clinicians consulted, results of two-tier serology are usually positive in patients presenting with multiple erythema migrans.

Serologic testing must be performed on all such patients so that the case can be reported to public health officials and potentially included in the MADO registry. However, a negative result should not be used to rule out a Lyme disease diagnosis, since the sensitivity of serologic tests is quite low at the early disseminated stage. Health care professionals could consider carrying out a second serologic analysis four to six weeks later, in order to give the body's immune response time to be fully activated.

When a patient presents with multiple erythema migrans and there is a strong suspicion of Lyme disease, the clinician may choose to begin antibiotic treatment before receiving the results of the serologic analysis. A specialist should be consulted before such a decision is made.

Key Takeaways

Serologic testing should be performed on patients presenting with multiple erythema migrans so that their case can potentially be included in the MADO registry. However, although the sensitivity of these tests increases progressively as the bacteria spreads, a negative result should not be used to rule out a diagnosis of Lyme disease. When applicable, clinicians should reconsider other possible clinical conditions and discuss with a specialist the relevance of conducting a second serologic analysis four to six weeks later.

When a patient presents with multiple erythema migrans and there is a strong suspicion of Lyme disease, the clinician may choose to begin antibiotic treatment before receiving the results of the serologic analysis. Such a decision should be made jointly with a specialist.

6.3.2. Manifestations suggestive of the early disseminated stage

Multiple erythema migrans is a manifestation that is suggestive of the early disseminated stage. It is addressed in the previous section.

6.3.2.1. Clinical practice guides and guidelines

According to the GAPAH, serologic testing is often negative in patients presenting with general systemic symptoms and should therefore not be used [Huppertz et al., 2012].

All of the CPGs recommend serologic testing in cases of cardiac or nervous-system symptoms [NICE, 2018a; HAS, 2018a; Rauer et al., 2018; Huppertz et al., 2012; Wormser et al., 2006]. While the test is generally positive, NICE mentions that a negative result should not be used to rule out the diagnosis if strong suspicion remains.

The HAS guidelines are the only ones that address non-neurological ocular impairment. HAS recommends two-tier serology for patients with a compatible clinical picture, and mentions that PCR on aqueous humour may be recommended as a second-line approach in the event of diagnostic doubt [HAS, 2018a].

In cases involving neurological damage, HAS recommends a lumbar puncture if there is the slightest suspicion of infectious disease amenable to specific treatment with CSF cytology and biochemistry and after determining the anti-*B. burgdorferi* s.l. antibody index (CSF/serum comparison). HAS specifies, however, that lumbar punctures should not be a first-line analysis for children in cases of facial palsy when there is no history of erythema migrans and no sign of meningeal disease [HAS, 2018a].

IDSA and the GAPAH recommend not performing PCR on CSF [Huppertz et al., 2012; Wormser et al., 2006]. The GDN recommends that this analysis be used for patients with unclear differential diagnosis. A negative result does not rule out the disease, and a positive result must be confirmed with a different method [Rauer et al., 2018].

For all symptoms associated with the early disseminated stage, the CPGs mention that it could be useful to perform a second analysis two to four weeks later in cases when the initial serology comes back negative but suspicion of Lyme disease remains strong [NICE, 2018a; HAS, 2018a; Rauer et al., 2018; Huppertz et al., 2012; Wormser et al., 2006].

6.3.2.2. Scientific data

6.3.2.2.1. Results from systematic reviews

No systematic reviews addressing the diagnostic value of two-tier serology and PCR in the context of Lyme disease in the early disseminated stage contracted in North America were retained (see the "Description of documents" section). However, the studies included in the NICE systematic review [2018a] as well as those conducted by HAS [2018a], Cook and Puri [2016], and Waddell et al. [2016] were considered in the literature search.

One systematic review was retained to assess the diagnostic value of two-tier serology in the context of Lyme disease in the early disseminated stage contracted in Europe, and no such reviews were found to inform the assessment of the diagnostic value of PCR. According to Leeflang's [2016] meta-analysis, two-tier serology (all approaches considered) performed with tests commercially available in Europe had a sensitivity ranging from 41% to 87% in the 15 patients with neuroborreliosis contracted in Europe and a specificity ranging from 88% to 94% in the 100 controls (Appendix J of this report's supplementary appendices document).

6.3.2.2.2. Results from primary studies – Two-tier serology

No studies addressing the diagnostic value of two-tier serology for non-neurological ocular impairment were identified.

One study addressing the diagnostic value of these tests in the context of Lyme carditis contracted in North America was identified, but it was not retained due to the small number of patients included.

No studies addressing the diagnostic value of two-tier serology in the context of Lyme carditis contracted in Europe were identified.

One study was retained to assess the diagnostic value of two-tier serology (tests commercially available in North America) in the context of systemic symptoms attributable to Lyme disease contracted in North America [Eckman et al., 2018]. Two-tier serology had a sensitivity ranging from 29% to 59% in the 60 patients with systemic symptoms associated with Lyme disease and a specificity ranging from 90% to 100% in the 34 controls who were healthy or presented with another condition. The difference in sensitivity may be due to patient characteristics: non-neuroinflammatory cognitive impairment caused by Lyme disease as compared to non-neuroinflammatory headache caused by Lyme disease. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix R of this report's supplementary appendices document).

No studies addressing the diagnostic value of two-tier serology for general systemic symptoms due to Lyme disease contracted in Europe were identified.

Four studies were retained to assess the diagnostic value of two-tier serology (tests commercially available in North America) for neuroborreliosis contracted in North America [Eckman et al., 2018; Molins et al., 2016; Wormser et al., 2014; Wormser et al., 2013]. Two-tier serology had a sensitivity ranging from 36% to 100% in the 65 patients with neuroborreliosis, a specificity of 99% to 100% in the 2,248 healthy controls and a specificity of 99% to 100% in the 2,801 controls who were healthy or presented with another condition. There is no ready

explanation for the variation in sensitivity beyond the fact that the results were all obtained from cohorts of no more than 20 patients. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix R of this report's supplementary appendices document).

Two studies were retained to assess the diagnostic value of two-tier serology (tests commercially available in North America) in the context of neuroborreliosis contracted in Europe [Wormser et al., 2014; Branda et al., 2013]. Two-tier serology had a sensitivity of 20% and 40% in the 25 patients with neuroborreliosis and a specificity of 100% in the 100 healthy controls. The variation in sensitivity may be due to the small number of participants included in the cohorts. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix R of this report's supplementary appendices document).

6.3.2.2.3 Results from primary studies – PCR

One study addressing the diagnostic value of PCR on a blood sample in the context of Lyme carditis contracted in North America was identified but, due to the small number of patients included, it was not retained.

No studies addressing the diagnostic value of PCR on a blood sample in the context of Lyme carditis contracted in Europe were identified.

One study addressing the diagnostic value of PCR on a blood sample in the context of neuroborreliosis contracted in North America was identified but, due to the small number of patients included, it was not retained.

One study was retained to assess the diagnostic value of PCR on a blood sample in the context of neuroborreliosis contracted in Europe [Cerar et al., 2008]. The PCR had a sensitivity of 10% and 85% in the 48 patients with neuroborreliosis, depending on the selected PCR target, and a specificity of 97% in the 63 controls who were healthy or presented with another condition, regardless of the selected PCR target. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix R of this report's supplementary appendices document).

One study addressing the diagnostic value of PCR on CSF in the context of neuroborreliosis contracted in North America was identified, but it was not retained because it was published in 1996.

Eight studies were retained to assess the diagnostic value of PCR on CSF in the context of neuroborreliosis contracted in Europe [Barstad et al., 2018; Forselv et al., 2018; De Leeuw et al., 2014; Cerar et al., 2008; Lebech et al., 2000; Lebech et al., 1998; Priem et al., 1997; Lebech et Hansen, 1992]. PCR had a sensitivity ranging from 12% to 79% in the 525 patients with neuroborreliosis and a specificity of 97% to 100% in the 737 controls who were healthy or presented with another condition. The variation in sensitivity may be due to the different PCR targets and to the reference test used to establish a neuroborreliosis diagnosis (clinical diagnosis compared with a diagnosis based on laboratory analysis). When the result considering the positivity of either target is excluded, the sensitivity ranges only from 12% to 50% (8 studies, N = 506). Based on the assessment criteria, the level of scientific evidence was rated as low (Appendix R of this report's supplementary appendices document)

Key Takeaways

At the early disseminated stage:

- Two-tier serology has variable sensitivity (36% to 100%).
- PCR on a blood sample has variable sensitivity (10% to 85%).
- PCR on cerebrospinal fluid has low sensitivity (below 50%).

Tests commercially available in North America have low sensitivity for the detection of neuroborreliosis contracted in Europe.

The level of scientific evidence for the statements is generally insufficient.

In summary:

- In cases of systemic symptoms caused by Lyme disease, two-tier serology (tests commercially available in North America) has a sensitivity ranging from 29% to 59% in the context of Lyme disease contracted in North America (1 study, N = 60, insufficient level of evidence).
- In patients with neuroborreliosis, two-tier serology (tests commercially available in North America) has a sensitivity ranging from 36% to 100% in the context of Lyme disease contracted in North America (4 studies, N = 65, insufficient level of evidence), and a sensitivity ranging from 20% to 40% in the context of Lyme disease contracted in Europe (2 studies, N = 25, insufficient level of evidence).
- In patients with neuroborreliosis, two-tier serology (tests commercially available in Europe) has a sensitivity ranging from 41% to 87% in the context of Lyme disease contracted in Europe.
- In patients with neuroborreliosis, PCR on a blood sample has a sensitivity ranging from 10% to 85% in the context of Lyme disease contracted in Europe (1 study, N = 48, insufficient level of evidence).
- In patients with neuroborreliosis, PCR on a blood sample has a sensitivity ranging from 12% to 50% in the context of Lyme disease contracted in Europe (8 studies, N = 506, low level of evidence).

6.3.2.3. Contextual and experiential data

The members of the advisory committee all agreed that two-tier serology is appropriate in cases of manifestations that are suggestive of the early disseminated stage of Lyme disease. However, a negative result should not be used to rule out a Lyme diagnosis. In such cases, and following a discussion with a specialist, a second serologic analysis could be carried out four to six weeks later, in order to give the body's immune response time to be fully activated.

When a patient presents with manifestations of the early disseminated stage and there is a strong suspicion of Lyme disease, the clinician may decide to begin antibiotic therapy before getting the serology results back. A specialist should be consulted before such a decision is made.

According to the physicians consulted, both PCR and testing for antibodies in cerebrospinal fluid should be requested and interpreted by specialists. These tests should be used in early stages, when serology is less sensitive, rather than in patients who have had symptoms for a long time. Some of the professionals consulted explained that it can take a long time to get results back for these tests, and that while they can provide useful information, these tests have little bearing on the diagnostic process. As mentioned above, a negative result should not be used to rule out a diagnosis of Lyme disease given the intrinsic limits of such sampling. Currently, testing for antibodies in cerebrospinal fluid is rarely done in Quebec. Some clinicians reported logistical problems in this sense.

Key Takeaways

Two-tier serology is indicated in cases of manifestations that are suggestive of the early disseminated stage of Lyme disease (e.g., heart and brain disorders) and a compatible clinical picture. However, a negative result on its own should not be used to rule out a diagnosis of Lyme disease, because the sensitivity of serologic tests is highly variable at this stage. In such cases, the clinician should reconsider other possible clinical conditions, then seek a specialist's opinion about the relevance of a second serologic analysis four to six weeks later.

When a patient presents with manifestations of the early disseminated stage and there is a strong suspicion of Lyme disease, the clinician may decide to begin antibiotic therapy before getting the serology results back. A specialist should be consulted before such a decision is made.

Both PCR and testing for antibodies in cerebrospinal fluid are analyses that should be used by specialists. A negative result should not be used to rule out a diagnosis of Lyme disease given the intrinsic limits of such sampling, and these analyses should not be performed on patients who have had symptoms for a long time.

6.3.3. Manifestations suggestive of the late disseminated stage

6.3.3.1. Clinical practice guides and guidelines

The CPGs retained all recommend laboratory analysis to support the diagnosis of Lyme arthritis:

- IDSA recommends serologic testing to confirm the diagnosis of Lyme arthritis. In seropositive patients, a positive PCR on synovial fluid increases confidence in the diagnosis. The authors do not, however, recognize any particular diagnostic value of PCR on synovial fluid in seronegative patients [Wormser et al., 2006].
- NICE recommends laboratory analysis (serology) on patients who present with joint manifestations. However, the diagnosis must be based on a combination of the clinical picture and the analysis results: negative results should not be used to rule out a diagnosis of Lyme disease if clinical suspicion remains strong [NICE, 2018a].
- According to HAS, a diagnosis of Lyme arthritis relies on the confirmation of a recent tick bite, recent erythema migrans or positive two-tier serology (ELISA or immunoblotting), in

conjunction (if required) with PCR on the synovial fluid. The diagnosis may be put forward regardless of the PCR results when serology is positive and there are no other explanatory causes, or when PCR is positive [HAS, 2018a].

- The GKJR and the DGKJ recommend using two-tier serology to confirm the diagnosis of Lyme arthritis. Both organizations affirm that clinicians can use synovial fluid aspiration to eliminate a diagnosis of septic arthritis when there is clinical suspicion, and that lymphocyte transformation tests do not contribute to the diagnosis [Huppertz et Tzaribachev, 2013].

Using PCR as part of the follow up to Lyme arthritis is not recommended by any of the CPGs consulted.

6.3.3.2. Scientific data

6.3.3.2.1. Results from systematic reviews

No systematic reviews addressing the diagnostic value of two-tier serology and PCR in the context of Lyme disease in the late disseminated stage were retained (see the “Description of documents” section). However, the studies included in the NICE systematic review [2018a] as well as those conducted by HAS [2018a], Cook and Puri [2016], and Waddell et al. [2016] were considered in the literature search.

6.3.3.2.2. Results from primary studies – Two-tier serology

Three studies were retained to assess the diagnostic value of two-tier serology (tests commercially available in North America) in the context of Lyme arthritis contracted in North America [Molins et al., 2016; Wormser et al., 2014; Wormser et al., 2013]. Two-tier serology had a sensitivity of 95% to 100% in the 184 patients with Lyme arthritis, a specificity of 99% to 100% in the 2,248 healthy controls and a specificity of 99% to 100% in the 915 controls who were healthy or presented with another condition. Based on the assessment criteria, the level of scientific evidence was rated as low (Appendix R of this report’s supplementary appendices document).

Two studies were retained to assess the diagnostic value of two-tier serology (tests commercially available in North America) in the context of Lyme arthritis contracted in Europe [Wormser et al., 2014; Branda et al., 2013]. Two-tier serology had a sensitivity of 50% and 67% in the 25 patients with Lyme arthritis and a specificity of 100% in the 100 healthy controls. The difference in sensitivity may be due to the composition of the cohorts: one of them included both patients with acrodermatitis chronica atrophicans and others with Lyme arthritis. Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix R of this report’s supplementary appendices document).

6.3.3.2.3. Results from primary studies – PCR

Three studies were retained to assess the diagnostic value of PCR on synovial fluid in the context of Lyme arthritis contracted in North America [Molins et al., 2014; Deanehan et al., 2013; Nocton et al., 1994]. PCR had a sensitivity ranging from 39% to 85% in the 154 patients with Lyme arthritis and a specificity of 100% in the 64 controls who had another form of arthritis. If the study published in 1994 is excluded, the sensitivity ranges only from 39% to

48% (2 studies, N = 66). Based on the assessment criteria, the level of scientific evidence was rated as insufficient (Appendix R of this report's supplementary appendices document).

Four studies addressing the diagnostic value of PCR on synovial fluid in the context of Lyme arthritis contracted in Europe were identified, but because they were all published prior to 2002, none were retained.

Key Takeaways

In the late disseminated stage:

- Two-tier serology has high sensitivity (95% to 100%).
- PCR on synovial fluid has variable sensitivity (39% to 85%).

Tests commercially available in North America have low sensitivity for the detection of Lyme arthritis contracted in Europe.

The level of scientific evidence for the statements is generally insufficient.

In summary:

- In patients with Lyme arthritis, two-tier serology (tests commercially available in North America) has a sensitivity of 95% to 100% in the context of Lyme disease contracted in North America (3 studies, N = 184, low level of evidence) and a sensitivity ranging from 50% to 67% in the context of Lyme disease contracted in Europe (2 studies, N = 25, insufficient level of evidence).
- In patients with Lyme arthritis, PCR on synovial fluid has a sensitivity ranging from 39% to 85% in the context of Lyme disease contracted in North America (3 studies, N = 154, insufficient level of evidence).

6.3.3.3. Contextual and experiential data

According to the members of the advisory committee, serology is important in diagnosing Lyme arthritis because several other conditions can produce similar signs and symptoms. And, while the results will usually be positive, there are cases in which they can come back negative. All aspects of the clinical picture must be brought to bear in the interpretation of the results. The relevance of a second set of serologic tests after a negative result should be discussed with a specialist.

The members of the advisory committee were of the opinion that PCR on synovial fluid may sometimes be indicated, but that it should not be the first course of action for all patients with a suspicion of Lyme arthritis. When synovial fluid aspiration is ordered for another purpose, the opinion of a specialist chosen among those available in the community (rheumatologist, microbiologist / infectious diseases specialist, orthopedist or internist) is required before requesting PCR. While the aspiration can be performed by a primary care physician, the PCR results must be interpreted by a specialist. As mentioned above, a negative result should not be used to rule out the diagnosis given the intrinsic limits of such sampling. Joint fluid aspiration is not a common practice in children unless septic arthritis is suspected, and PCR is therefore not used in children in most cases. Some of the clinicians consulted explained that it

can take a long time to get PCR results back, and that while PCR results can provide useful information, they have little bearing on the diagnostic process.

Key Takeaways

Two-tier serology is appropriate for patients with manifestations that are suggestive of the late disseminated stage of the disease and a compatible clinical picture. A negative result on its own should not be used to rule out the diagnosis. The clinician should reconsider other possible clinical conditions then speak to a specialist in order to decide the best way to handle the patient's care and to determine the relevance of a second set of serologic tests.

6.4. Interpretation of Serology Results and Information to Transmit

6.4.1. Clinical practice guides and guidelines

According to the CPGs consulted, the two-tier serology screening and confirmation tests should be used together in order to achieve the greatest possible sensitivity and specificity [NICE, 2018a; HAS, 2018a; Hofmann et al., 2017; Huppertz et al., 2012; Wormser et al., 2006]. The use of the screening test by itself to establish a diagnosis is not recommended by the learned societies and assessment agencies whose documents were consulted.

Two-tier serology measures the immune response elicited by genospecies of the *B. burgdorferi* s.l. complex. According to German CPGs, IgM antibodies can be detected three to six weeks following infection, while IgGs reach peak levels weeks or even months later [Hofmann et al., 2017; Huppertz et al., 2012]. The sensitivity of serologic tests hinges on the activation of the immune response. According to recent CPGs, a negative serology result should not, on its own, be used to rule out Lyme disease when suspicion of such a diagnosis remains strong [NICE, 2018a; HAS, 2018a].

According to IDSA's CPG, patients whose symptoms have lasted longer than four weeks should have a positive IgG result [Wormser *et al.*, 2006], and the GDS adds that a positive IgM result by itself (coupled with a negative IgG result) militates against a diagnosis of Lyme disease in the disseminated stage in immunocompetent patients [Hofmann *et al.*, 2017]. In fact, CDC's algorithm for the use of serologic tests suggests testing IgMs and IgGs by immunoblotting when signs and symptoms have lasted for 30 days or less, and IgGs only when manifestations have been present longer than 30 days.[7] Some studies report a high frequency of false positives (30%) in IgM immunoblotting tests (with negative IgG results) [Lantos et al., 2016; Seriburi et al., 2012].

The CPGs consulted also mention that serologic testing does not draw a clear distinction between an active infection and a past infection, so patients' clinical pictures should always be taken into account in the interpretation of results. Because antibodies can remain for several weeks or even months after the infection has been eradicated, serologic tests should not be

[7] Centers for Disease Control and Prevention (CDC). Lyme Disease. Two-step Laboratory Testing Process [website]. Available at https://www.cdc.gov/lyme/diagnosistesting/labtest/twostep/index.html (accessed February 17, 2019).

used in patients who do not present any of the manifestations that are suggestive of the disease, nor to measure the efficacy of a particular treatment.

The CPGs consulted do not address the diagnostic value of serologic tests as a function of the geographic area where the disease was contracted, nor the information that must be transmitted with serology requests.

6.4.2. Scientific data

The systematic review conducted by INESSS of the scientific literature on the diagnostic value of laboratory tests showed that the screening test used by itself has a slightly higher sensitivity, but slightly lower specificity, than when it is used as part of two-tier serology [INESSS, 2019d]. It should be noted, however, that the designs of the studies included in the systematic review were, for the most part, inappropriate and that their level of scientific evidence was low or insufficient.

The results of the systematic review of the scientific literature conducted by INESSS show that the sensitivity of serologic testing is low at the localized stage (25% to 60%, depending on the study and approach), that it gradually increases over time (40% to 100%, depending on the study and approach, and the severity of the disease) and that it is high in individuals with Lyme arthritis (95% to 100%, depending on the study and approach) [INESSS, 2019d].

6.4.3. Contextual and experiential data

The clinicians consulted acknowledge that two-tier serology does not distinguish between an active infection and a past infection, and that the time required to activate the body's immune response varies from one individual to another. They are therefore of the opinion that the interpretation of two-tier serology results should take into account the patient's overall clinical picture.

The seroprevalence of antibodies against antigens of bacteria of the *B. burgdorferi* s.l. complex is not documented in Quebec's population, but according to IDSA, this figure may be higher than 4% in some parts of the United States [Wormser et al., 2006]. According to public health physicians, the seroprevalence of antibodies against antigens of bacteria of the *B. burgdorferi* s.l. complex is likely low in Quebec since the disease is relatively new. However, the clinicians consulted are of the opinion that two-tier serology may yield false positives and should therefore not be performed in the absence of symptoms and a clinical picture that are compatible with Lyme disease.

Some specialists pointed out that IgM results are often non-specific (not only in the context of Lyme disease) and that they do not prove that the disease is active. A positive IgM result coupled with a negative IgG result actually militates against a diagnosis of Lyme disease. In such cases, it is best to revisit other possible conditions, consult with a specialist and consider a second series of serologic tests four to six weeks later.

Some of the clinicians consulted issued a caveat about interpreting serology results in individuals who have received antibiotic treatment, because antibiotics may mitigate immune response, particularly at the beginning of an infection. In this context, a negative result should not be used to rule out the disease. These clinicians added that two-tier serology should not be

used to measure the efficacy of antibiotic treatment since antibodies can remain in the body for a long period. *Borrelia* genospecies and related strains are not evenly distributed throughout geographic areas (see the "Genospecies of the *Borrelia burgdorferi* sensu lato complex" section). Moreover, because of their varying genetic baggage, different genospecies do not all elicit the same immune response against the same antigens in their hosts. Although this topic is not addressed in the CPGs consulted, the systematic review of the scientific literature on the diagnostic value of laboratory tests did show that two-tier serology done with tests commercially available in North America has a lesser diagnostic value in the context of Lyme disease contracted in Europe than Lyme disease contracted in North America (e.g., a sensitivity of 50% to 70% in individuals who contracted Lyme arthritis in Europe, compared with a sensitivity of 95% to 100% in individuals who contracted the disease in North America) [INESSS, 2019d]. Furthermore, a Canadian study of 2,524 samples showed geographic and interannual variability in the profile of IgG antibodies produced following infection from North American strains of *B. burgdorferi* [Ogden et al., 2017]. The clinicians consulted acknowledged the importance of documenting the continent where exposure occurred and indicating it on the serology request so that the appropriate immunoblotting tests are used. They added, however, that it is sometimes difficult to gather this information as patients may not initially disclose it.

The members of the advisory committee acknowledge that the time elapsed since the appearance of the first symptoms is an important piece of information when it comes to deciding whether it is relevant to perform serologic testing and which immunoblotting tests to use. They are of the opinion, however, that the above-mentioned CDC algorithm for the use of serologic tests is too restrictive with respect to the interpretation of serologic tests since the time it takes for the body's immune response to be activated varies from one individual to another. And while they agree that it is important to indicate on the serology request when the first symptoms of the disease appeared, they emphasized that this information is not always easy to collect and analyze.

Key Takeaways

The ELISA test and the two-tier serology immunoblotting test must be used together to achieve the greatest possible sensitivity and specificity.

Interpreting the results of two-tier serology is complex and must take patients' clinical pictures into account:

- A positive IgG result (with or without IgM) in a patient who does not have any of the manifestations that are suggestive of Lyme disease does not confirm the disease, since the tests do not distinguish between an active infection and a past infection.
- A positive IgG result (with or without IgM) in a patient whose clinical picture is compatible with Lyme disease is one factor in favour of the diagnosis and should be considered in conjunction with the clinical picture.
- An IgM result by itself (without IgG) is likely to be a false positive.
- A negative result in a patient who has manifestations suggestive of Lyme disease does not rule out the disease without an overall assessment of the clinical picture, because it takes time for the body's immune response to be activated and because the various

genospecies of the *B. burgdorferi* s.l. complex and their respective strains do not elicit an immune response against the same antigens.

The interpretation of two-tier serology results is different in the context of antibiotic treatment. While a negative result should not be used to rule out the diagnosis, since antibiotics may deregulate the immune system, a positive result does not mean that the disease is active, since antibodies can remain in the blood for some time, depending on the individual. Serologic tests should not be used to measure the efficacy of antibiotic treatment.

The date when the first symptoms of Lyme disease appeared should be indicated on the serology request as it has an impact on the clinical relevance of testing and on the immunoblotting tests to be used (IgG and IgM, or IgG only).

The continent (or continents) where exposure to ticks may have occurred should be indicated on the serology request as it also has an impact on the immunoblotting tests to be used (the diagnostic value of North American tests in the context of Lyme disease contracted in Europe is low).

7. TREATMENT

Clinical aspects – Treatment
To promote optimal medication use: • Under what circumstances could an antibiotic be prescribed without laboratory test results? • Are some antibiotics more effective than others at treating various clinical manifestations of Lyme disease? • What are the adverse effects associated with studied antibiotics used for the prevention or treatment of Lyme disease caused by *Borrelia burgdorferi* sensu stricto in adults or children, as compared to a placebo, no treatment or another antibiotic? • What are the adverse effects associated with the use of oral doxycycline (for any indication) in infants in utero, breastfeeding infants or children under the age of eight, as compared to a placebo, no treatment or another antibiotic? • For patients for whom doxycycline is contraindicated and who have a history of penicillin allergy, what are the preferred antibiotics for safely treating Lyme disease, depending on the severity of the prior allergic reaction(s) and the risk of cross reaction? • How should antibiotics prescribed by a health care professional be used to treat the various stages of Lyme disease (e.g., type, route of administration, dose, duration, contraindications, precautions) for patients diagnosed with Lyme disease? • What are the impacts on care experience and cost of using an intravenous antibiotic prescribed in an outpatient setting to a patient diagnosed with Lyme disease? • Are there medications that could be prescribed in conjunction with antibiotic treatment to relieve symptoms? • Are there drug classes that should be avoided or carefully considered when a patient diagnosed with Lyme disease is undergoing antibiotic treatment? • To encourage treatment success, what information and instructions should be given to patients with a prescription for antibiotics to treat Lyme disease?

7.1. Antibiotic Treatment Indications

7.1.1. Clinical practice guides and guidelines

The documents consulted do not give any specific information on the circumstances in which antibiotic treatment can begin, other than when a clear diagnosis has been made.

7.1.2. Contextual and experiential data

Members of the advisory committee explained that once the physician or specialized nurse practitioner has assessed the risk of exposure to black-legged ticks, confirmed the patient's clinical presentation of the disease and excluded all other differential diagnoses, and if the patient presents with typical solitary erythema migrans or a clinical picture strongly suggestive of Lyme disease, antibiotics can be prescribed. In some cases, it may be indicated to begin

antibiotic treatment before getting serology results back, but the decision to do so should be made in consultation with a specialist or an experienced colleague. The clinicians consulted affirmed that in case of uncertainty, it may be best to wait for the serology results before beginning antibiotic treatment.

More specifically, if a rash is less than five centimetres in diameter and if there is reason to believe it is caused by Lyme disease, observation may be the best course of action. In such cases, the outline of the rash should be traced and its diameter measured, either by the patient or a health care professional, in order to monitor any growth. The patient could take a photo with the measurement and keep it on file. However, when the lesion is already larger than 5 cm at the time of the consultation, its growth does not necessarily have to be tracked, as it is likely to stabilize, according to MADO surveys in Montérégie.

The rash may be mistakenly interpreted as a symptom of a condition other than erythema migrans, such as infectious cellulitis or an allergic reaction to an insect bite by primary care clinicians. Member clinicians consulted are of the opinion that in the event of hesitation between infectious cellulitis and a rash that could be a manifestation of solitary typical or atypical erythema migrans, a treatment that targets cellulitis but to which *Borrelia* bacteria are also sensitive (e.g., cefuroxime axetil) should be offered.

The clinicians consulted also insisted on the importance of confirming the absence of other signs and symptoms suggestive of the disseminated stages of Lyme disease in order to adjust the type of antibiotic, route of administration and duration of treatment accordingly.

Lastly, when serologic analysis yields a negative result despite a compatible clinical picture, and other probable clinical conditions have been ruled out, it would be preferable to consult one or more specialists to decide on the best treatment option or the best way to handle the patient's care.

Key Takeaways

- A thorough assessment of the patient's general condition is essential before selecting an antibiotic and determining how it will be taken, because undetected manifestations of the early disseminated stage could lead to the wrong choice of antibiotic or a treatment duration that is not appropriate to the patient's condition.
- In the event of hesitation between infectious cellulitis and solitary erythema migrans (typical or atypical), a treatment that targets cellulitis but to which *Borrelia* bacteria are also sensitive (e.g., cefuroxime axetil) should be offered.
- When doubt remains as to whether erythema migrans is the cause of a rash (e.g., an isolated atypical symptom with no other manifestations that are suggestive of the disseminated stage) the decision to prescribe an antibiotic and perform serologic analysis should be made only after consulting with a specialist or an experienced colleague.
- In cases of neurological, cutaneous (multiple erythema migrans), cardiac or joint symptoms that may be due to Lyme disease according to the clinical picture, and while

waiting for the results of laboratory analysis, antibiotic treatment could be started following consultation with one or more specialists or experienced colleagues.

- It is important to wait for the results of serologic analysis regarding other manifestations of Lyme disease before prescribing an antibiotic, because many differential diagnoses have the same signs and symptoms.
- The decision to prescribe an antibiotic despite a negative result could be made by specialists on a case-by-case basis, depending on the risk of exposure to ticks, the clinical picture, the exclusion of other probable clinical conditions and the risk associated with taking antibiotics for several weeks.

7.2. Choice of Antibiotic Treatment – Pharmacokinetic and Pharmacodynamic Parameters

According to information published in monographs, doxycycline is an antibiotic that can cross the blood-brain barrier and has good tissue distribution because of its lipophilic properties.

Amoxicillin, on the other hand, diffuses more readily in most tissues and fluids (e.g., middle ear fluid, synovial fluid) and has variable tissue concentrations, with higher rates in the kidneys and lower rates in the liver, skin and intestines. It also reaches the central nervous system, but to a minimal degree, with very low concentrations detected in cerebrospinal fluid.

Cefuroxime axetil is an antibiotic with an abundant distribution throughout the body's tissues and fluids. It can cross the placenta, be present in breastmilk and penetrate non-inflamed meninges. Ceftriaxone, too, is distributed abundantly throughout tissues and fluids, including—particularly in the case of inflamed meninges—cerebrospinal fluid.

Azithromycin is quickly absorbed and distributed throughout the whole body after oral administration. The drug travels rapidly from the blood to the tissues, but there are no scientific data on the presence of the antibiotic in nervous tissues, whereas clarithromycin is known to easily penetrate most tissues. Erythromycin also easily spreads through most bodily fluids: low concentrations are usually found in cerebrospinal fluid, but in cases of meningitis, there is an increased transfer of the medication through the blood-brain barrier. In order to complement the information found in monographs, a review of the scientific literature on the sensitivity of *B. burgdorferi* s.l. genospecies to various IDSA-recommended antibiotics was undertaken. The results tend to show that all genospecies are sensitive in vitro, regardless of origin—i.e., whether they were isolated from ticks or clinical samples.

Key Takeaways

The antibiotics with the best tissue distribution and capacity to cross the blood-brain barrier are doxycycline, cefuroxime axetil and ceftriaxone.

7.3. Choice of Antibiotic Treatment – Efficacy and Safety

7.3.1. Antibiotics studied in the context of erythema migrans (solitary or multiple) attributable to Lyme disease with or without general systemic symptoms

The twenty studies included in NICE's systematic review and the two found by INESSS that were published after the conclusion of NICE's research were analyzed. The characteristics and results of each study are presented in Appendix K of this report's supplementary appendices document.

The studies chosen are generally small and heterogeneous—with variations with respect to types of treatment, duration and outcomes, follow-up duration, etc.—and many of them were conducted in Europe, which might pose a problem in terms of generalizability to the North American context. The studies also often included patients in the localized and early disseminated stages of the disease: two studies focused largely or solely on individuals with multiple erythema migrans and systemic symptoms [Stupica et al., 2018; Dattwyler et al., 1997]. As for their methodological quality, the NICE authors deem it to be virtually always low or very low.

Almost all of the primary studies considered and presented in the section on solitary erythema migrans included participants in the localized or early disseminated stage of the disease, and did not distinguish the results by disease stage.

The statements of scientific evidence and the levels of evidence for each outcome considered, depending on the comparison of antibiotics (type, duration, population) are presented in Appendix S of this report's supplementary appendices document.

7.3.1.1. Doxycycline

In the primary studies analyzed, the efficacy of doxycycline was compared to that of cefuroxime axetil (three RCTs [Cerar et al., 2010; Luger et al., 1995; Nadelman et al., 1992]), amoxicillin + probenecid (two RCTs [Massarotti et al., 1992; Dattwyler et al., 1990]), azithromycin (two RCTs [Barsic et al., 2000; Massarotti et al., 1992]) and phenoxymethylpenicillin (one RCT [Strle et al., 1992]). The studies differed in the dosage and treatment duration analyzed, as well as the outcomes investigated (definition and timing of occurrence). Furthermore, two studies (one RCT and one non-inferiority trial) compared different doxycycline treatment durations (10 days vs. 15 days, and 10 days vs. 20 days) [Stupica et al., 2012; Wormser et al., 2003].

In this context, recovery could mean the resolution of erythema migrans and concomitant symptoms without the appearance of clinical manifestations during follow-up (which varied from one study to another), or the resolution of these symptoms and the return to pre-Lyme disease health status. The reduction of symptoms could be defined as the complete resolution of erythema migrans, but coupled with the incomplete resolution—or the appearance—of other symptoms during follow-up. Depending on the study, relapse could mean the lack of improvement, or recurrence, of erythema migrans and the other symptoms during follow-up. Moreover, the studies measured the occurrence of various outcomes at different times: for

example, at the end of antibiotic treatment (e.g., 14 days) or at different points in the follow-up period (e.g., 1, 2, 6 or 12 months).

The dosage schedule also varied from one study to another. Doxycycline, always administered in doses of 100 mg, was generally given twice daily (three times per day in one study) for 10, 14, 15 or 20 days, depending on the study.

Despite their different protocols, none of the studies found statistically significant differences regarding recovery, symptom reduction or the relapse of erythema migrans and associated symptoms when comparing doxycycline to other antibiotics, namely cefuroxime axetil, amoxicillin + probenecid, azithromycin and phenoxymethylpenicillin. The two studies that compared doxycycline treatment durations came to the same conclusion: recovery from erythema migrans and associated symptoms after a 10-day treatment is not statistically different from the recovery observed after a 15- or 20-day treatment. The same holds true for all three outcomes considered when comparing treatment durations of 10 and 20 days.

Although the studies reviewed had the recruitment of young participants (≥ 12 years old) as an inclusion criterion, youth were generally a minority in the study populations. No analyses or studies were conducted exclusively on young participants, and none of the primary studies on Lyme disease that were selected included pregnant or breastfeeding women.

Other than the results of the comparison of doxycycline and cefuroxime axetil (recovery, reduction of symptoms and relapse), which are supported by a moderate level of scientific evidence, the conclusions have a low level of scientific evidence for the absence of statistically significant differences between antibiotics and treatment durations studied.

None of the studies analyzed included pregnant women or children under 12 years of age. The level of scientific evidence for these populations is therefore insufficient.

7.3.1.2. Amoxicillin

In the primary studies analyzed, amoxicillin (+ probenecid) was compared to doxycycline in two RCTs [Massarotti et al., 1992; Dattwyler et al., 1990] that used the same dosage but studied two different treatment durations (10 days and 21 days). The intrinsic limits of these studies are similar to the ones described above in the section on doxycycline. The compilation of their results (meta-analysis) showed no statistically significant difference with respect to recovery from and symptom relapse of erythema migrans and associated symptoms. One RCT [Luft et al., 1996] found a greater efficacy for amoxicillin (500 mg BID x 20 days) than azithromycin (500 mg QD x 7 days) in terms of recovery (RR = 1.16; 95% CI [1.02; 1.32]) and relapse (RR = 0.24; 95% CI [0.08; 0.70]). However, the reduction of symptoms is similar in the two groups (RR = 0.57; 95% CI [0.31; 1.05]), and when the combination of amoxicillin + probenecid (500 mg TID each x 10 days) was compared to azithromycin (500 mg QD the first day, then 250 mg QD for four days), the authors found no statistically significant difference between the two treatments with respect to the occurrence of recovery and relapse [Massarotti et al., 1992].

Among the studies analyzed, two compared the efficacy of amoxicillin to that of cefuroxime (low and high dosages) [Eppes and Childs, 2002] and azithromycin [Arnež et al., 2002] in children. Amoxicillin (50 mg/kg/day x 20 days) was found to be as effective as cefuroxime

administered at a dose of 20 or 30 mg/kg/day for 20 days for recovery from erythema migrans and associated symptoms. However, these results are supported by only one small study, with low methodological quality. There were also no statistically significant differences found between the use of amoxicillin (50 mg/kg/day x 14 days) and that of azithromycin (20 mg/kg the first day, then 10 mg/kg for four days) for recovery from erythema migrans and concomitant symptoms, with recovery defined by the duration of these clinical manifestations after the start of antibiotic treatment.

In adults, with the exception of the result regarding the occurrence of symptom relapse when amoxicillin was compared to azithromycin (moderate level of scientific evidence indicating that amoxicillin is 1.16 times more effective than azithromycin), all of the results presented here have a low level of scientific evidence for the absence of statistically significant differences between antibiotics and treatment durations studied. In children, all of the results presented here have a low level of scientific evidence for the absence of statistically significant differences between antibiotics.

None of the studies analyzed included pregnant women. The level of scientific evidence for this population is therefore insufficient.

7.3.1.3. Cefuroxime axetil

This antibiotic was compared only to doxycycline in the primary studies analyzed. The three RCTs in question found no statistically significant difference between the use of doxycycline (100 mg BID/TID x 15–20 days) and that of cefuroxime axetil (500 mg BID x 15–20 days) with respect to recovery, symptom reduction or relapse in the case of erythema migrans and associated symptoms [Cerar et al., 2010; Luger et al., 1995; Nadelman et al., 1992]. The intrinsic limits of these studies are similar to the ones described above in the section on doxycycline.

The efficacy of this antibiotic in children was compared, in two separate studies, to that of amoxicillin [Eppes and Childs, 2002] and phenoxymethylpenicillin [Arnež et al., 1999]. No statistically significant difference was found between the use of cefuroxime axetil and amoxicillin (see the section on this antibiotic) and the use of cefuroxime axetil (30 mg/kg/day x 14 days) and phenoxymethylpenicillin (100,000 IU/kg/day x 14 days), nor between the two dosages (low and high) of this antibiotic, with respect to recovery from erythema migrans and concomitant symptoms, defined by the duration of clinical manifestations after the start of antibiotic treatment.

In adults, with the exception of results from the comparison of doxycycline and cefuroxime axetil with respect to recovery, symptom reduction and relapse (moderate level of scientific evidence for the absence of statistically significant differences between the two antibiotics), the conclusions have a low level of scientific evidence for the antibiotics and dosage schedules studied.

In children, all of the results presented here have a low level of scientific evidence for the absence of statistically significant differences between antibiotics.

None of the studies analyzed included pregnant women. The level of scientific evidence for this population is therefore insufficient.

7.3.1.4. Macrolides (azithromycin and erythromycin)

Eight of the primary studies analyzed focused on macrolides. Azithromycin was compared to doxycycline [Barsic et al., 2000; Massarotti et al., 1992], to amoxicillin on its own [Luft et al., 1996] or combined with probenecid [Massarotti et al., 1992], and phenoxymethylpenicillin [Weber et al., 1993]. One study compared erythromycin to phenoxymethylpenicillin and to tetracyclines [Steere et al., 1983]. The intrinsic limits of these studies are similar to those previously described. With the exception of one study that found a greater efficacy of amoxicillin on its own as compared to azithromycin, no statistically significant difference was found between the use of the macrolides considered and the use of the other antibiotics to which they were compared.

In the studies analyzed that focused solely on children, azithromycin was compared to amoxicillin [Arnež and Ružić-Sabljić, 2015] and phenoxymethylpenicillin [Arnež et al., 2002]. Neither of these studies found any statistically significant differences between the use of azithromycin and amoxicillin (see the section on this antibiotic) and the use of azithromycin (20 mg/kg the first day and 10 mg/kg thereafter for 4 days) and phenoxymethylpenicillin (100,000 IU/kg/day x 14 days) with respect to the occurrence of recovery from erythema migrans and concomitant symptoms, with recovery defined by the duration of these clinical manifestations after the start of antibiotic treatment.

In adults, with the exception of the result cited above with respect to the relapse of symptoms when amoxicillin was compared to azithromycin (moderate level of scientific evidence indicating that amoxicillin is 1.16 times more effective than azithromycin) [Luft et al. 1996], all of the results presented here have a low level of scientific evidence for the absence of statistically significant differences between the antibiotics studied.

In children, all of the results presented here have a low level of scientific evidence for the absence of statistically significant differences between antibiotics.

None of the studies analyzed included pregnant women. The level of scientific evidence for this population is therefore insufficient.

7.3.1.5. Other antibiotics studied

Phenoxymethylpenicillin and tetracyclines other than doxycycline, including minocycline, were also compared in some of the studies considered. Phenoxymethylpenicillin was compared to doxycycline [Strle et al., 1992], tetracyclines [Steere et al., 1983], minocycline [Breier et al., 1996] and ceftriaxone [Weber et al., 1990]. Once again, however, no statistically significant difference was found between the groups compared with respect to recovery, symptom reduction or relapse. All of the results presented here have a low level of scientific evidence for the absence of statistically significant differences between the antibiotics studied.

None of the studies analyzed included children or pregnant women. The level of scientific evidence for these two populations is therefore insufficient.

7.3.2. Multiple erythema migrans associated with Lyme disease

Two RCTs that were analyzed focused largely or wholly on participants with multiple erythema migrans associated with general systemic symptoms. The first trial compared ceftriaxone IV

with doxycycline PO administered during 21 days to patients at the early disseminated stage, with multiple erythema migrans and without meningitis. This study concluded that both treatments were equally effective at achieving recovery, defined as resolution of the erythema migrans and concomitant symptoms, and prevention of late-onset manifestations of the disease [Dattwyler et al., 1997]. The second trial [Stupica et al., 2018] included patients who all presented with multiple erythema migrans and who had received either doxycycline PO or ceftriaxone IV for 14 days. The authors concluded that doxycycline PO administered for 14 days was no less effective than ceftriaxone IV in patients at the early disseminated stage, characterized by multiple erythema migrans. The methodological quality of both studies was deemed poor. The level of scientific evidence for the absence of statistically significant differences between the antibiotics studied in adults for each of the questions addressed in these studies is low (Appendix T of this report's supplementary appendices document).

None of the studies analyzed included children or pregnant women. The level of scientific evidence for these two populations is therefore insufficient.

7.3.3. Safety

The studies chosen and described in the section on the efficacy of treatments for erythema migrans also addressed the safety of these treatments. Virtually all of the studies found no differences between the antibiotics assessed to treat this condition.

However, although the results were all statistically insignificant, doxycycline produced more adverse effects than the antibiotics to which it was compared, namely phenoxymethylpenicillin, azithromycin and cefuroxime axetil. Meanwhile, no statistically significant difference with respect to adverse effects was found between a 10-day course of doxycycline and a 20-day course of the drug. Photosensitivity and digestive symptoms are the adverse effects most commonly reported in CPGs, which is why patients are advised not to take the medication with dairy products and to limit their exposure to the sun or use sunscreen for the duration of the treatment.

Compared to phenoxymethylpenicillin, both minocycline [Breier et al., 1996] and azithromycin [Weber et al., 1993; Strle et al., 1992] increase the risk of adverse effects (RR = 3.50; 95% CI [1.37; 8.96] and RR = 2.41; 95% CI [1.02; 5.69], respectively) (low level of scientific evidence) (Appendix S of this report's supplementary appendices document).

Cefuroxime axetil was associated with an increased risk of adverse effects in children as compared to phenoxymethylpenicillin [Arnež et al., 1999]; when given at a high dose (30 mg/kg/day), it increases the risk of diarrhea as compared to a lower dose (20 mg/kg/day) (low level of scientific evidence) [Eppes and Childs, 2002] (Appendix S of this report's supplementary appendices document).

The two studies that included exclusively or almost exclusively patients with multiple erythema migrans found no statistically significant difference with respect to adverse effects after the administration of doxycycline (100 mg BID x 14–21 days) as compared to ceftriaxone (2 g QD x 14 days) (RR = 1.33; 95% CI [0.95; 1.86]) [Stupica et al., 2018; Dattwyler et al., 1997] (low level of scientific evidence) (Appendix T of this report's supplementary appendices document).

For data on doxycycline's safety (not in connection to Lyme disease) in children exposed in utero, during breastfeeding or before age 8, refer to the supporting report for PEP knowledge transfer tools [INESSS, 2019b].

7.4. Antibiotics Studied in the Context of Lyme Carditis

No systematic reviews or primary studies addressing the treatment of Lyme carditis were identified. The level of scientific evidence for the comparative efficacy of antibiotics for this clinical condition is therefore insufficient across all populations.

7.5. Antibiotics Studied in the Context of Neuroborreliosis

The studies included in NICE's systemic review were for the most part conducted in Europe, their methodological quality is poor (bias, small samples, etc.) and they are heterogeneous — patients with peripheral or central damage, varying follow-up durations, etc. The following types of neurological manifestations were addressed in the studies:

- Participants with facial palsy (cohorts, United States) [Jowett et al., 2017]
- Participants with either: 1) clinical signs of acute lymphocytic meningoradiculitis (Bannwarth's syndrome) with severe radicular pain and lymphocytic pleocytosis in the CSF, high antibody titers against *B. burgdorferi* or a history of arthropod bites or erythema migrans; or 2) meningitis (neuroborreliosis) with a history of tick bites or erythema migrans and high antibody titers against *B. burgdorferi* (RCT – Germany) [Pfister et al., 1989]
- Participants with Lyme neuroborreliosis, most of whom presented with typical Bannwarth's syndrome: intense radicular pain and lymphocytic pleocytosis in the CSF (RCT – Germany) [Pfister et al., 1991]
- Participants with high-titer *B. burgdorferi*-specific antibodies in the serum and at least three of the following symptoms or conditions: radicular pain, meningitis symptoms, cranial neuritis, sensory or motor radiculitis, arthritis or carditis, tick bite or erythema migrans, antibody-specific titers (serum or CSF), lymphocytic pleocytosis, high protein levels (> 50 mg/dl), high IgM/IgG/IgA levels (RCT – Germany) [Kohlhepp et al., 1989]
- Participants with clinical signs and symptoms compatible with neuroborreliosis and pleocytosis, as well as systemic symptoms (RCT – Sweden [Karlsson et al., 1994]
- Participants with neurological symptoms compatible with neuroborreliosis: two papers published by Ljøstad et al., the first in 2008 and the second in 2010; the 2010 paper presented the results of the follow-up of the population studied in the 2008 paper (RCT – Norway) [Ljøstad and Mygland, 2010; Ljøstad et al., 2008]

In the primary studies analyzed that address the treatment of neuroborreliosis, doxycycline (200 mg QD) was compared to penicillin G (20 mega units / day IV) (10-day treatment course for both antibiotics); two RCTs [Karlsson et al., 1994; Kohlhepp et al., 1989] and to ceftriaxone (2 g IV) (14-day treatment course for both antibiotics); one RCT [Ljøstad and Mygland, 2010; Ljøstad et al., 2008]. The two other RCTs compared a 10-day course of cefotaxime (2 g TID)

to a treatment course of the same duration with penicillin G (4 x 5 million U/day) [Pfister et al., 1989] or ceftriaxone (2 g IV) [Pfister et al., 1991].

All of these studies concluded that there was no statistically significant difference between the treatments considered with respect to recovery from neurological damage and symptom reduction. However, the studies are of poor methodological quality (small size, bias, etc.). The definition of the questions studied and the timing of their assessment differ from one study to another. For example, recovery can be interpreted as the absence of residual symptoms at various follow-up stages or the resolution of symptoms at the end of the follow-up. Lastly, one study (cohorts [Jowett et al., 2017]) looked at the efficacy of antibiotics with or without corticosteroids in cases of facial palsy, and it concluded that the reduction of symptoms was greater following antibiotics alone than the combination of antibiotics and corticosteroids. However, the study's methodological quality was poor (small size, bias, etc.) and the antibiotics administered were not described in detail.

All of the outcomes considered for the treatment of neuroborreliosis in adults based on the studies considered here have a low level of scientific evidence for the absence of statistically significant differences between the antibiotics studied (Appendix U of this report's supplementary appendices document).

None of the studies analyzed included children or pregnant women. The level of scientific evidence for these two populations is therefore insufficient.

7.5.1. Safety

The studies on the treatment of neuroborreliosis concluded that there was no statistically significant difference in the occurrence of adverse effects between the use of doxycycline (200 mg QD PO x 14 days) and benzylpenicillin (3 g IV every 6 hours x 14 days; RR [95% CI] = 0.99 [0.24; 4.05]) or ceftriaxone (2 g IV QD x 14 days; RR [95% CI] = 0.79 [0.51 to 1.23]), nor between cefotaxime (3 x 2 g QD x 10 days) and ceftriaxone (2 g QD x 10 days) (RR [95% CI] = 2.63 [0.31; 22.46])—low level of scientific evidence for the absence of statistically significant differences between the antibiotics studied (Appendix U of this report's supplementary appendices document).

7.6. Antibiotics Studied in the Context of Non-Neurological Lyme-Related Ocular Disorders

No systematic reviews or primary studies that address the treatment of Lyme-related ocular disorders were identified. The level of scientific evidence of the comparative efficacy of antibiotics for this clinical condition is therefore insufficient for all populations.

7.7. Antibiotics Studied in the Context of Lyme Arthritis

7.7.1. Efficacy in the active phase

Of the four primary studies retained (all conducted in the United States), two included adults only [Caperton et al., 2010; Dattwyler et al., 1988], one included participants aged 8 and older [Steere et al., 1985] and one included participants aged 13 and older [Steere et al., 1994].

One of the studies found no statistically significant difference with respect to recovery from Lyme arthritis (RR = 1.01; 95% CI [0.81; 1.26]), future complications or the appearance of other late-onset manifestations (RR = 0.36; 95% CI [0.08; 1.59]) between a 30-day treatment course with doxycycline PO (100 mg BID) and with amoxicillin + probenecid PO (500 mg QID each) [Steere et al., 1994]. Two studies concluded that ceftriaxone IV (2 g/day x 14 days) was more effective than a placebo in reducing the symptoms of Lyme arthritis (RR = 4.87; 95% CI [1.26; 18.86]) and than penicillin G IV (24 million units/day x 10 days) in decreasing the rate of treatment failure [Caperton et al., 2010; Dattwyler et al., 1988]. The last study showed that penicillin G IV (2.4 million U per week for 3 weeks) led to a greater resolution of Lyme arthritis symptoms than a placebo (RR = 10.63; 95% CI [2.12; 53.21]) [Steere et al., 1985]. However, all of these results are based on studies of poor methodological quality (small sample, bias, etc.)

All of the studies retained for the treatment of arthritis in adults have a low level of scientific evidence for the absence of statistically significant differences between the antibiotics studied (Appendix V of this report's supplementary appendices document).

All of the results for children that are presented here have a low level of scientific evidence for the absence of statistically significant differences between the antibiotics studied (Appendix V of this report's supplementary appendices document).

None of the studies analyzed included pregnant women. The level of scientific evidence for this population is therefore insufficient.

7.7.2. Safety

The four trials that assessed the efficacy of treatments for patients with Lyme arthritis also studied their safety. They concluded that doxycycline PO was associated with a lower risk of adverse effects as compared to amoxicillin + probenecid PO (OR = 0.09 [0.02; 0.47]) [Steere et al., 1994]. Ceftriaxone IV was concluded to produce more adverse effects than the placebo, but there is no statistically significant difference when compared to penicillin G IV [Dattwyler et al., 1988]—low level of scientific evidence for the absence of statistically significant differences between the antibiotics studied. The statements of scientific evidence for each outcome considered, depending on the antibiotic comparisons, are presented in Appendix V of this report's supplementary appendices document.

7.8. Antibiotics Studied in the Context of Persistent Symptoms After Treatment

7.8.1. Efficacy

The primary studies retained compared different combinations of treatments—either two antibiotics administered successively for different durations and compared to another combination of antibiotics or a placebo, or a single antibiotic compared to a placebo.

One study [Cameron, 2008], found that amoxicillin (3 g QD x 3 months) led to improvements in quality of life with respect to mental health, but not physical health, as compared to a placebo.

In another study, for which extreme fatigue was an inclusion criterion for participants [Krupp et al., 2003], ceftriaxone (2 g QD x 28 days) induced a reduction of the symptom of fatigue (at

six months) as compared to a placebo—high level of scientific evidence that the antibiotic yields superior benefits as compared to a placebo—but no cognitive improvement was found. The authors concluded that their study did not support an additional ceftriaxone IV antibiotic treatment in patients with persistent symptoms (Appendix W of this report's supplementary appendices document).

A third study [Fallon et al., 2008] also compared ceftriaxone to a placebo for a 10-week treatment course. While an improvement in cognitive performance was recorded in week 12 of follow-up in the group that was given the ceftriaxone, the improvement was short-lived, as it was followed by a relapse in week 24.

The other studies did not find a statistically significant difference following long-term treatment between the antibiotics administered and a placebo, for the other outcomes considered—quality of life with respect to mental and physical health, cognition, and neuropsychological tests.

Ceftriaxone (2 g QD x 28–30 days) followed by doxycycline (200 mg QD x 60 days) did not produce significant differences as compared to the placebo with respect to improving quality of life and scores on neuropsychological tests assessing learning and memory, sustained attention and information processing speed, verbal fluidity, symptoms of depression (at 90 and 180 days) and cognitive function (at six months)—low level of scientific evidence for both outcomes with respect to the absence of a statistically significant difference between doxycycline and a placebo given following a first 30-day course of ceftriaxone [Kaplan et al., 2003; Klempner et al., 2001] (Appendix W of this report's supplementary appendices document).

No statistically significant difference was found with respect to improving quality of life (at six months) following treatment with ceftriaxone (2 g QD x 14 days) then doxycycline (100 mg BID x 12 weeks), or with ceftriaxone (2 g QD x 14 days) then a placebo (12 weeks), as compared to ceftriaxone (2 g QD x 14 days) followed by clarithromycin (500 mg BID PO x 12 weeks) + hydroxychloroquine (200 mg BID PO x 12 weeks) [Berende et al., 2016]—low level of scientific evidence for the absence of statistically significant differences between doxycycline or clarithromycin combined to hydroxychloroquine, as compared to a placebo, all administered following a first 14-day treatment course with ceftriaxone in adults (Appendix W of this report's supplementary appendices document).

None of the studies analyzed included children or pregnant women. The level of scientific evidence for these two populations is therefore insufficient.

7.8.2. Safety

The studies that addressed persistent symptoms and assessed the safety of treatments did not find any statistically significant difference between the antibiotics considered.

Similar adverse effects were found to be associated with:

- Ceftriaxone (2 g QD IV x 30 days) followed by doxycycline (200 mg QD PO x 60 days), as compared to a placebo (IV + PO x 60 days) (RR [95% CI] = 1.48 [0.74; 2.93])

[Klempner et al., 2001] (low level of scientific evidence) (Appendix W of this report's supplementary appendices document)

- Ceftriaxone (2 g QD IV x 10 weeks) as compared to a placebo (0.9% saline IV x 10 weeks) (RR [95% CI] = 3.65 [0.49; 27.26]) [Fallon et al., 2008] (low level of scientific evidence) (Appendix W of this report's supplementary appendices document)
- Ceftriaxone (2 g QD IV x 2 weeks) followed by doxycycline (PO 100 mg BID x 12 weeks), as compared to ceftriaxone (2 g QD IV x 2 weeks) followed by clarithromycin (500 mg BID PO) + hydroxychloroquine (200 mg BID PO) x 12 weeks (adverse effects: RR [95% CI] = 1.12 [0.82; 1.53]); treatment discontinuation due to adverse effects: RR (95% CI) = 0.48 (0.13; 1.79) [Berende et al., 2016] (low level of scientific evidence) (Appendix W of this report's supplementary appendices document)
- Ceftriaxone (2 g QD IV x 2 weeks) followed by doxycycline (PO 100 mg BID x 12 weeks), as compared to ceftriaxone (2 g QD IV x 2 weeks) followed by a placebo (PO x 12 weeks) (adverse effects: RR [95% CI] = 1.41 [0.99; 1.99]) (moderate level of scientific evidence); treatment discontinuation due to adverse effects: RR (95% CI) = 0.85 (0.20; 3.71) (low level of scientific evidence) [Berende et al., 2016] (Appendix W of this report's supplementary appendices document)
- Ceftriaxone (2 g QD IV x 2 weeks) followed by clarithromycin (500 mg BID PO) + hydroxychloroquine (200 mg BID PO x 12 weeks), as compared to ceftriaxone (2 g QD IV x 2 weeks) followed by a placebo (PO x 12 weeks) (adverse effects: RR [95% CI] = 1.26 [0.89; 1.80]; treatment discontinuation due to adverse effects: RR [95% CI] = 1.79 [0.54; 5.91]) (low level of scientific evidence) [Berende et al., 2016] (Appendix W of this report's supplementary appendices document)
- Amoxicillin (3 g QD PO x 3 months) as compared to a placebo (PO x 3 months) RR [95% CI] = 1.09 [0.62; 1.93]) (low level of scientific evidence) [Cameron, 2008] (Appendix W of this report's supplementary appendices document)

None of the studies analyzed included pregnant women. The level of scientific evidence for this population is therefore insufficient.

Key Takeaways

No matter the clinical manifestation of Lyme disease being studied, the scientific publications selected generally concluded that there was no statistically significant difference with respect to the efficacy of the antibiotics compared. The level of scientific evidence was largely deemed to be low.

With respect to skin lesions:

- All of the primary studies retained included patients with solitary or multiple erythema migrans, either with or without general systemic symptoms (the conclusions of these studies are presented in the section on solitary erythema migrans), and two of the studies focused largely or wholly on patients with multiple erythema migrans.

- No statistically significant difference was found with respect to the efficacy of 10, 15 or 20 days of treatment with doxycycline for solitary erythema migrans (low level of scientific evidence). However, no publications studying shorter courses of treatment with amoxicillin or cefuroxime axetil were identified.
- Doxycycline PO given for 14 days performs as well as ceftriaxone IV when administered to patients in the early disseminated stage, characterized by the presence of multiple erythema migrans (low level of scientific evidence).

With respect to arthritis:

- No statistically significant difference was found with respect to recovery from Lyme arthritis, future complications or the appearance of other late-onset manifestations between treatment with doxycycline PO and with amoxicillin + probenecid PO (low level of scientific evidence).
- Ceftriaxone IV is more effective than a placebo and penicillin G IV in reducing the symptoms of Lyme arthritis and decreasing the rate of treatment failure (low level of evidence).
- Penicillin G IV resolves the symptoms of Lyme arthritis more successfully than a placebo (low level of evidence).

Virtually none of the studies selected found statistically significant differences with respect to the safety of the antibiotics assessed in the context of Lyme disease (low level of scientific evidence). However, although the results were all statistically insignificant, doxycycline produced more adverse effects than the antibiotics to which it was compared in the context of erythema migrans (azithromycin, cefuroxime axetil, phenoxymethylpenicillin). This result was not observed in the studies on neuroborreliosis or Lyme arthritis. Photosensitivity and digestive symptoms are the most commonly reported adverse effects associated with doxycycline.

No systematic reviews or primary studies addressing the treatment of Lyme carditis or non-neurological Lyme-related ocular disorders were found.

The current state of knowledge suggests that using antibiotics to treat persistent symptoms after a first course of antibiotics does not yield any benefits with respect to cognition or quality of life associated with physical health.

The publications examined did not take into account the long-term effects of antibiotic treatment on gut microbiota nor the emergence of bacterial resistance.

7.9. Choice of Antibiotic Treatment – Directives for Use in the Treatment of Erythema Migrans Associated with Lyme Disease

7.9.1. Clinical practice guides, guidelines and reference books

Four of the CPGs that were identified (IDSA, SAD, GDS, NICE) as well as the 2018 *Red Book* address the treatment of erythema migrans with or without general systemic symptoms [HAS, 2018; Kimberlin et al., 2018; NICE, 2018; Hofmann et al., 2017; Wormser et al., 2006]. As a

general rule, these documents recommend the oral administration of antibiotics. None of the CPGs recommend parenteral antibiotics to treat multiple erythema migrans, whether or not there are systemic symptoms, and none provides information on a second-line antibiotic treatment after the failure of the first course of antibiotics prescribed to treat multiple erythema migrans with or without systemic symptoms. HAS mentions that the post-treatment prognosis is generally good and that in cases of non-regression, it is important to follow treatment guidelines, assess the possibility of another etiological condition and seek the opinion of a dermatologist or other specialists, depending on the symptoms associated with the lesion. The recommendations regarding antibiotics issued in the documents consulted are available at Appendix X of this report's supplementary appendices document.

7.9.1.1. Doxycycline

All of the guides recommend doxycycline as a first-line treatment for erythema migrans, at a dosage of 200 mg per day (200 mg QD or 100 mg BID). The duration of treatment, however, differs from one CPG to another, varying from two to three weeks, with the exception of the ILADS guide, which recommends 14 days but also puts forth a range of 10 to 21 days. HAS recommends a treatment duration of 14 days, while NICE recommends 21 days. These differences may be due to the fact that HAS considers erythema migrans as a localized form of Lyme borreliosis, whereas NICE recommends treating erythema migrans whether or not general systemic (focal) symptoms appear once the bacteria disseminate.

As a general rule, the GDS suggests treating localized or early disseminated skin manifestations for 10 to 21 days, depending on the duration and severity of clinical symptoms. According to this CPG, localized erythema migrans without any general systemic symptoms should only be treated for 10 to 14 days. This guideline is based on a study that compared 10-day and 14-day courses of doxycycline and found no significant difference between the two treatment groups [Stupica et al., 2012]. ILADS, on the other hand, recommends a much longer duration, ranging from four to six weeks, pointing to a treatment failure rate reported in some studies that was deemed too high. NICE recommends a duration of 21 days, explaining that treatment courses of two to three weeks are standard practice and that a longer duration would enhance symptom reduction without increasing adverse effects, while shorter durations would lead to more treatment failures.

The arguments reported by the CPGs are often based on the efficacy of doxycycline in treating erythema migrans and on the drug's ability to cross the blood-brain barrier and thus prevent the eventual spread of the bacteria to the nervous system. Additionally, doxycycline is also effective in treating human granulocytic anaplasmosis, an infection that can occur simultaneously with Lyme disease, since the bacteria that causes it (*Anaplasma phagocytophilum*) is also transmitted by ticks. Finally, doxycycline's administration schedule contributes to treatment compliance.

With the exception of ILADS, whose guide does not address the topic of pregnant or breastfeeding women, the four other CPGs recommend the same treatment for pregnant or breastfeeding women as for other women, but taking into consideration the pregnancy trimester. Only doxycycline is contraindicated during pregnancy or breastfeeding. NICE and the GDS published recommendations for pregnant women, but none for breastfeeding women.

The contraindication of doxycycline for children under the age of 8 (or 9, for NICE and the GDS) is reported in virtually all of the documents selected, due to the risk of permanent tooth staining and enamel hypoplasia. Only the 2018 *Red Book* recommends administering this antibiotic to children of all ages for a short duration (maximum of 21 days, depending on the disease). When indicated, this tetracycline is recommended by IDSA, ILADS, HAS and the GDS as a first-line treatment, at a dose of 4 mg/kg/day, divided into two doses. NICE, however, recommends a dose of 5 mg/kg divided into two doses the first day, then 2.5 mg/kg/day in one or two doses for the remaining of treatment duration, while for severe infections, it recommends a higher dose, up to a maximum of 5 mg/kg/day for the 21 days of treatment. The 2018 *Red Book* suggests a dose of 4.4 mg/kg/day PO, divided into two doses.

There are some differences with respect to the maximum recommended dose: some agencies express it on a per-dose basis, others on a per-day basis. IDSA recommends a maximum of 100 mg/dose, ILADS recommends a maximum of 200 mg/day, the Canadian Paediatric Society (CPS) recommends a maximum of 200 mg/dose, the GDS recommends a maximum of 200 mg/day, and HAS recommends a maximum of 100 mg/dose. The 2018 *Red Book* recommends a maximum dose of 200 mg/day.

Recommended treatment durations are the same as those for adults: 14 days (10–21 days) for IDSA, 14–21 days for the CPS, 10–14 days for the GDS, 14 days for HAS, 21 days for NICE and four to six weeks for ILADS. The *Red Book* recommends a 10-day treatment course.

For reviews of the clinical recommendations regarding doxycycline's safety (not in connection to Lyme disease) in children exposed in utero, during breastfeeding or before age 8, refer to the supporting report for PEP knowledge transfer tools [INESSS, 2019b].

7.9.1.2. Amoxicillin

Amoxicillin is also one of the first-line antibiotics recommended by four of the five CPGs—NICE suggests using this beta-lactam antibiotic as the primary alternative to doxycycline—but IDSA recommended dosage is lower than the ones recommended by other learned societies and health assessment agencies. IDSA suggests a dosage schedule of 500 mg TID for two weeks, while ILADS recommends 1,500 to 2,000 mg/day for four to six weeks. The GDS recommends 500 to 1,000 mg TID of amoxicillin for two weeks. HAS and NICE recommend 1 g TID for two and three weeks respectively.

In France, amoxicillin is recommended in this context at doses varying from 500 to 1,000 mg TID (max. 4 g/day) for 10 to 21 days. HAS favours a dose of 1 g TID, among other reasons to avoid the risk of late-onset complications in the event of an insufficient dose. NICE also recommends a higher dose, because the studies that assessed the efficacy of amoxicillin also used probenecid, a medication designed to increase the concentration of amoxicillin.

HAS recommends the use of amoxicillin as a first-line treatment for pregnant or breastfeeding women: 1 g TID; 50 mg/kg up to a maximum of 4 g/day x 14 days for solitary erythema migrans, and 1 to 2 g/day x 21 days for multiple erythema migrans. The GDS also recommends amoxicillin as a first-line treatment for pregnant women (500 to 1,000 mg TID x 14 days for solitary erythema migrans and 21 days for multiple erythema migrans), and adds penicillin G (IV) as another option.

Amoxicillin is often recommended by CPGs and reference books as a treatment of choice, or a first-line treatment, for children under age 8 (or under age 9 in the case of NICE and the GDS). IDSA, ILADS, the 2018 *Red Book*, the CPS, the GDS and HAS all recommend a dosage of 50 mg/kg/day, often divided into three doses. NICE, however, suggests a dosage of 30 mg/kg TID for children (≤ 12 years) who weigh 33 kg (73 lbs.) or less, and a higher dose of 1 g (TID) for children age 12 and older.

The maximum dosages reported by some CPGs and guidelines vary from 500 mg/dose (IDSA) to 1,500 mg/day (ILADS, CPS and the 2018 *Red Book*).

Amoxicillin treatment durations for children presenting with erythema migrans are the same as those recommended for adults: 14 days (14–21 days) for IDSA, 14–21 days for the CPS, 10–14 days for the GDS, 14 days for HAS, 21 days for NICE, four to six weeks for ILADS, and 14 days according to the 2018 *Red Book*.

7.9.1.3. Cefuroxime axetil

Only three of the five CPGs present cefuroxime axetil as a treatment option: IDSA and ILADS consider it to be a first-line treatment, while the GDS guide describes it as an alternate treatment. The dosages are similar (500 mg BID), and the recommended treatment durations are two weeks (up to three for IDSA) and four to six weeks (ILADS).

Although HAS acknowledges the efficacy of this antibiotic in treating EM, it does not recommend it as a treatment option, endorsing instead older, more narrow spectrum antibiotics that are better tolerated and less expensive—specifically, doxycycline and amoxicillin. NICE's committee deems the evidence for the efficacy of this cephalosporin to be insufficient and its cost too high compared to other treatment options.

Cefuroxime axetil is one of the medications recommended by the GDS for pregnant women who are allergic to penicillin, but dosage schedules are not specified.

Only five of the seven sources selected recommend cefuroxime axetil. IDSA presents it as a first-line treatment for children under age 8, at a dosage of 30 mg/kg/day (divided into two doses, with a maximum of 500 mg/dose), while the GDS recommends it as an alternate treatment at the same dosage. The CPS and 2018 *Red Book* recommend a dosage of 30 mg/kg/day, divided into two doses and with a maximum of 1 g/day. ILADS recommends treating localized erythema migrans with 20 to 30 mg/kg/day cefuroxime axetil, up to a maximum of 1,000 mg/day.

Once again, recommended treatment durations are the same as those for adults: 14 days (14–21 days) for IDSA, 14–21 days for the CPS, 10–14 days for the GDS, four to six weeks for ILADS, and 14 days according to the 2018 *Red Book*.

7.9.1.4. Macrolides

IDSA's and the GDS's CPGs are the only ones that recommend clarithromycin as a treatment option for patients with solitary erythema migrans. IDSA recommends a dosage of 500 mg BID for 14 to 21 days for individuals who cannot tolerate or should not take amoxicillin, doxycycline or cefuroxime axetil. However, the GDS CPG does not specify the dosage schedule.

Only IDSA considers erythromycin as a treatment option, recommending a dosage of 500 mg QID for 14 to 21 days. As with clarithromycin, it should be administered when amoxicillin, doxycycline and cefuroxime axetil cannot be. The GDS does not recommend it due to bacterial resistance and uncertainty about its resorption.

Azithromycin is recommended by all five CPGs as another treatment option for EM, but the recommended dosage schedules vary from one guide to another. IDSA considers this antibiotic, at a dosage of 500 mg for 7 to 10 days, to be an alternate treatment for patients who cannot tolerate or should not take amoxicillin, doxycycline or cefuroxime axetil. ILADS deems it an acceptable agent, particularly in Europe, at a dosage of 250 to 500 mg QD for at least 21 days, while the GDS recommends a dosage of 250 mg BID for 5 to 10 days. According to HAS, azithromycin is best seen as a second-line treatment given for a 7-day course: 1,000 mg the first day and 500 mg thereafter. NICE recommends azithromycin as a second choice after amoxicillin, at a dosage of 500 mg for 17 days, and justifies the longer treatment duration by pointing to azithromycin's bacteriostatic properties. But, because of azithromycin's long half-life, the recommended treatment course is still shorter than that for doxycycline and beta-lactam antibiotics.

Clarithromycin is recommended only by IDSA (7.5 mg/kg BID, up to a maximum 500 mg/dose x 14–21 days) and the GDS (15 mg/kg/day, divided into two doses, but with no treatment duration specified).

Only IDSA recommends erythromycin (12.5 mg/kg/day QID, up to a maximum 500 mg/dose), for a duration of 14 to 21 days.

The five CPGs and the 2018 *Red Book* all recommend azithromycin as another treatment option, either as a second-line treatment or for patients who cannot take beta-lactams or doxycycline; only the Canadian Paediatric Society does not recommend it. Dosages differ from one guide to another. IDSA recommends 10 mg/kg/day (max. 500 mg/day) for 7 to 10 days. ILADS suggests giving 10 mg/kg the first day and 5–10 mg/kg/day (maximum dose of 500 mg/day) thereafter for at least 21 days. The GDS recommends treatment courses of 5 to 10 days of azithromycin at a dose of 5–10 mg/kg/day, while HAS recommends a single daily dose of 20 mg/kg (up to a 500 mg maximum dose) for 7 days. The 2018 *Red Book* recommends a dosage of 10 mg/kg/day once daily for 7 days. Lastly, NICE recommends azithromycin as a first choice for children under age 9 and who weigh 50 kg or less, at a dosage of 10 mg/kg/day, and as a second choice for children 9 and older: a dosage of 10 mg/kg/day for children aged 9 to 12 who weigh 50 kg or less, and 500 mg/day for children 12 and older.

HAS suggests azithromycin as a second-line treatment for pregnant and breastfeeding women, starting in the second trimester of pregnancy, at a dosage of 1,000 mg the first day and 500 mg/day thereafter for 6 or 9 days. The total treatment duration is 7 days for solitary erythema migrans and 10 days for multiple erythema migrans. In cases of penicillin allergies, the GDS also recommends treatment with oral azithromycin.

7.9.2. Contextual and experiential data

Table 11 outlines the adverse effects most commonly reported in Canadian monographs for the antibiotics recommended by learned societies and health care technology assessment agencies.

Table 11 Most frequent adverse effects of antibiotics reported in monographs

Antibiotic	Most Frequent Adverse Effects
Doxycycline (tetracycline)	Anorexia, epigastric discomfort, nausea, vomiting, diarrhea, soft stools, vulvovaginal candidosis, photosensitivity
Amoxicillin	Diarrhea (0.5%–5% of adults; up to 20% of children), nausea, vomiting (2%), skin eruptions (≤ 10%)
Penicillin	Diarrhea, nausea, vomiting, skin eruptions (non-exhaustive list)
Cefuroxime axetil	Diarrhea (3.7%–11%), decrease in hemoglobin and hematocrit levels (10%), eosinophilia (7%), increased hepatic enzyme activity (4%), mild or moderate pain at the IM injection site (≤ 95%), thrombophlebitis (2%)
Ceftriaxone IV	Eosinophilia (6%), thrombocytosis (5%), leukopenia (2%), increased AST and ALT (4%–5%), skin eruptions (2%), transient diarrhea (3%), pain (IM injection) (9.4%), induration, insensitivity (IM/IV) (1–2%)
Cefotaxime IV	Colitis, diarrhea, nausea and vomiting (1.7%); skin eruption, pruritis, fever (1.8%); inflammation at the injection site after administration by IV; pain, induration and sensitivity post-IM injection (5%).
Azithromycin	Treatments with multiple doses (oral route, for three to five days): diarrhea / soft stools (4%–5%), abdominal pain (2%–3%), vomiting (1%) and nausea (3%–4%)
Clarithromycin	Diarrhea, taste perversion and nausea
Erythromycin	Abdominal cramps and discomfort, nausea, vomiting, diarrhea and anorexia

Acronyms: ALT: alanine aminotransferase; AST: aspartate aminotransferase; IM: intramuscular; IV: intravenous.

As a general rule, the clinicians and experts consulted follow IDSA's recommendations in treating patients with solitary erythema migrans and no other signs or symptoms of the disseminated stage, and they therefore prefer the oral route of administration.

Doxycycline—100 mg BID for adults, and 4.4 mg/kg/day divided into two doses (maximum 100 mg/dose) for children, as per the 2018 *Red Book* recommendation—for a 10-day duration (range of 10 to 14 days) is the generally accepted first-line treatment.

Furthermore, in cases of atypical erythema migrans (diagnostic less obvious than the typical form) in a high-risk area, committee members explained that they prefer to treat patients despite the risk of overtreatment. They are of the opinion that there are undertreated cases of atypical erythema migrans in high-risk geographic areas.

Amoxicillin is also among the treatment choices of the clinician members of the advisory committee, administered for 14 days (range of 14 to 21 days) as per IDSA's recommendation.

None of the members prescribe probenecid along with amoxicillin, despite the several scientific studies of this drug combination. In their experience, amoxicillin on its own is sufficiently effective, and they maintain that there is no reason to prescribe a higher dose than that recommended by IDSA and the *Red Book*, even though some learned societies and assessment agencies, such as NICE and HAS, recommend doing so.

Given that the members of the advisory committee follow IDSA's directives, which recommend cefuroxime axetil as a treatment choice, the clinician members also choose this antibiotic to treat erythema migrans for 14 days, but they rarely prescribe it.

Members of the advisory committee tend not to prescribe macrolides to treat erythema migrans because they are deemed less effective than the other recommended antibiotics. None of the members of the advisory committee had ever prescribed phenoxymethylpenicillin or minocycline to treat erythema migrans.

According to the members of the advisory committee, severe adverse effects following the administration of doxycycline, amoxicillin or cefuroxime axetil are rare. Tetracyclines prescribed for an extended period may cause headaches, high blood pressure and visual impairment. Doxycycline may also induce a photosensitivity reaction, which constitutes a contraindication with respect to its re-administration.

Prescribing cefuroxime axetil to children is an issue that needs to be examined: the bad taste of the oral suspension makes administering it difficult, thus making the problem of missed doses more common and compromising the medication's efficacy in treating the disease in children who are unable to swallow a pill, according to practising pediatricians on the advisory committee.

According to the monograph and most of the sources consulted, doxycycline is contraindicated for pregnant or breastfeeding women, and for children younger than 8. However, based on the fact that tetracycline can cross the blood-brain barrier and conceal anaplasmosis (a co--infection transmitted by ticks), and supported by the available scientific data on its safety (see supporting report for PEP tools [INESSS, 2019b]), most committee members agreed that this medication could be suggested as a first-line treatment for erythema migrans in children under 8 and breastfeeding women, but only after an informed discussion between the clinician and the patient or the child's parent (or guardian). Doxycycline remains contraindicated for the treatment of Lyme disease in pregnant women, according to the clinicians consulted.

Key Takeaways

- All of the selected CPGs recommend 100 mg doxycycline PO BID as a first-line treatment for solitary erythema migrans. Treatment durations vary from two to three weeks—according to IDSA and the GDS, 10 days may be sufficient, but ILADS recommends four to six weeks.
- According to most CPGs, amoxicillin PO could also be given as a first-line treatment for solitary erythema migrans, but dosages vary from 500 mg to 1 g TID depending on the continent. As for treatment duration, three of the five CPGs recommend 14 days of amoxicillin (up to 21 days for IDSA), while NICE suggests 21 days. ILADS

recommends administering the antibiotic for four to six weeks. No CPG recommends a combination of amoxicillin and probenecid.

- Only IDSA, ILADS and the GDS recommend cefuroxime axetil to treat localized erythema migrans. While the recommended dose is consistent (500 mg BID), treatment duration varies from two to six weeks from one CPG to another.
- Only some of the CPGs recommend macrolides (clarithromycin, erythromycin and azithromycin), and generally only as an alternate treatment for patients who are intolerant to amoxicillin, doxycycline and cefuroxime axetil or for whom their use is contraindicated.
- As a general rule, the CPGs recommend the same treatments for pregnant or breastfeeding women as for all other women, taking into account possible contraindications (e.g., doxycycline), pregnancy trimester and breastfeeding constraints.
- The recommendations for treating erythema migrans in children are similar to those for adults, except for doxycycline, which is generally contraindicated for children under age 8 or 9. Dosages were modified to reflect this, but treatment durations are the same as for adults.
- According to the stakeholders consulted, doxycycline for 10 to 14 days is the preferred treatment option for solitary erythema migrans. The medication is also an option for children under 8 and breastfeeding women, but only after an informed discussion between the clinician and the patient or the child's parent (or guardian). Amoxicillin and cefuroxime are regarded as alternate treatment options.

7.10. Choice of Antibiotic Treatment – Indications for Use in the Treatment of Multiple Erythema Migrans Associated with Lyme Disease

7.10.1. Clinical practice guides and guidelines

The IDSA, SAD, GDS and NICE CPGs, as well as the 2018 *Red Book*, address the treatment of erythema migrans with and without general systemic symptoms [HAS, 2018; Kimberlin et al., 2018; NICE, 2018; Hofmann et al., 2017; Wormser et al., 2006]. These documents generally express a preference for administering antibiotics orally. None of the CPGs recommend parenteral antibiotics to treat multiple erythema migrans, whether or not there are systemic symptoms.

In short, in the CPGs that also address solitary erythema migrans, the antibiotic dosage—whether of doxycycline, amoxicillin, cefuroxime axetil or macrolides—stays the same for both adults and children, but the durations differ. IDSA does not distinguish between solitary and multiple erythema migrans, recommending a 14-day treatment course except in the case of macrolides. A duration of 7 to 10 days is advised for azithromycin and 14 to 21 days for the other antibiotics in the same class. NICE also does not distinguish between solitary and multiple erythema migrans, but it does mention the presence or absence of general systemic symptoms. The recommended duration of doxycycline- or amoxicillin-based antibiotic

treatment is 21 days, whereas it is 17 days for azithromycin. NICE recommends doxycycline as the first-line treatment, while amoxicillin is the first alternate treatment followed by azithromycin. The GDS does differentiate between solitary erythema migrans (with or without general systemic symptoms) and multiple erythema migrans. While a duration of 10 to 14 days is recommended to treat solitary erythema migrans, the recommended duration increases to 14 to 21 days—depending on the severity of the symptoms—for multiple erythema migrans or if there are general systemic symptoms. Azithromycin treatment duration is 5 to 10 days, as for solitary erythema migrans. The GDS does not distinguish between antibiotics, and seems to recommend all of them as first-line treatment options. HAS, on the other hand, has published specific recommendations for multiple erythema migrans, without specifying the presence or absence of general systemic symptoms. The recommended duration is 21 days, except in the case of azithromycin, for which it is 10 days. HAS considers azithromycin to be an alternate treatment when neither doxycycline nor amoxicillin can be administered—terminology used by HAS = second-line.

None of the CPGs provide information on a second-line antibiotic treatment after the failure of the first course of antibiotics prescribed to treat multiple erythema migrans with or without systemic symptoms.

The recommendations on antibiotic treatments contained in the various CPGs are available in Appendix X of this report's supplementary appendices document.

7.10.2. Contextual and experiential data

The clinicians and experts consulted typically follow IDSA's recommendations for treating patients with multiple erythema migrans, preferring an oral route of administration except in cases of neurological damage requiring IV treatment. In such cases, the approach is the same as that used to treat neuroborreliosis.

Doxycycline (100 mg BID for adults; 4.4 mg/kg/day divided into two doses—maximum 100 mg/dose—for children) will generally be considered as a first-line treatment for a duration of 14 days (range of 14 to 21 days). As is the case for solitary erythema migrans, this tetracycline can be administered to children under age 8 and to breastfeeding women, but only after an informed discussion between the clinician and the patient or the child's parent (or guardian).

Key Takeaways

- According to the different CPGs and the 2018 *Red Book*, treatment of multiple erythema migrans generally lasts between 10 and 21 days, except in the case of macrolides.
- In first-line treatment, oral antibiotics are preferred.
- None of the CPGs found provide information on a second-line antibiotic treatment after the failure of the first course of antibiotics prescribed to treat multiple erythema migrans with or without general systemic symptoms.
- Doxycycline for 14 days (range of 14 to 21 days) is the preferred treatment option for multiple erythema migrans. The medication is also an option for children under 8 and breastfeeding women, but only after an informed discussion between the clinician and

the patient or the child's parent (or guardian). Amoxicillin and cefuroxime are regarded as alternate treatment options.

7.10.3. Choice of antibiotic treatment – Indications for use in the treatment of general systemic symptoms

7.10.3.1. Clinical practice guides and guidelines

The NICE CPG is the only one that recommends treatment when a patient's only manifestation of Lyme disease is systemic symptoms, on the condition that the patient has undergone serologic testing that came back positive for Lyme. The recommended duration is the same as for erythema migrans: 21 days of a first-line PO treatment. NICE made no recommendations applicable to systemic symptoms. In the event of persistent symptoms or a relapse, it is recommended to assess the possibility of other etiological conditions, a new infection or the failure of the antibiotic treatment. A second course of antibiotics may be considered if the first seems to have failed [NICE, 2018a].

7.10.4. Contextual and experiential data

According to the members of the advisory committee, the mere presence of general systemic symptoms without any other manifestations compatible with Lyme disease does not provide grounds for starting a patient on antibiotics, unless a specialist advises otherwise—for example, in a region where ticks are endemic. However, committee members are of the opinion that a treatment course of 14 to 21 days could be prescribed if the symptoms are accompanied by typical erythema migrans, since this would indicate that the bacteria had disseminated.

Key Takeaways

- The NICE CPG is the only one that recommends antibiotic treatment for patients whose only manifestation of Lyme disease is general systemic symptoms, conditional on a positive serology result for Lyme disease.
- According to the stakeholders consulted, the mere presence of general systemic symptoms without any other manifestations compatible with Lyme disease does not provide grounds for starting a patient on antibiotics, unless a specialist advises otherwise and all other possible clinical conditions have been ruled out.
- However, a treatment course of 14 to 21 days could be prescribed when there are signs that the bacteria have disseminated, i.e., when general systemic symptoms are accompanied by one or more symptoms compatible with Lyme disease.

7.11. Choice of Antibiotic Treatment – Indications for use in the Treatment of Neuroborreliosis

7.11.1. Clinical practice guides and guidelines

The antibiotics considered in the selected CPGs for treating neuroborreliosis are in general the same as those recommended to treat other clinical manifestations, with variations regarding

treatment order (first-line or second-line) and duration. The CPGs do, however, differ on whether to administer treatment orally or by IV, depending on the specific manifestations and whether the neuroborreliosis is in the early or late stage.

IDSA recommends oral antibiotics for 14 to 21 days as first-line treatment in both adults and children to treat cranial nerve palsy. If, however, there are signs of meningeal disease or radiculitis, intravenous antibiotics are preferred, for a treatment course of 10 to 28 days.

The American Academy of Neurology's CPG recommends a 14-day oral treatment course for cranial mononeuritis and mild radiculoneuritis, but the authors note that the data used were obtained from durations ranging from 10 to 28 days. Doxycycline is the preferred treatment barring any contraindications, in which case amoxicillin or cefuroxime axetil are prescribed. IV treatment is recommended in cases of meningitis (particularly if the condition is severe—otherwise, oral doxycycline is also an option), central nervous system symptoms (particularly if they are severe—otherwise, oral doxycycline is also an option), severe radiculopathy, encephalopathy and encephalomyelitis. The American Academy of Neurology recommends the same antibiotics and dosages as IDSA.

NICE opts for oral antibiotics as a first-line treatment in both adults and children in cases of peripheral nervous system symptoms, and for a 21-day IV course of ceftriaxone (2 g BID or 4 g QD) as a first-line treatment of central nervous system symptoms, with oral doxycycline (200 mg BID or 400 mg QD) for 21 days as the primary alternative to ceftriaxone in such cases.

HAS's and the GDN's recommendations hinge on whether the neuroborreliosis is in the early or late stage, and do not distinguish between particular nervous system manifestations nor consider their location. For early-stage disease, which is more common in North America, the GDN recommends a 14-day treatment duration, while HAS recommends 21 days, whether or not there are meningeal symptoms, but does not specify the preferred route of administration. Both agencies recommend oral doxycycline and ceftriaxone IV, and the GDN also recommends cefotaxime IV and penicillin G IV. HAS adds oral amoxicillin as a treatment option for neuroborreliosis in children.

The treatment duration for late-stage neuroborreliosis, specific to European *Borrelia* strains, is longer than for early-stage disease: HAS recommends 28 days, while the GDN recommends 14 to 21 days. Moreover, according to HAS, the first-line treatment of the late stage should be intravenous antibiotics, while oral antibiotics are considered an alternate second-line treatment rather than an option in case of failure of the first-line treatment.

The 2018 *Red Book* issues recommendations only for isolated facial palsy and meningitis. It suggests treating facial palsy with doxycycline (4.4 mg/kg/day PO, in two doses, maximum 200 mg/day) for 14 days, and specifies that corticosteroids should not be given for this clinical manifestation. As for amoxicillin, there are no studies on its use in children with facial palsy. The *Red Book* also explains that treatment prevents the development of late manifestations but does not help resolve facial palsy. Lastly, the 2018 *Red Book* recommends doxycycline (4.4 mg/kg/day PO, in one or two doses, maximum 200 mg/day) or ceftriaxone sodium (50–75 mg/kg IV once daily, maximum 2 g/day) for 14 days to treat meningitis [Kimberlin et al., 2018].

The recommendations regarding antibiotics issued in the documents consulted are available at Appendix X of this report's supplementary appendices document.

7.11.2. Contextual and experiential data

The members of the advisory committee are of the opinion that oral administration is appropriate for peripheral nervous system disease—for example, in cases of cranial mononeuritis or multiple mononeuritis, plexopathy or radiculopathy, while IV treatment is best for cases involving the central nervous system, including optic neuritis and meningeal disease.

IDSA recommends parenteral administration in cases of radiculopathy, which is a peripheral nerve disease, pointing to the prevalent physio-pathological rationale according to which root involvement is due to the presence of bacteria in the CSF. Another hypothesis is that the root involvement is due to vasculitis, without bacteria having disseminated into the CSF. Most of the specialists consulted had never prescribed cefotaxime or penicillin G to treat neuroborreliosis in cases in which IV treatment is indicated.

Doxycycline (100 mg BID for adults; 4.4 mg/kg/day divided into two doses and a maximum of 100 mg/dose for children) remains the primary first-line treatment choice for adults (other than pregnant women) as well as the pediatric population. However, clinicians should only resort to this treatment for children under age 8 and breastfeeding women after an informed discussion between the clinician and the patient or the child's parent (or guardian). Amoxicillin and cefuroxime are also proposed as alternate treatment options. Dosages and durations of oral antibiotics are the same as for other symptoms of the early disseminated stage.

Most of the members of the advisory committee were of the opinion that for central nervous system or meningeal symptoms, 2,000 mg QD of ceftriaxone for adults and 75 to 100 mg/kg/day (in a single dose—maximum 2 g) for children is preferable, given that this dosage is used to treat bacterial meningitis. Other treatment options include penicillin G and cefotaxime. Cefotaxime should be given at the same dosage as when treating bacterial meningitis: 225–300 mg/kg/day (divided into three or four doses; maximum 12 g/day) as recommended in the CPGs specialized in the treatment of this disease. The duration of IV treatments is 14 days, with a range of 10 to 28 days for both adults and children, as per IDSA's recommendation.

The advisory committee members also agreed that it is preferable not to administer corticosteroids in cases of facial palsy due to Lyme disease; in practice, however, such cases are often misdiagnosed as Bell palsy and treated with steroids—Bell palsy is in fact a much more common etiology than Lyme disease for facial palsy. It is therefore important to strongly suspect LD in cases presenting with facial palsy—e.g., isolated palsy, other signs pointing to Lyme disease such as a heart block, concomitant arthritis, a history of erythema migrans, etc.—in order to avoid prescribing corticosteroids.

Key Takeaways

- Recommended treatment options depend on the clinical manifestations, according to some CPGs (IDSA and NICE), and on the neuroborreliosis stage—early or late—

according to others (HAS and the GDN). The 2018 *Red Book* issues recommendations only for isolated facial palsy and meningitis.

- Recommended treatment durations generally vary from 14 to 21 days.
- The selected documents differ in their recommendations of IV or oral routes of administration. IV antibiotics are considered as a first-line treatment by IDSA in cases of radicular or meningeal symptoms, while NICE recommends this option only if there is central nervous system involvement. The AAN recommends IV treatment if the meningeal or central nervous system symptoms are severe. The 2018 *Red Book* recommends it as one treatment option in cases of meningitis. Oral antibiotics are first-line treatment options for patients with cranial nerve palsy, according to IDSA and the 2018 *Red Book*, or peripheral nervous system symptoms, according to NICE. When oral treatment is indicated, doxycycline is always the first choice barring any contraindications.
- These two types of treatment (IV and PO) are recommended by the 2018 *Red Book* in cases of meningitis and by HAS and the GDN for early-stage neuroborreliosis, regardless of whether or not there is meningeal involvement.
- The 2018 *Red Book* recommends not administering corticosteroids to treat cranial nerve palsy.
- According to the stakeholders consulted, doxycycline is the first treatment choice for both adults (except pregnant women) and children when oral administration is indicated. However, the clinician must first have an informed discussion with breastfeeding patients or with the parent (or guardian) of patients under age 8 before considering it as a treatment option. When IV treatment is required, ceftriaxone is the top first-line choice.

7.12. Choice of Antibiotic Treatment – Indications for Use in the Treatment of Lyme Carditis

7.12.1. Clinical practice guides and guidelines

The antibiotics considered in the selected CPGs for the treatment of Lyme carditis are the same as those recommended to treat other clinical manifestations, with variations regarding treatment order (first-line or second-line) and duration.

For example, parenteral administration is recommended as a first-line treatment for both children and adults when the patient is hospitalized or hemodynamically unstable. All of the documents mention that the treatment can then be continued via oral administration in an outpatient setting.

NICE recommends oral doxycycline as a first-line treatment for hemodynamically stable patients over the age of 12 and patients between 9 and 12 years of age independently of their hemodynamical status. In those cases, ceftriaxone IV is the first alternate option while it is the first-line treatment recommended for hemodynamically unstable patients over the age of 12 as well as children under 9, with no alternate treatment suggested.

HAS emphasizes that if the treatment can be administered in an outpatient setting, oral doxycycline or amoxicillin are the top choices. IDSA also recommends oral administration for patients who are not hospitalized.

HAS and NICE recommend a treatment duration of 21 days, while IDSA recommends a range of 14 to 21 days.

NICE is the only agency that specifies in its CPG that azithromycin should be contraindicated for patients with a heart anomaly due to the drug's effect on QT interval prolongation. NICE also points out that clinicians treating patients under 18 should consider seeking the opinion of a specialist to confirm a Lyme carditis diagnosis and ensure optimal treatment.

The 2018 *Red Book* recommends oral antibiotics (same medication and dosage as for solitary erythema migrans) for 14 days for patients with carditis or an AV block who can be treated in an outpatient clinic. However, patients whose condition (e.g., a high-grade AV block) requires them to be hospitalized must first be treated by parenteral route (50-75 mg/kg ceftriaxone IV, once daily, maximum 2 g/day), and once they are stabilized and can leave the hospital, the treatment course can be continued with oral antibiotics for a total duration of 14 to 21 days [Kimberlin et al., 2018].

The recommendations regarding antibiotics issued in the documents consulted are available at Appendix X of this report's supplementary appendices document.

7.12.2. Contextual and experiential data

The clinician members of the advisory committee have little experience with Lyme carditis, so they follow most of IDSA's recommendations in treating their patients.

Orally administered treatments are prescribed for first-degree atrioventricular blocks with a PR interval less than 300 ms. Doxycycline is recommended as a first-line treatment for both adults (except for pregnant women) and children, but only after an informed discussion with the patient or parent (or guardian) in the case of children under age 8 and breastfeeding women. The dosages are the same as those for other early disseminated stage symptoms.

The IV route of administration is preferred for high-degree atrioventricular blocks (first degree with a PR interval longer than 300 ms, or second or third degree) and cases of myocarditis and pericarditis, with or without block. Ceftriaxone is the first-line treatment, while cefotaxime and penicillin G are alternate treatments. Members of the advisory committee agree that 75 to 100 mg/kg/day is an appropriate dosage for children (in a single dose, with a maximum 2 g/day), since this is the dosage they use to treat certain neurological symptoms and arthritis relapses with ceftriaxone—IDSA recommends 50 to 75 mg/kg/day in a single dose, up to a maximum of 2 g.

Whether IV or PO, treatment should be prescribed for 14 days or, in severe cases and out of clinical precaution, up to 21 days.

Key Takeaways

- The three CPGs and the 2018 *Red Book* recommend parenteral administration as first-line treatment in both adults and children when the patient is hospitalized or hemodynamically unstable.
- Oral antibiotics may be considered if outpatient treatment is possible or to complete a treatment course begun with parenteral administration, once the patient is stabilized and can leave the hospital.
- The recommended antibiotics are the same as those prescribed for other clinical manifestations of Lyme disease, and the appropriate treatment duration to treat Lyme carditis is 14 to 21 days.
- Azithromycin should not be prescribed for patients with a cardiac malformation (QT interval prolongation).
- For Lyme carditis with a high-degree atrioventricular block (first degree with a PR interval > 300 ms, or second or third degree), or myocarditis or pericarditis (with or without block), the stakeholders consulted recommend ceftriaxone IV for 14 to 21 days—maximum duration out of clinical precaution and as warranted by the severity of the symptoms. Oral antibiotics may be administered in cases of first-degree heart block with a PR interval < 300 ms or, once the patient is stabilized, to complete an IV treatment course. Doxycycline could also be considered as a first-line treatment for children under age 8 and breastfeeding women after an informed discussion between the clinician and the patient or the child's parent (or guardian).

7.13. Choice of Antibiotic Treatment – Indications for Use in the Treatment of Non-Neurological Ocular Impairment

7.13.1. Clinical practice guides and guidelines

HAS and NICE advise seeking the opinion of an ophthalmologist when this manifestation is observed.

While NICE refrains from treatment recommendations for this isolated condition, HAS mentions that if antibiotic treatment is required, the same medications recommended for neuroborreliosis could be considered, but the authors note that, as of yet, no consensus protocol has been validated for ocular manifestations of Lyme disease.

7.13.2. Contextual and experiential data

The clinician members of the advisory committee have no experience with ocular disorders associated with Lyme disease. They agree that in such cases, it would be best to refer the patient to an ophthalmologist, who could decide—depending on the degree to which they suspect Lyme disease—whether or not to begin antibiotics.

Key Takeaway

The decision to begin treatment in cases of ocular disorders associated with non-neurological Lyme disease should be made by an ophthalmologist.

7.14. Choice of Antibiotic Treatment – Indications for Use in the Treatment of Lyme Arthritis (Active Phase)

7.14.1. Clinical practice guides and guidelines

The oral antibiotics considered in the reference books and selected documents for the treatment of Lyme arthritis are in general the same as those recommended to treat EM—namely, doxycycline, amoxicillin, cefuroxime axetil and macrolides—at the same dosages but for different durations.

As a general rule, the oral administration of antibiotics is preferred over the parenteral route of administration when there are no neurological symptoms, even in cases of relapse.

According to the GKJR and the DGKJ, parenteral treatment should be offered if symptoms persist for several weeks after a first course of oral antibiotics, while IDSA recommends the parenteral route of administration in cases of clinical manifestations of neurological or cardiac involvement, or if oral antibiotics are contraindicated. HAS recommends IV treatment in cases of contraindications to doxycycline (ceftriaxone for pregnant women or children under age 9), while NICE adds that IV administration is also indicated in cases of contraindications to oral amoxicillin.

Unlike NICE, which recommends oral doxycycline as a first-line treatment and oral amoxicillin as an alternate possibility, IDSA does not take a clear position on the choice of first-line treatment. NICE does not consider cefuroxime axetil to be an appropriate treatment option, as there is no clinical evidence supporting its use in this context and it is more expensive than other oral antibiotics. Doxycycline is the only oral antibiotic recommended by HAS for treating Lyme arthritis, unless it is contraindicated—for example, for pregnant women and children under 9.

The GKJR and DGKJ recommend oral doxycycline and amoxicillin to treat Lyme arthritis, at the same dosages as those indicated by IDSA, but for 30 days. Macrolides are also an option for patients with a history of allergies to these two antibiotics.

The 2018 *Red Book* recommends oral doxycycline, amoxicillin and cefuroxime axetil. These are the same antibiotics recommended for early disseminated Lyme disease, but the recommended treatment duration is longer for Lyme arthritis. The *Red Book* does, however, recommend oral antibiotics other than doxycycline for children under 8, due to very low data on the safety of administering doxycycline to young children for longer than 21 days. The Canadian Paediatric Society recommends the same oral antibiotics as the 2018 *Red Book*.

Ceftriaxone is among the IV treatments recommended for adults by IDSA, HAS (for pregnant women) and NICE, at a dosage of 2 g QD. NICE specifies that it is a second-line treatment chiefly suited to patients with neurological or cardiac signs and symptoms, or in cases of contraindications to doxycycline and amoxicillin. IDSA also recommends cefotaxime (2 g TID) and penicillin G (18–24 million U per day, every 4 hours).

The same IV antibiotics are recommended to treat Lyme arthritis in children, but at different dosages. IDSA recommends 50–75 mg/kg/day ceftriaxone in a single dose (max. 2 g), 150–200 mg/kg/day cefotaxime divided into three or four doses (max. 6 g/day) and 200,000–

400,000 U/kg/day penicillin G every 4 hours (max. 18–24 million U/day). The GKJR–DGKJ also recommends these three antibiotics, at the following dosages: 50 mg/kg QD ceftriaxone (max. 2 g); six daily doses (dosage not indicated) cefotaxime; 50 mg QD penicillin G (max. 2 g/day). HAS and NICE, on the other hand, recommend only ceftriaxone for children weighing less than 50 kg; NICE recommends a dosage of 80 mg/kg/day, while HAS recommends 100 mg/kg/day (max. 2 g/day).

Despite the evidence of penicillin G's efficacy in treating Lyme arthritis, NICE does not recommend it because the injection is painful and several daily injections are required, as opposed to a single daily injection of ceftriaxone.

As for treatment duration, IDSA, HAS, NICE, the 2018 *Red Book* and the Canadian Paediatric Society recommend a 28-day treatment course of both oral and IV antibiotics for adults and children.

The GKJR and DGKJ CPGs differ from the others in their recommendation of parenteral antibiotic treatment (ceftriaxone, cefotaxime and penicillin G) of a shorter duration: 14 days for children with Lyme arthritis. Although the guide does not mention that this option applies to relapse after a first course of oral antibiotics, the authors do state that if arthritis symptoms persist for several weeks after an antibiotic treatment, another treatment course should be given and that at least one of the two treatments offered should be with an IV antibiotic.

According to the GKJR and DGKJ, non-steroidal anti-inflammatory drugs (NSAIDs) could be used only to complete an antibiotic treatment course, but not concomitantly; the same holds true for physiotherapy and a cold compress applied to the affected area. IDSA recommends NSAIDs before undertaking a new antibiotic treatment in cases of persistent or returning symptoms (e.g., joint swelling) after a first course of antibiotics. The 2018 *Red Book* recommends NSAIDs only in cases of persistent synovitis.

IDSA advises against intra-articular corticosteroid injections, while HAS recommends waiting at least three weeks after the end of an antibiotic treatment before trying this course of action.

The recommendations regarding antibiotic treatment and supporting treatments that are made in the selected documents are available in Appendix X of this report's supplementary appendices document.

7.14.2. Contextual and experiential data

The clinician members of the advisory committee generally follow IDSA's recommendations to treat patients (adults and children) with Lyme arthritis. The oral administration of medications, typically for 28 days, is favoured when no other symptoms are present or suspected. Ceftriaxone IV is only prescribed for patients who have both neurological and joint manifestations. Most of the specialists consulted have never prescribed cefotaxime or penicillin G in this context, while ceftriaxone is generally administered by IV.

Since doxycycline is contraindicated for children under age 8, amoxicillin is the first choice, while ceftriaxone (but not cefuroxime axetil) is another treatment option if amoxicillin fails. The use of a cefuroxime axetil oral suspension presents the same problem as explained above in the case of children who are unable to swallow a pill.

Even though the 2018 *Red Book* recommends doxycycline for treating Lyme arthritis in children under 8, the members of the advisory committee are not comfortable prescribing this tetracycline as a first-line treatment for this population because of the lack of reliable data on treatment durations longer than 21 days.

According to the *Red Book*, prolonged doxycycline treatment is appropriate in cases of severe infection, if there are complications or risk of death. It is also recommended for the treatment of other infectious diseases in children under 8, including Q fever, the plague, tularemia, typhus, rickettsial diseases transmitted by ticks, and anthrax exposure. Recommended durations range from 5 to 60 days depending on the diagnosis (see the supporting report for PEP tools [INESSS, 2019b]). Committee members explained that several steps must be taken before considering prescribing doxycycline for 28 days: for example, performing provocative testing to screen for an amoxicillin allergy; administering cefuroxime axetil with something else to mask its bitter taste; considering a lengthy course of doxycycline on a case-by-case basis, but not as a general treatment approach. However, committee members agree that doxycycline is a good treatment option for patients—including children under 8 and breastfeeding women—with a history of severe allergies to penicillin drugs.

In cases of arthritis relapse, a second treatment will be recommended, with a duration of 28 days for antibiotics administered orally (doxycycline, amoxicillin and cefuroxime axetil; same dosages as for the first treatment) or 14 to 28 days for IV antibiotics. In such cases, ceftriaxone (2 g QD for adults; 75–100 mg/kg/day for children) will be given as first-line treatment, with cefotaxime (2 g TID for adults; 150–200 mg/kg/day for children) and penicillin G IV (18–24 million units every 4 hours for adults; 200,000–400,000 U/kg/day for children) as second-line treatment options.

Key Takeaways

- Oral administration is preferred for treating Lyme arthritis, and the drugs and dosages are generally the same as those recommended to treat EM, but treatment duration is longer (28 to 30 days). HAS is the only agency that recommends only doxycycline for oral antibiotic treatments.
- IV is the preferred route of administration in cases of contraindications, neurological or heart co-manifestations, or symptoms that persist for several weeks after a first course of antibiotics. Ceftriaxone is the IV antibiotic most often recommended in the documents consulted. IDSA and the GKJR-DGKJ also suggest cefotaxime and penicillin G to treat Lyme arthritis. All sources recommend a 28-day IV treatment course, except the GKJR-DGKJ, which suggests a duration of 14 days.
- According to the stakeholders consulted, IDSA's recommendations are generally followed, with oral doxycycline being the top first-line treatment choice unless there are any contraindications, in which case amoxicillin is recommended.
- However, for patients who have had a previous severe allergic reaction to beta-lactams, doxycycline could be considered for children under 8 or breastfeeding women following an informed discussion with the patient or the child's parent (or guardian).

- Ceftriaxone IV is only prescribed for patients who have neurological manifestations in addition to joint symptoms. Most of the specialists consulted have never prescribed cefotaxime or penicillin G in this context, while ceftriaxone is generally administered by IV.
- Arthritis relapses can be treated with a second, 28-day course of oral antibiotics or a shorter course (14 to 28 days) of IV antibiotics, using the same medications as the initial treatment.

7.15. Choice of Antibiotic Treatment – Indications for Use in the Treatment of Lyme Arthritis – Persistent Symptoms

7.15.1. Clinical practice guides and guidelines

All of the documents that address persistent symptoms in the context of Lyme arthritis define the situation as follows: patients who continue to have symptoms several weeks after two courses of oral or parenteral antibiotic treatment and who show no evidence of the presence of *B. burgdorferi* deoxyribonucleic acid (DNA) in the synovial fluid, as measured by a PCR test.

In such cases, according to HAS, an intra-articular corticosteroid injection could be done on the advice of a specialist. The GKJR and the DGKJ mention that this treatment, followed by methotrexate, a disease-modifying anti-rheumatic drug (DMARD), should be administered by a rheumatologist. IDSA advises the same approach and specifies that the objective is to treat the symptoms and not the infection, which is resolved with antibiotic treatment. If symptoms persist in this context, IDSA recommends NSAIDs, intra-articular corticosteroid injections or DMARDs such as hydroxychloroquine, if recommended by a rheumatologist. If the persistent symptoms are accompanied by pain or if they limit the patient's daily activities, it is suggested that arthroscopic synovectomy could reduce the duration of inflammation of the affected joints.

Only HAS specifically advises against the use of oral corticosteroids. The other documents do not address this option.

7.15.2. Contextual and experiential data

The clinician members of the committee recommend a second course of antibiotics for 28 days if Lyme arthritis symptoms persist. The infection will be deemed resolved after two antibiotic treatments (maximum number of treatments), but if a patient continues to exhibit symptoms, intra-articular corticosteroid injections will be considered.

One patient partner was treated with intra-articular corticosteroid injections, and experienced relief from pain. The physicians following the patient are considering prescribing methotrexate and a synovectomy.

Key Takeaways

- A patient is deemed to have persistent symptoms if the symptoms are still present after a first antibiotic treatment course against Lyme disease.
- None of the CPGs recommend an additional antibiotic treatment (beyond the first two courses) or a treatment of a longer duration.

- The documents that published clinical recommendations do not provide detailed descriptions of the treatment of persistent post-treatment symptoms, which is a clear reflection of the scientific shortcomings in this area of research.
- According to the members of the advisory committee, no more than two treatments should be administered to patients with persistent post-treatment symptoms, as it is thought that the *B. burgdorferi* infection should be eradicated by such dosages of antibiotics. However, the members acknowledge that the scientific data currently available do not allow researchers to reliably determine the cause of this persistence beyond the damage caused by the infection.
- The GKJR and the DGKJ suggest that NSAIDs could be used to complete an antibiotic treatment, but only at the end, not concomitantly; the same holds true for physiotherapy and cold compresses applied to the affected area in patients with Lyme arthritis.
- IDSA recommends NSAIDs before undertaking a new antibiotic treatment in cases of persistent or returning symptoms (e.g., joint swelling) after a first course of antibiotics.
- The use of corticosteroids should be avoided during an antibiotic treatment for Lyme arthritis, according to the stakeholders consulted. Non-steroidal anti-inflammatory drugs could be considered for ad hoc pain relief in conjunction with antibiotics.
- An intra-articular corticosteroid injection or a disease-modifying anti-rheumatic drug could be considered after an antibiotic treatment, according to the experts consulted. The opinion of a specialist or an experienced colleague should be sought in such cases.

7.16. Choice of Antibiotic Treatment – Cost

All of the antibiotics recommended and presented to treat manifestations of Lyme disease are on the RAMQ's List of Medications. Oral antibiotics are generally inexpensive, as generic versions are available. However, those administered by IV, such as ceftriaxone, are more expensive for patients.

For information purposes, tables 12 and 13 present the cost of treatments for those manifestations of erythema migrans and Lyme arthritis that require the shortest and longest treatment durations.

Table 12 Cost of erythema migrans treatments for adults

Medication	Dosage	Approximate RAMQ price	
		Unit price	Total cost of treatment
Doxycycline	200 mg QD x 10–14 days	$0.5860 (100 mg tablet)	$1.17 x 10 = $11.72 $1.17 x 14 = $16.41
Amoxicillin	500 mg TID x 14 days	$0.1750 (250 mg tablet)	$1.05 x 14 = $14.70

Cefuroxime axetil	500 mg BID x 14 days	$0.7236 (250 mg tablet)	$2.89 x 14 = $40.46
		$1.4336 (500 mg tablet)	$2.87 x 14 = $40.14
Ceftriaxone	2 g QD x 14 days	$24.13 (2 g)	$24.13 x 14 = $337.82
Azithromycin	500 mg QD x 7 days	$0.9410 (250 mg tablet)	$1.88 x 7 = $13.17
Clarithromycin	500 mg BID x 14 days	$1.6292 (500 mg tablet)	$3.38 x 14 = $47.38
Erythromycin	500 mg QID x 14 days	$0.1828 (250 mg tablet)	$1.46 x 14 = $20.00
		$0.2211 (250 mg capsule)	$1.77 x 14 = $25.00
		$0.8837 (500 mg tablet)	$3.53 x 14 = $49.00
Cefotaxime	2 g TID x 14 days	$16.6860 (2 g injection)	$50.06 x 14 = $700.81
Penicillin	18–24 million U/day x 14 days	$2.40 for a 1-million-U package	$43.20 x 14 = $604.80 $57.60 x 14 = $806.40

Acronyms and abbreviations: BID: *bis in die*: twice daily; QD: *quaque die*: once daily; mg: milligram; QID: *quater in die*: four times daily; TID: *ter in die*: three times daily; U: unit.

Table 13 Cost of Lyme arthritis treatments for adults

Medication	Dosage	Approximate RAMQ price	
		Unit price	Total cost of treatment
Doxycycline	200 mg QD x 28 days	$0.5860 (100 mg tablet)	$1.17 x 28 = $32.80
Amoxicillin	500 mg TID x 28 days	$0.1750 (250 mg tablet)	$1.05 x 28 = $29.40
Cefuroxime axetil	500 mg BID x 28 days	$0.7236 (250 mg tablet)	$2.89 x 28 = $81.00
		$1.4336 (500 mg tablet)	$2.87 x 28 = $80.30
Ceftriaxone	2 g QD x 28 days	$24.13 (2 g)	$24.13 x 28 = $675.64
Cefotaxime	2 g TID x 28 days	$16.6860 (2 g injection)	$50.06 x 28 = $1,401.62
Penicillin	18–24 million U/ day x 28 days	$2.40 for a 1-million-U package	$43.20 x 28 = $1,209.60 $57.60 x 28 = $1,612.80

Acronyms and abbreviations: BID: *bis in die*: twice daily; QD: *quaque die*: once daily; mg: milligram; QID: *quater in die*: four times daily; TID: *ter in die*: three times daily; U: unit.

7.17. Choice of Antibiotic Treatment – History of Allergic Reaction to Penicillin

7.17.1. Clinical practice guides and guidelines

The documents retained recommend cephalosporins or macrolides for patients with a penicillin allergy, but they do not take into account the severity of previous allergic reactions, the type of allergy or the risk of cross-reactions. Specifically, macrolides could be administered for the localized stage of Lyme disease if the patient has had a previous allergic reaction to beta-lactams and cannot take doxycycline.

7.17.2. Contextual and experiential data

In 2017, INESSS developed tools to help clinicians decide which beta-lactams to administer to patients who have had a previous allergic reaction to penicillin, based on the severity of the reaction, the type of allergy, how long ago the reaction occurred and the risk of cross-reactions. The members of the advisory committee who are familiar with these tools mentioned that an algorithm based on the INESSS recommendations but designed specifically for Lyme disease would be useful, especially for populations for which doxycycline is contraindicated. Macrolides should be considered for treating solitary erythema migrans only; other clinical manifestations of Lyme disease require a consultation with a specialist.

In cases of very severe previous reactions and when beta-lactams cannot be prescribed unless recommended by an allergist, some committee members consider azithromycin and clarithromycin to be the most appropriate macrolides, given that erythromycin's administration schedule—with its four daily doses—can be an obstacle to treatment compliance.

Doxycycline could be prescribed to children under age 8 or breastfeeding women who have arthritis and who have had a previous severe allergic reaction to beta-lactams, but only after an informed discussion between the clinician and the patient or the child's parent (or guardian). This option should be avoided entirely for pregnant women.

Key Takeaways

- The documents retained recommend cephalosporins or macrolides to treat some manifestations of Lyme disease in patients with allergies to penicillin, but they do not take into account the severity of previous allergic reactions, the type of allergy or the risk of cross-reactions.
- The stakeholders consulted mentioned that it would be useful to have a Lyme disease-specific version of the INESSS algorithm to help clinicians decide which antibiotic to prescribe for patients who have had a previous allergic reaction to penicillin.

7.18. Supportive Treatments to Relieve Symptoms

7.18.1. Clinical practice guides and guidelines

The documents analyzed did not make specific recommendations about the use of supportive treatments, except in the context of Lyme arthritis. According to the GKJR and DGKJ,

non-steroidal anti-inflammatory drugs (NSAIDs) could be used only to complete an anti-inflammatory treatment course, but not concomitantly; the same holds true for physiotherapy and a cold compress applied to the affected area in patients with Lyme arthritis. IDSA recommends NSAIDs before undertaking a new antibiotic treatment in cases of persistent or returning symptoms (e.g., joint swelling) after a first course of antibiotics. The 2018 *Red Book* recommends NSAIDs only in cases of persistent synovitis.

IDSA advises against intra-articular corticosteroid injections, while HAS recommends waiting at least three weeks after the end of an antibiotic treatment before trying this course of action.

7.18.2. Contextual and experiential data

According to the members of the advisory committee, NSAIDs are indicated for certain symptoms. These medications can be prescribed on an ad hoc basis at the same time as antibiotics. The committee's clinicians who practise in pediatrics report that children with Lyme arthritis generally have only mild pain.

With respect to supportive treatments, some members of the advisory committee are of the opinion that NSAIDs are indicated for certain symptoms. These medications can be prescribed on an ad hoc basis at the same time as antibiotics. However, children generally have only mild pain.

One patient partner was prescribed anti-inflammatories and experienced pain relief (500 mg naproxen daily).

Key Takeaways

- The documents analyzed did not make specific recommendations about the use of supportive treatments, except in the context of Lyme arthritis.
- To relieve pain and non-specific systemic symptoms, prescribing an antipyretic/analgesic (e.g., acetaminophen, ibuprofen) in addition to antibiotics could be considered, according to the stakeholders consulted.

7.19. Information and Instructions to Give to Patients

7.19.1. Persistent post-treatment symptoms

7.19.1.1. Clinical practice guides and guidelines

NICE conducted a literature review to compile a list of information that should be given to patients who have received a Lyme disease diagnosis. This information includes: Lyme disease is caused by a bacterial infection that can be treated with antibiotics; most patients make a full recovery; when treatment is started soon after the first symptoms appear, the risk of further symptoms appearing is reduced and the probability of a full recovery is increased; it may take some time before symptoms regress, but patients' condition should improve in the months after treatment begins; additional treatment may be required to relieve symptoms (but without specifying what treatment this may be); patients should talk to their doctor if their symptoms do not improve or if symptoms return after the end of the course of antibiotics;

taking antibiotics does not provide lifelong immunity against future infection, and patients can be re-infected if they are bitten by another tick.

7.19.1.2. Contextual and experiential data

The members of the advisory committee are in general agreement with these statements. They also consider it important to inform patients of the symptoms that are suggestive of the disseminated stages of Lyme disease that they must look out for, and that they should contact a health care professional if these symptoms appear. Committee members, including patient partners, also think it is important to explain to patients that some symptoms may persist for a few weeks or even months after the antibiotic treatment. However, the scientific data currently available do not allow researchers to reliably determine the cause of this persistence beyond the damage caused by the infection. Clinicians are often at a loss when patients' symptoms persist, which is why it is relevant to reassess whether these symptoms could be caused by another clinical condition—for example, an autoimmune disease or a non-bacterial infection transmitted by ticks. This topic will be addressed in the second phase of the INESSS project. If such an explanation seems likely, it could be appropriate to reassess the symptoms in collaboration with one or more specialists.

7.19.2. Jarisch-Herxheimer reaction

7.19.2.1. Clinical practice guides and guidelines

NICE and HAS highlight the possibility of a Jarisch-Herxheimer reaction occurring following antibiotic treatment. HAS explains that [Translation] "studies estimate that this transient aggravation of symptoms (of varying intensity and duration, sometimes referred to as 'Jarisch-Herxheimer reaction') after the start of treatment occurs in approximately 15% (5%–25%) of cases. Fever is less common, occurring in approximately 2% of cases. This is a mild reaction which does not justify stopping the treatment and requires symptomatic treatment." NICE explains that this reaction can cause symptoms to worsen at the start of treatment due to the death of spirochete bacteria brought about by the antibiotics. The authors note that patients who experience such a reaction should contact their physician, but they should not stop taking the antibiotic treatment.

NICE recommends closely monitoring for signs of an allergy to the antibiotic during the course of treatment or of the Jarisch-Herxheimer reaction. The latter can exacerbate symptoms, but—contrary to an allergic reaction—does not require the patient to stop treatment. HAS specifies that the Jarisch-Herxheimer reaction can temporarily worsen symptoms after a patient takes antibiotics and that the exacerbation may sometimes continue for a longer period, with alternating phases of improvement and of aggravation. According to HAS, this reaction occurs in 5%–25% of patients with an infection caused by spirochete bacteria, including *Borrelia*.

7.19.2.2. Scientific data

A review that addresses this reaction was identified in the systematic search of the scientific literature. The authors report that the Jarisch-Herxheimer reaction is a systemic inflammatory reaction that can occur following the treatment of an infection. It is caused by spirochete bacteria such as those from the *Borrelia burgdorferi* sensu lato group. According to the authors, the reaction is often undiagnosed or misdiagnosed as an allergy to medication. Its

symptoms, which include shivers, fever, myalgia and skin eruptions, are typically ignored or under-reported because they often occur prior to treatment [Butler, 2017]. The authors of the review are of the opinion that physicians should anticipate such a reaction and inform their patients.

None of the antibiotics used to treat the various manifestations of Lyme disease increase the risk of a Jarisch-Herxheimer reaction, according to the RCTs that studied both the efficacy and safety of these medications and the Jarisch-Herxheimer reaction. However, studying this reaction was not the primary objective of these trials, and it is possible that they did not have the statistical power to confirm the association (low N).

7.19.2.3. Contextual and experiential data

While clinician committee members are familiar with the Jarisch-Herxheimer reaction, they have little or no experience treating patients who have developed the reaction, particularly in connection with Lyme disease. The clinicians mentioned that they have seen the reaction more often in patients with syphilis. One member reported having observed a slight exacerbation of symptoms in cases of early disseminated Lyme disease. Furthermore, patients are more likely to wait for symptoms to spontaneously disappear than to return to the physician who prescribed the antibiotic for a second consultation (data from surveys conducted by the Montérégie DSP).

One patient partner reported having experienced adverse effects and the Jarisch-Herxheimer reaction multiple times (with different treatments). Among other symptoms, this person suffered emotional symptoms at the beginning of a ceftriaxone treatment. The person also experienced very severe headaches during the last two weeks of the first course of ceftriaxone, but was unable to reach a physician to ask whether or not the treatment should be continued.

The AQML representatives consulted reported that antibiotic treatment can precipitate a Jarisch-Herxheimer reaction in up to 90% individuals with Lyme disease, for whom the AQML suggests a diagnosis of *Borrelia* infection. However, not all physicians are familiar with this infection, which is often mistaken for an allergic reaction to medication.

The clinician members of the advisory committee agree that prescribers should expect such a reaction in Lyme disease patients, that it is important to inform patients that it can occur within 24 to 48 hours of the start of treatment and that, if it does, they must continue to take the antibiotic. Patients should be told to contact a health care professional if they have any questions or concerns.

Key Takeaways

- According to the documents consulted, NICE is one of the only organizations that have issued directives regarding the information that should be given to patients.
- The stakeholders consulted agree that patients should be informed that some symptoms may persist for a few weeks or even months after the antibiotic treatment. The scientific data currently available do not allow researchers to reliably determine the cause of this persistence beyond the damage caused by the infection.

- It is also important to inform the patient of the symptoms suggestive of Lyme disease to watch for, and to tell them to contact a health care professional if they have any questions or concerns, if their rash gets bigger or if new symptoms appear.
- Lastly, although the Jarisch-Herxheimer reaction is relatively rare, patients should be informed that it could occur within 24 to 48 hours of the start of treatment and that, if it does, they must continue to take the antibiotic. Patients should be told to contact a health care professional if they have any questions or concerns.

8. FOLLOW-UP, REASONS FOR CONSULTING A SPECIALIST OR REFERRING PATIENTS TO SPECIALIZED SERVICES

Assessment Questions
To optimize the overall care and patients' care experience: • Under what circumstances should a primary care health professional (such as a specialized nurse practitioner, general practitioner or emergency physician) 1) consult one or more specialists and/or 2) refer a patient to a specialist? • What would be the optimal follow-up for patients who have been diagnosed and prescribed treatment?

8.1. Clinical Practice Guides and Guidelines

NICE recommends discussing the diagnosis and care of patients under 18 years old with a specialist, unless the patient presents with solitary erythema migrans and no other symptoms compatible with Lyme disease. The choice of specialist should be based on the patient's symptoms [NICE, 2018a].

For patients with carditis and a high-grade atrioventricular block, HAS recommends monitored follow-up for patients with high clinical suspicion of Lyme borreliosis and who present with syncope or a second- or third-degree atrioventricular block. IDSA recommends cardiac monitoring for patients with an atrioventricular block (first-degree block with a PR interval longer than 300 ms, or a second- or third-degree block), and it indicates that a temporary pacemaker could be implanted in such patients.

8.2. Contextual and Experiential Data

Several members of the advisory committee insisted that clinicians should consult with specialists regarding the care provided to patients diagnosed with the disseminated stage of the disease, except in the case of patients who have skin symptoms only. Some committee members mentioned that serial electrocardiograms (ECGs) may be required as follow-up in order to ensure that a first-degree atrioventricular block has been favourably resolved after an oral course of antibiotic treatment. Members were also in agreement with the HAS recommendation regarding cardiac monitoring for patients with a second- or third-degree block treated with IV antibiotics.

The Service Request Dispatch Centre (CRDS in French), created in 2017, facilitates access to specialists by making it possible for primary care clinicians to establish priority levels that will determine how long a patient will wait before being seen by an appropriate specialist, as per the clinician's professional judgment. It was mentioned that primary care clinicians should not hesitate to consult a specialist to help them with challenging decisions about patient care. For example, a microbiologist / infectious diseases specialist could be consulted to arrive at a joint decision to promptly start antibiotic treatment if indicated, in order to avoid complications.

The on-call system in which microbiologists / infectious diseases specialists participate within each institution (or CISSS/CIUSSS) is a winning condition for such collaboration—but only if the system is actually used, which, according to some of the stakeholders consulted, does not seem to be the case currently with respect to Lyme disease. Specialists can also offer advice or contribute to decisions about whether to conduct serologic testing or start antibiotic treatment before getting test results back. Consulting one or more specialists may also be appropriate when a patient's test results are negative but the clinical picture is compatible with Lyme disease and all other clinical conditions have been ruled out.

Key Takeaways

With the exception of NICE's recommendations, there are few directives available on cases that call for the opinion of a specialist, since the CPGs are typically intended for use by specialists, not primary care clinicians.

The stakeholders consulted believe that it may be relevant to speak to one or more specialists in the following cases:

- When doubt remains as to whether observed symptoms are caused by Lyme disease and a decision must be made about conducting serologic tests or starting antibiotic treatment
- When the serology results come back negative but the clinical picture is compatible with Lyme disease and all other clinical conditions have been ruled out

The care provided to patients diagnosed in the disseminated stages of the disease should be discussed with a specialist.

DISCUSSION

The objective of this report was to develop recommendations with respect to diagnosing, treating and following patients with localized or disseminated Lyme disease.

Summary of Key Takeaways

The key takeaways presented in this section are based on scientific data, best practice recommendations, contextual information and experiential knowledge.

The clinical presentation of Lyme disease varies from one patient to another, in terms of both the manifestations and their intensity and the speed at which the disease progresses. In addition to the bull's eye rash typical of solitary erythema migrans, other symptoms that should lead physicians to suspect Lyme disease include multiple erythema migrans, facial palsy and joint swelling.

Evaluating patients' clinical picture is a key to diagnosis, as symptoms of the disease are relatively non-specific and can be compatible with numerous other diseases. The evaluation of the compatibility of the clinical picture with Lyme disease should take into account the risk of exposure to ticks, the patient's signs and symptoms, and all other possible clinical conditions. While some points may be in favour of a Lyme diagnosis (e.g., documented tick bite), others may decrease the probability without completely ruling it out (e.g., ambiguity about the risk of exposure to ticks).

Establishing a diagnosis is the primary challenge of dealing with Lyme disease. With the exception of isolated erythema migrans, no manifestations have a sufficiently high diagnostic value to establish the diagnosis in a patient with a compatible clinical picture. Moreover, the low sensitivity of currently available serologic tests at the beginning of the infection and the inability of these tests to distinguish between an active infection and a past infection mean that, on their own, they are more useful in fleshing out the clinical picture than in establishing or ruling out the diagnosis.

Once the diagnosis of Lyme disease has been established, the care and treatment of either the localized or disseminated stage do not present any particular difficulty. However, a thorough assessment of the patient's general condition is required, as symptoms of the early disseminated stage that go undetected could result in the wrong treatment duration or choice of antibiotics for the patient's condition.

Although the current state of knowledge does not allow for any statistically significant differences to be identified with respect to the efficacy and safety of the antibiotics studied in various contexts, the pharmacodynamic and pharmacokinetic properties of ceftriaxone and doxycycline make them top choices among clinicians, depending on whether intravenous or oral administration is required. But, because monographs on tetracycline (including doxycycline) advise against their use during tooth formation, doxycycline was not, until very recently, an option recommended for the oral treatment of Lyme disease in children under age 8 and breastfeeding women. Results of available analytic studies now show, however, that doxycycline administered to children under 8 at average dosages of 2 to 10 mg/kg/day for an average total duration of 5.5 to 21 days has no impact on children's permanent teeth

(modification of tooth shade or appearance of a particular colouration) (low level of evidence). This is why, in the summer of 2018, the *Red Book* began recommending doxycycline as a first-line treatment of Lyme disease in this population. INESSS has followed suit, but insists that such a treatment decision should only be made after an informed discussion about the medication's risks and benefits with the patient or the child's parent (or guardian).

Moreover, while the scientific data and the experience of the consulted clinicians support the purported efficacy of antibiotic treatment, symptoms may appear if the choice of antibiotics is not well suited to the patient's condition, and they may persist for a relatively long period if the patient has been diagnosed at the disseminated stages of the disease. The patient should be informed of these possibilities and of the risk of developing a Jarisch-Herxheimer reaction within 24 to 48 hours of the start of treatment.

Finally, it is a good idea to consult a specialist when doubt remains about whether symptoms are due to Lyme disease, when a decision must be made about performing serologic testing or about the relevance of antibiotic treatment, and when serology results came back negative for a patient whose clinical picture is compatible with Lyme disease (other possible clinical conditions having been ruled out).

Strengths and Limitations

One of the primary strengths of the work carried out by INESSS is the rigorous scientific literature search and the critical assessment of the data collected, as well as the triangulation of scientific, contextual and experiential data. The scientific data presented in this report come from a systematic inventory of documents outlining clinical best practices, systematic reviews and primary studies, the data from which have been reanalyzed based on where the disease was contracted (North America versus Europe, in order to account for different genospecies). The contextual data were obtained from key stakeholders and public documents. And, lastly, the experiential knowledge was gathered by consulting members of an advisory committee composed of clinicians, including specialists from various medical fields, an expert in laboratory analysis and acarological monitoring, one patient partner with neuroborreliosis and one patient partner with Lyme arthritis. The collection of experiential knowledge was rounded out through discussions with AQML representatives and interviews with eight Lyme disease patients.

A number of systematic reviews of the scientific literature were conducted to complete the work presented in this report, in particular to assess the diagnostic value of certain manifestations of the disease; the diagnostic value of laboratory analysis; the efficacy and safety of antibiotics; the efficacy and safety of doxycycline in children exposed in utero or through breastfeeding or who are under 8 years of age; the impact of Lyme disease on patients' quality of life; and clinicians' perspective of the disease. Finally, a systematic review of documents containing clinical recommendations was also conducted.

This work sets itself apart from published clinical practice guides chiefly by accounting for the diagnostic value of laboratory analysis and signs and symptoms in a North American context. The analysis and determination of levels of scientific evidence regarding the comparative efficacy of various antibiotics were also carried out in this context. The clinical practice guides

included in the analysis, on the other hand, issued their recommendations without regard for where the disease was contracted or where the tests were conducted. Moreover, unlike INESSS, some documents do not present the logic or data in support of their recommendations. The wealth and diversity of know-how within the advisory committee whose members contributed to developing the recommendations and knowledge transfer tools is another element that elevates the INESSS work above that of other agencies that have published guidelines.

Lastly, even though this report is supported by scientific data and the triangulation of three sources of data, some limitations are worth noting. First and foremost, the level of scientific evidence is primarily low or insufficient due to the study designs as well as the number of subjects and methodological limitations of the studies. For example, most of the diagnostic studies were case-control studies, which are relatively inappropriate in this context because the sensitivity is estimated in a group of patients whose tests are very likely to be positive and because the specificity is estimated in a group of individuals in whom the disease is very likely absent (e.g., healthy donors). There are relatively few studies on the comparative efficacy of antibiotics (with the exception of those addressing EM), and the studies are almost always of low quality (small number of patients, bias, etc.) and not designed to demonstrate differences in the frequency and severity of adverse effects.

Clinical Impact of the Work

The INESSS work [INESSS, 2019a], highlighted health care professionals' lack of knowledge when it comes to assessing the risk of tick exposure as well as the information to consider in establishing the diagnosis. This shortcoming must be analyzed with a view to implementing high-level, uniform standards of care across Quebec for individuals who have been bitten by a tick and are suspected of having contracted Lyme disease. The decision support tools developed by INESSS are expected to support clinicians in their practice and promote earlier diagnosis in patients with symptoms of the disseminated stage. These tools should also lead to a more judicious use of laboratory analysis and improved interpretation of its results, and they should also ensure the optimal use of antibiotics, depending on clinical presentation.

Impact of the Work on Research

The work highlighted the lack of data relative to the:

- Diagnostic value of serologic tests used in Quebec and outcomes for seropositive and seronegative patients
- Efficacy of antibiotics—with respect to dosage, formulation and duration—recommended for the treatment of Lyme carditis and central nervous system symptoms, including optical nerve involvement
- Efficacy and safety of doxycycline for the treatment of manifestations for which the oral route of administration is recommended, in children under age 8

To bolster the medical community's response to this emerging disease, funds could be granted to researchers or research institutes. This support would help focus further work on the areas where it is most needed, as shown by the INESSS.

CONCLUSION

Given the complex and multisystem nature of Lyme disease, clinicians should aim for a comprehensive, patient-centred approach. The experience of Quebec clinicians with Lyme disease is currently limited and concentrated in high-risk regions like Estrie and Montérégie. Since Lyme disease is an emerging disease and Quebecers tend to travel around the province, cases of Lyme disease will likely occur more and more frequently outside of high-risk regions. The knowledge transfer tools developed based on this document's clinical recommendations will support health care professionals in making clinical decisions with respect to diagnosing the disease and choosing the right antibiotic treatment. Distributing and adopting these clinical decision support tools is a first step toward addressing certain diagnostic shortcomings, thus ushering in changes to medical practice and providing an improved care experience. The INESSS work will be completed by a set of recommendations addressing the controversial form of Lyme disease (sometimes referred to as "chronic") and co-infections. These recommendations will be published in 2020.

CLINICAL RECOMMENDATIONS

DIAGNOSIS	Consensus decision reached by advisory committee members
Recommendations pertaining to history taking	
Given that Lyme disease can affect several systems, the possibility of exposure to ticks should be assessed in patients presenting with: o One or more reddish skin lesions that have persisted for more than 48 hours and are spreading o Neurological signs such as cranial neuritis (particularly facial palsy), mononeuropathy, multiple mononeuritis, radiculopathy with no other cause, plexopathy or aseptic meningitis o Cardiac symptoms such as arrhythmia, cardiac conduction disorders, pericarditis or myocarditis o Musculoskeletal symptoms such as significant joint swelling (primarily of the knee), oligoarthritis and periods of arthritis interspersed with periods of remission without treatment	**> 80%**
When signs that are suggestive of Lyme disease are present, questions about possible exposure to black-legged ticks should be added to the patient assessment questionnaire (e.g., questions about the lifestyle of the patient and close family members, outdoor activities [leisure or work], geographic areas where the patient lives or has visited, level of contact with outdoor pets).	**Unanimous**
Given that the possibility of tick exposure is an important aspect of the clinical picture, the assessment questionnaire should take into account the possible locations where tick exposure may have occurred, i.e., the countries and regions visited by the patient.	**Unanimous**
Given that ticks can travel throughout Quebec and that the areas of endemicity, as illustrated by the INSPQ map, have a public health objective, rather than a clinical objective, the map should be used to evaluate the probability of significant contact with ticks, but not to rule out the diagnosis.	**Unanimous**
The geographic zones located near the areas where ticks are endemic, as illustrated by the INSPQ map, should be considered at-risk areas for Lyme disease.	**> 80%**

A documented tick bite should be interpreted as meaning that there is a possibility of exposure to ticks. *If exposure has occurred in a high-risk area, it is significant for a Lyme disease diagnosis.*	**Unanimous**
The absence of a documented tick bite should not be used to rule out Lyme disease.	**Unanimous**
When manifestations suggestive of Lyme disease are present, it is necessary to perform a physical exam (including a neurological exam) and search for a skin lesion that could be erythema migrans or another manifestation suggestive of the early disseminated stage.	**Unanimous**
Since manifestations suggestive of Lyme disease are also compatible with various other diseases, the other clinical conditions that could explain these manifestations should be considered when taking a patient's history. *The prioritization of differential diagnoses should take into account the patient's clinical picture, the possibility of exposure to ticks and the area where exposure may have occurred.*	**Unanimous**
Recommendations pertaining to establishing the diagnosis in the presence of erythema migrans *The recommendations below apply to patients who present with manifestations suggestive of Lyme disease at consultation and whose clinical picture is compatible with Lyme disease, as determined following a physical exam and an assessment of the risk of tick exposure, and giving due consideration to other possible clinical conditions.*	
A lesion that meets the following definition should be considered typical solitary erythema migrans: "Circular skin rash, generally progressive, that is at least 5 cm in diameter, lasts at least 48 hours and is associated with little or no pain or itching. The lesion may be homogenous or ring-shaped and does not always look like a bull's eye. It may also be very pale and have poorly defined margins."	**Unanimous**
When a patient has typical solitary erythema migrans, Lyme disease should be diagnosed without performing serologic testing to decide whether to start treatment.	**> 80%**
Given that serology results are not sensitive in cases of solitary erythema migrans, whether typical or not, serologic tests should not be performed.	**> 80%**
Should it be necessary to document the serology of a patient with solitary erythema migrans (whether typical or not), the serology request should be delayed four to six weeks, and the decision to perform such testing should be discussed with a specialist.	**> 80%**
If a clinician suspects that a rash less than 5 cm in diameter may be caused by Lyme disease or that a skin lesion is in fact atypical solitary erythema migrans, without any other symptoms of the early disseminated stage, observation may be the best course of action.	**> 80%**

Observation should include the following elements: ● The outline of the rash should be traced and the diameter measured (by the patient or a health care professional) in order to document any potential expansion. ● A photo with a measuring object could be taken and kept by the patient. ● The patient should be asked to trace the outline of the rash again and to take photos with a measuring object if they notice any expansion. ● The patient should be informed of the signs and symptoms suggestive of Lyme disease to watch for, and told of the importance of consulting a health care professional if they have any questions or concerns or if they notice that the rash or atypical lesion has expanded.	**Unanimous**
In the case of a skin lesion that is not typical solitary erythema migrans and whose progression has not been documented, a discussion with an experienced colleague or a specialist should be considering before establishing a diagnosis of Lyme disease.	**> 80%**
Recommendations pertaining to establishing the diagnosis in the presence of manifestations that are suggestive of the early and late disseminated stages (absence of a skin lesion that could be typical erythema migrans, as that would be sufficient grounds for the diagnosis) *The recommendations below apply to patients who present with manifestations suggestive of Lyme disease at consultation and whose clinical picture is compatible with Lyme disease, as determined following a physical exam and an assessment of the risk of tick exposure, and giving due consideration to other possible clinical conditions. It does not apply to patients with typical solitary erythema migrans, but it does apply to patients with a skin lesion that does not meet the criteria of typical solitary erythema migrans.*	
In cases of signs and symptoms that are suggestive of the disseminated stages (multiple skin lesions; neurological, cardiac or joint manifestations), and a strong suspicion of Lyme disease, serologic testing should be done.	**Unanimous**
In certain conditions, it may be indicated to start antibiotic treatment as soon as the serologic testing is requested (e.g., in cases of multiple erythema migrans coupled with a strong suspicion of Lyme disease); a discussion with an experienced colleague or a specialist should be considered before making this decision.	**Unanimous**
In the presence of signs and symptoms that are suggestive of the early disseminated stage of Lyme disease (multiple skin lesions, neurological or cardiac manifestations), and a strong suspicion of Lyme disease, a diagnosis of Lyme disease should not be ruled out solely on the basis of a negative serology result.	**> 80%**
When a negative serology result is obtained for a patient presenting with signs and symptoms that are suggestive of the early and late disseminated stages	**Unanimous**

(e.g., multiple skin lesions; neurological, cardiac and joint manifestations), and there is a strong suspicion of Lyme disease, a discussion with an experienced colleague or a specialist should be considered before ruling out a Lyme disease diagnosis and in order to assess the need to perform further serologic testing in four to six weeks.	
When joint or cerebrospinal fluid aspiration is being considered in a patient for whom Lyme disease is among the suspected diagnoses, a discussion with an experienced colleague or a specialist should be considered in order to assess the need for PCR testing (on joint or cerebrospinal fluid) or for testing to detect antibodies (cerebrospinal fluid).	**> 80%**
The results of PCR testing on joint or cerebrospinal fluid and of testing to detect antibodies in cerebrospinal fluid should be analyzed with a specialist.	**> 80%**
Recommendations pertaining to requests for serologic testing	
Given that serologic testing does not help distinguish between an active infection and a past infection, it should not be used to objectify the response to antibiotic treatment.	**Unanimous**
Given that serologic testing does not help distinguish between an active infection and a past infection, and that the level of seroprevalence in the population varies from one area to another, and in order to avoid diagnostic errors, serology testing should not be requested for a patient who has none of the signs and symptoms that are suggestive of Lyme disease or whose clinical picture is not compatible with Lyme disease.	**Unanimous**
Given that the amount of time between the appearance of the first manifestations of Lyme disease and the request for serology testing is relevant in deciding which serologic tests to perform, the serology request form should indicate when these first symptoms occurred, in order to make the best use of laboratory analysis.	**> 80%**
Given that the immunoblotting tests commercially available in North America have low sensitivity for the detection of Lyme disease contracted in Europe, the continent(s) on which exposure to ticks may have occurred should be specified on the serology request form so that the relevant immunoblotting tests are used.	**Unanimous**
Recommendations pertaining to the interpretation of immunoblotting tests	
Given the low diagnostic value of IgM results, a positive IgM immunoblotting result and negative IgG result should not be used as an argument for diagnosing an infection from bacteria of the *B. burgdorferi* s.l. complex. *If there is a strong suspicion of Lyme disease, a discussion with an experienced colleague or a specialist should be considered in order to assess the need to perform further serologic testing in four to six weeks.*	**> 80%**
A positive IgG result obtained by immunoblotting (following a positive or inconclusive ELISA) in a patient with signs and symptoms that are suggestive of	**Unanimous**

Lyme disease and for whom there is a strong suspicion of the disease should suggest an infection from bacteria of the *B. burgdorferi* s.l. complex, regardless of the IgM result.	
Given the current state of knowledge, a positive ELISA test result using VlsE (synthetic peptide or whole protein) as the antigen should not be used without a confirmation test to complement the clinical picture in patients suspected of having Lyme disease.	**Unanimous**

TREATMENT	Consensus decision reached by advisory committee members
Treatment principles	
The decision to start antibiotic treatment should be based on the assessment of the risk of exposure to black-legged ticks, the clinical picture and the exclusion of other possible clinical conditions. If doubt persists, the opinion of an experienced colleague or a specialist should be sought.	**> 80%**
Before prescribing an antibiotic to treat a manifestation (whether related to the skin, heart or peripheral nervous system) that is very likely caused by Lyme disease, clinicians should ensure there are no central nervous system manifestations (e.g., optical neuritis, encephalomyelitis), meningeal manifestations or joint manifestations that are suggestive of Lyme arthritis, in order to select the appropriate antibiotic and treatment duration.	**Unanimous**
If a rash less than 5 cm in diameter is suspected of being caused by Lyme disease and there are no other symptoms that are suggestive of the disseminated stage, observation may be an appropriate course of action.	**> 80%**
The outline of a rash less than 5 cm in diameter should be traced and the diameter measured (by the patient or a health care professional) in order to be able to objectify any possible expansion. A photo with a measuring object could be taken and kept by the patient. When the lesion is already larger than 5 cm at the time of the consultation, its expansion does not necessarily have to be tracked, as it is likely to stabilize.	**Unanimous**
In the event of hesitation between infectious cellulitis and a rash that could be typical or atypical solitary erythema migrans, a treatment that targets both conditions should be prescribed (e.g., cefuroxime axetil). Clinicians can consult the two INESSS OUGs on treating infectious cellulitis in children and adults.	**Unanimous**
When a patient with solitary erythema migrans has had a previous very severe allergic reaction to penicillin antibiotics and doxycycline is contraindicated, azithromycin or clarithromycin should be prescribed.	**Unanimous**
When a patient under age 8 with Lyme arthritis has had a previous very severe allergic reaction to penicillin antibiotics, doxycycline could be considered.	**> 80%**
When a breastfeeding patient with Lyme arthritis has had a previous very severe allergic reaction to penicillin antibiotics, doxycycline could be considered.	**> 80%**
When a patient has had a previous very severe allergic reaction to penicillin or tetracycline antibiotics, an allergy specialist should be consulted.	**> 80%**

Given the current state of scientific knowledge and the availability of other equally effective treatment options, doxycycline should not be prescribed to pregnant women (except in some specific cases and on the advice of a specialist) diagnosed with Lyme disease.	**Unanimous**
Erythema migrans	
Before prescribing an antibiotic to treat solitary erythema migrans, the absence of other signs and symptoms should be confirmed in order to adjust the type and duration of antibiotic treatment accordingly.	**Unanimous**
Oral doxycycline (100 mg BID) x 10 days (10–14 days) should be preferred for adults other than pregnant women who present with a rash compatible with solitary erythema migrans AND NO general systemic symptoms, and when there is a strong suspicion of Lyme disease.	**Unanimous**
Oral amoxicillin (500 mg TID) x 14 days (14–21 days) or oral cefuroxime axetil (500 mg BID) x 14 days (14–21 days) should be alternate solutions to doxycycline for adults who present with a rash compatible with solitary erythema migrans AND NO general systemic symptoms, and when there is a strong suspicion of Lyme disease, when doxycycline is absolutely contraindicated.	**Unanimous**
Oral doxycycline (4.4 mg/kg/day divided into two doses [max. 100 mg/dose]) x 10 days (10–14 days) should be preferred for children aged 8 and up who present with a rash compatible with solitary erythema migrans AND NO general systemic symptoms, and when there is a strong suspicion of Lyme disease.	**> 80%**
Oral doxycycline (4.4 mg/kg/day divided into two doses [max. 100 mg/dose]) x 10 days (10–14 days) could be preferred for children under 8 who present with a rash compatible with solitary erythema migrans AND NO general systemic symptoms, and when there is a strong suspicion of Lyme disease, following an informed discussion with the patient's parent (or guardian).	**> 80%**
Oral amoxicillin (50 mg/kg/day divided into three doses [max. 500 mg/dose]) x 14 days (14–21 days) or oral cefuroxime axetil (30 mg/kg/day divided into two doses [max. 500 mg/dose]) x 14 days (14–21 days) should be alternate solutions to doxycycline for children who present with a rash compatible with solitary erythema migrans AND NO general systemic symptoms, and when there is a strong suspicion of Lyme disease.	**> 80%**
Oral doxycycline (100 mg BID) x 14 days (14–21 days) should be preferred for adults other than pregnant women who present with a rash compatible with solitary erythema migrans AND general systemic symptoms, OR multiple erythema migrans with or without general systemic symptoms, and when there is a strong suspicion of Lyme disease.	**> 80%**
Oral amoxicillin (500 mg TID) x 14 days (14–21 days) or oral cefuroxime axetil (500 mg BID) x 14 days (14–21 days) should be alternate solutions to doxycycline, when doxycycline is absolutely contraindicated, for adults who	**> 80%**

present with a rash compatible with solitary erythema migrans AND general systemic symptoms, OR multiple erythema migrans with or without general systemic symptoms, and when there is a strong suspicion of Lyme disease.	
Oral doxycycline (4.4 mg/kg/day divided into two doses [max. 100 mg/dose]) x 14 days (14–21 days) should be preferred for children aged 8 and up who present with a rash compatible with solitary erythema migrans AND general systemic symptoms, OR multiple erythema migrans with or without general systemic symptoms, and when there is a strong suspicion of Lyme disease.	**> 80%**
Oral doxycycline (4.4 mg/kg/day divided into two doses [max. 100 mg/dose]) x 14 days (14–21 days) could be preferred for children under 8 who present with a rash compatible with solitary erythema migrans AND general systemic symptoms, OR multiple erythema migrans with or without general systemic symptoms, following an informed discussion with the patient's parent (or guardian).	**> 80%**
Oral amoxicillin (50 mg/kg/day divided into three doses [max. 500 mg/dose]) x 14 days (14–21 days) or oral cefuroxime axetil (30 mg/kg/day divided into two doses [max. 500 mg/dose]) x 14 days (14–21 days) should be alternate solutions to doxycycline, when doxycycline is absolutely contraindicated, for children who present with a rash compatible with solitary erythema migrans AND general systemic symptoms, OR multiple erythema migrans with or without general systemic symptoms and when there is a strong suspicion of Lyme disease.	**> 80%**
If, during the course of antibiotic treatment for skin symptoms, neurological, cardiac, eye or joint symptoms appear, and all other probable clinical conditions have been ruled out, the decision to change antibiotics or modify their duration should be made jointly with a specialist or an experienced colleague.	**Unanimous**
In the event that the antibiotic treatment fails, the attribution of erythema migrans to Lyme disease should be re-evaluated. The opinion of a specialist or an experienced colleague should be sought in such cases.	**Unanimous**
Neuroborreliosis	
Before prescribing an antibiotic to treat a peripheral nervous system manifestation (e.g., cranial neuritis, mononeuropathy, multiple mononeuritis, radiculopathy, plexopathy or aseptic meningitis) attributable to Lyme disease, clinicians should ensure there are no central nervous system manifestations (e.g., optical neuritis, encephalomyelitis), meningeal manifestations or joint manifestations that are suggestive of Lyme arthritis, in order to select the appropriate antibiotic and treatment duration.	**Unanimous**
If, during the course of antibiotic treatment, joint manifestations that are suggestive of Lyme arthritis appear, and all other probable clinical conditions	**Unanimous**

have been ruled out, the decision to extend treatment duration (to 28 days) should be made jointly with a specialist or an experienced colleague.	
In the event that the antibiotic treatment fails, the attribution of neurological symptoms and signs to Lyme disease should be re-evaluated. The opinion of a specialist or an experienced colleague should be sought in such cases.	**> 80%**
Ceftriaxone IV (2 g QD x 14 days [10–28 days]) should be preferred for adults who present with neuroborreliosis and central nervous system involvement (e.g., optical neuritis) or meningeal manifestations, and when there is a strong suspicion of Lyme disease.	**> 80%**
Cefotaxime IV (2 g TID x 14 days [10–28 days]) or penicillin G IV (18–24 million units/day divided every 4 hours x 14 days) [10–28 days]) should be alternate solutions to ceftriaxone, when ceftriaxone is absolutely contraindicated, for adults who present with neuroborreliosis and central nervous system involvement (e.g., optical neuritis) or meningeal manifestations, and when there is a strong suspicion of Lyme disease.	**> 80%**
Oral doxycycline (100 mg BID) x 14 days (14–21 days) should be preferred for adults other than pregnant women who present with neuroborreliosis and peripheral nervous system manifestations such as cranial mononeuritis (except for optical neuritis), multiple mononeuritis, plexopathy or radiculopathy, and when there is a strong suspicion of Lyme disease.	**Unanimous**
Oral amoxicillin (500 mg TID) x 14 days (14–21 days) or oral cefuroxime axetil (500 mg BID) x 14 days (14–21 days) should be alternate solutions to doxycycline, when doxycycline is absolutely contraindicated, for adults who present with neuroborreliosis and peripheral nervous system manifestations such as cranial mononeuritis (except for optical neuritis), multiple mononeuritis, plexopathy or radiculopathy, and when there is a strong suspicion of Lyme disease.	**> 80%**
Ceftriaxone IV (75–100 mg/kg/day QD [max. 2,000 mg] x 14 days [10–28 days]) should be preferred for children who present with neuroborreliosis and central nervous system involvement (e.g., optical neuritis) or meningeal manifestations, and when there is a strong suspicion of Lyme disease.	**> 80%**
Cefotaxime IV (225–300 mg/kg/day divided into three or four doses [max. 12 g/day] x 14 days [10–28 days]) or penicillin G IV (0.2–0.4 million units/kg/day divided every 4 hours [max. 18–24 million units/day] x 14 days [10–28 days]) should be alternate solutions to ceftriaxone, when ceftriaxone is absolutely contraindicated, for children who present with neuroborreliosis and central nervous system involvement (e.g., optical neuritis) or meningeal manifestations, and when there is a strong suspicion of Lyme disease.	**> 80%**

Oral doxycycline (4.4 mg/kg/day divided into two doses [max. 100 mg/dose]) x 14 days [14–21 days]) should be preferred for children aged 8 and up who present with neuroborreliosis and peripheral nervous system manifestations such as cranial mononeuritis (except for optical neuritis), multiple mononeuritis, plexopathy or radiculopathy, and when there is a strong suspicion of Lyme disease.	**Unanimous**
Oral doxycycline (4.4 mg/kg/day divided into two doses [max. 100 mg/dose]) x 14 days (14–21 days) could be preferred for children under 8 who present with neuroborreliosis and peripheral nervous system manifestations such as cranial mononeuritis (except for optical neuritis), multiple mononeuritis, plexopathy or radiculopathy, and when there is a strong suspicion of Lyme disease, following an informed discussion with the patient's parent (or guardian).	**> 80%**
Oral amoxicillin (50 mg/kg/day divided into three doses [max. 500 mg/dose]) x 14 days (14–21 days) or oral cefuroxime axetil (30 mg/kg/day divided into two doses [max. 500 mg/dose]) x 14 days (14–21 days) should be alternate solutions to doxycycline, when doxycycline is absolutely contraindicated, for children who present with neuroborreliosis and peripheral nervous system manifestations such as cranial mononeuritis (except for optical neuritis), multiple mononeuritis, plexopathy or radiculopathy, and when there is a strong suspicion of Lyme disease.	**> 80%**
Lyme carditis	
Before prescribing an antibiotic to treat Lyme carditis, the absence of neurological and joint manifestations should be confirmed in order to select the appropriate antibiotic and treatment duration.	**Unanimous**
Oral doxycycline (100 mg BID) x 14 days (14–21 days) should be preferred for adults other than pregnant women who present with carditis with a first-degree atrioventricular block and a PR interval less than 300 ms, and when there is a strong suspicion of Lyme disease. Patient follow-up should include serial ECGs.	**Unanimous**
Oral amoxicillin (500 mg TID) x 14 days (14–21 days) or oral cefuroxime axetil (500 mg BID) x 14 days (14–21 days) should be alternate solutions to doxycycline, when doxycycline is absolutely contraindicated, for adults who present with carditis with a first-degree atrioventricular block and a PR interval less than 300 ms, and when there is a strong suspicion of Lyme disease. Patient follow-up should include serial ECGs.	**Unanimous**
Ceftriaxone IV (2 g QD) x 14 days (14–28 days) should be preferred for adults who present with carditis with a first-degree atrioventricular block and a PR interval longer than 300 ms, a second- or third-degree block, myocarditis or pericarditis (with or without block), and when there is a strong suspicion of Lyme disease. Cardiac monitoring should be conducted.	**Unanimous**

Cefotaxime IV (2 g TID x 14 days [14–28 days]) or penicillin G IV (18–24 million units/day divided every 4 hours x 14 days [14–28 days]) should be alternate solutions to ceftriaxone, when ceftriaxone is absolutely contraindicated, for adults who present with carditis with a first-degree atrioventricular block and a PR interval longer than 300 ms, a second- or third-degree block, myocarditis or pericarditis (with or without block), and when there is a strong suspicion of Lyme disease. Cardiac monitoring should be conducted.	**Unanimous**
Oral doxycycline (4.4 mg/kg/day divided into two doses [max. 100 mg/dose]) x 14 days (14–21 days) should be preferred for children aged 8 and up who present with carditis with a first-degree atrioventricular block and a PR interval less than 300 ms, and when there is a strong suspicion of Lyme disease. Patient follow-up should include serial ECGs.	**Unanimous**
Oral amoxicillin (50 mg/kg/day divided into three doses [max. 500 mg/dose]) x 14 days (14–21 days) or oral cefuroxime axetil (30 mg/kg/day divided into two doses [max. 500 mg/dose]) x 14 days (14–21 days) should be alternate solutions to doxycycline, when doxycycline is absolutely contraindicated, for children aged 8 and up who present with carditis with a first-degree atrioventricular block and a PR interval less than 300 ms, and when there is a strong suspicion of Lyme disease. Patient follow-up should include serial ECGs.	**Unanimous**
Oral doxycycline (4.4 mg/kg/day divided into two doses [max. 100 mg/dose]) x 14 days (14–21 days) could be preferred for children under 8 who present with carditis with a first-degree atrioventricular block and a PR interval less than 300 ms, and when there is a strong suspicion of Lyme disease, following an informed discussion with the patient's parent (or guardian). Patient follow-up should include serial ECGs.	**Unanimous**
Ceftriaxone IV (75–100 mg/kg/day in a single dose [max. 2 g]) x 14 days (14–28 days) should be preferred for children who present with carditis with a first-degree atrioventricular block and a PR interval longer than 300 ms, a second- or third-degree block, myocarditis or pericarditis (with or without block), and when there is a strong suspicion of Lyme disease. Cardiac monitoring should be conducted.	**Unanimous**
Cefotaxime IV (150–200 mg/kg/day divided into three or four doses [max. 6 g/day] x 14 days [14–28 days]) or penicillin G IV (200,000–400,000 U/kg/day divided every 4 hours [max. 18–24 million U/day] x 14 days [14–28 days]) should be alternate solutions to ceftriaxone, when ceftriaxone is absolutely contraindicated, for children who present with carditis with a first-degree atrioventricular block and a PR interval longer than 300 ms, a second- or third-degree block, myocarditis or pericarditis (with or without block), and when there is a strong suspicion of Lyme disease. Cardiac monitoring should be conducted.	**Unanimous**

In patients who present with a first-degree atrioventricular block and a PR interval longer than 300 ms, a second- or third-degree block, myocarditis or pericarditis (with or without block), and when there is a strong suspicion of Lyme disease, treatment should begin by intravenous route and be continued orally once the patient is stable and the block is in the process of being resolved.	**Unanimous**
If, during the course of antibiotic treatment for carditis, joint manifestations that are suggestive of Lyme arthritis appear, and all other probable clinical conditions have been ruled out, the decision to extend treatment duration (to 28 days) should be made jointly with a specialist or an experienced colleague.	**Unanimous**
In the event that the antibiotic treatment fails, the attribution of carditis to Lyme disease should be re-evaluated. The opinion of a specialist or an experienced colleague should be sought in such cases.	**Unanimous**
Non-neurological Lyme-related ocular impairment	
Patients with signs and symptoms of ocular involvement, whether or not there is a strong suspicion of Lyme disease, should be referred to an ophthalmologist.	**Unanimous**
Lyme arthritis	
Before prescribing an antibiotic to treat Lyme arthritis and in order to select the appropriate antibiotic, the absence of central nervous system and meningeal manifestations should be confirmed.	**Unanimous**
Oral doxycycline (100 mg BID) x 28 days should be preferred for adults other than pregnant women who present with Lyme arthritis, when there is a strong suspicion of Lyme disease.	**Unanimous**
Oral amoxicillin (500 mg TID) x 28 days or oral cefuroxime axetil (500 mg BID) x 28 days should be alternate solutions to doxycycline, when doxycycline is absolutely contraindicated, for adults who present with Lyme arthritis, when there is a strong suspicion of Lyme disease.	**Unanimous**
Oral doxycycline (100 mg BID) x 28 days or ceftriaxone IV (2 g QD) x 14–28 days should be preferred for adults who present with relapsing Lyme arthritis.	**> 80%**
Oral amoxicillin (500 mg TID) x 28 days, oral cefuroxime axetil (500 mg BID) x 28 days, cefotaxime IV (2 g TID) or penicillin G IV (18–24 million units/day divided every 4 hours) x 14–28 days should be alternate solutions to oral doxycycline or to ceftriaxone IV, when those antibiotics are absolutely contraindicated, for adults who present with relapsing Lyme arthritis.	**> 80%**
Oral doxycycline (4.4 mg/kg/day divided into two doses [max. 100 mg/dose]) x 28 days should be preferred for children aged 8 and up who present with Lyme arthritis, when there is a strong suspicion of Lyme disease.	**Unanimous**

Oral amoxicillin (50 mg/kg/day divided into three doses [max. 500 mg/dose]) x 28 days or oral cefuroxime axetil (30 mg/kg/day divided into two doses [max. 500 mg/dose]) x 28 days should be alternate solutions to doxycycline, when doxycycline is absolutely contraindicated, for children aged 8 and up who present with Lyme arthritis, when there is a strong suspicion of Lyme disease.	**> 80%**
Oral amoxicillin (50 mg/kg/day divided into three doses [max. 500 mg/dose]) x 28 days or oral cefuroxime axetil (30 mg/kg/day divided into two doses [max. 500 mg/dose]) x 28 days should be preferred for children under age 8 who present with Lyme arthritis, when there is a strong suspicion of Lyme disease, except for patients who have had a previous very severe allergic reaction to penicillin.	**> 80%**
Oral doxycycline (4.4 mg/kg/day divided into two doses [max. 100 mg/dose]) x 28 days or ceftriaxone IV (75–100 mg/kg/day QD [max. 2,000 mg]) x 14–28 days should be preferred for children aged 8 and up who present with relapsing Lyme arthritis.	**Unanimous**
Oral amoxicillin (50 mg/kg/day divided into three doses [max. 500 mg/dose]) x 28 days, oral cefuroxime axetil (30 mg/kg/day divided into two doses [max. 500 mg/dose]) x 28 days, cefotaxime IV (225–300 mg/kg/day divided into three or four doses [max. 12 g/day]) x 14–28 days, or penicillin G IV (0.2–0.4 million units/kg/day divided every 4 hours [max. 18–24 million units/day]) x 14–28 days should be treatment options for children aged 8 and up who present with relapsing Lyme arthritis if first-line antibiotics (oral doxycycline and ceftriaxone IV) cannot be administered.	**Unanimous**
Oral amoxicillin (50 mg/kg/day divided into three doses [max. 500 mg/dose]) x 28 days, oral cefuroxime axetil (30 mg/kg/day divided into two doses [max. 500 mg/dose]) x 28 days, or ceftriaxone IV (75–100 mg/kg/day QD [max. 2,000 mg] x 14–28 days should be preferred for children under 8 who present with relapsing Lyme arthritis.	**Unanimous**
Cefotaxime IV (225–300 mg/kg/day divided into three or four doses [max. 12 g/day] x 14–28 days) or penicillin G IV (0.2–0.4 million units/kg/day divided every 4 hours [max. 18–24 million units/day] x 14–28 days) should be treatment options for children under 8 who present with relapsing Lyme arthritis if first-line antibiotics (oral amoxicillin, oral cefuroxime axetil and ceftriaxone IV) cannot be administered.	**> 80%**
Oral doxycycline (4.4 mg/kg/day divided into two doses [max. 100 mg/dose]) x 28 days could be considered for children under 8 who present with relapsing Lyme arthritis and who have had a previous very severe allergic reaction to penicillin, following an informed discussion with the patient's parent (or guardian). Non-steroidal anti-inflammatory drugs could be considered for ad hoc pain relief in conjunction with antibiotics.	**Unanimous**

Corticosteroids should be avoided for patients being treated with antibiotics for Lyme arthritis.	**> 80%**
In the event that the first course of antibiotics fails, the attribution of arthritis to Lyme disease should be re-evaluated. The opinion of a specialist or an experienced colleague should be sought in such cases.	**> 80%**
If symptoms persist after two courses of antibiotics, the decision not to prescribe another antibiotic should be made on a case-by-case basis following a discussion with a specialist.	**Unanimous**
An intra-articular corticosteroid injection or a disease-modifying anti-rheumatic drug could be considered after an antibiotic treatment. The opinion of a specialist or an experienced colleague should be sought in such cases.	**Unanimous**
Information to give to patients or their families (or guardian)	
Patients should be informed that some symptoms may persist for a few weeks or even months after the antibiotic treatment. The scientific data currently available do not allow researchers to reliably determine the cause of this persistence beyond the damage caused by the infection.	**Unanimous**
To relieve pain and non-specific systemic symptoms, prescribing an antipyretic/analgesic (e.g., acetaminophen, ibuprofen) in addition to antibiotics could be considered.	**Unanimous**
Although the Jarisch-Herxheimer reaction is relatively rare, patients should be informed that it could occur within 24 to 48 hours of the start of treatment and that, if it does, they must continue to take the antibiotic. Patients should be told to contact a health care professional if they have any questions or concerns.	**Unanimous**
Patients should be informed of the symptoms suggestive of Lyme disease to watch for and told to contact a health care professional if they have any questions or concerns, if their rash gets bigger or if new symptoms appear.	**Unanimous**
Follow-up	
The clinical condition of a patient who has received a Lyme disease diagnosis and has persistent symptoms following antibiotic treatment, of an intensity and duration that seems unusual and cannot be attributed to other probable clinical conditions, should be reassessed in collaboration with one or many specialists, depending on the symptoms.	**Unanimous**

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APPENDIX A: Differences Between Genospecies of the *Borrelia burgdorferi* s.l. Complex

Table A1 Differences between genospecies of the *Borrelia burgdorferi* s.l. complex

GENOSPECIES	GEOGRAPHIC LOCATION	PRIMARY RESERVOIR	VECTOR (TICKS NOT ASSOCIATED WITH LYME DISEASE)	PATHOGENICITY IN HUMANS
B. burgdorferi sensu stricto	**North America** **Europe**	**Rodents** **Birds**	***I. scapularis*** ***I. pacificus*** ***I. ricinus***	**Yes**
B. bissettii	**United States** **Europe**	**Birds** **Rodents**	***I. scapularis*** ***I. pacificus*** ***I. ricinus*** ***(I. minor)***	**Yes**
B. mayonii	**United States (upper Midwest)**	**Rodents**	***I. scapularis***	**Yes**
B. andersonii	**United States**	**Rabbits**	***I. scapularis*** ***(I. dentatus)***	**Maybe[1]**
B. americana	**United States**	**Birds**	***I. pacificus*** ***(I. minor)***	**Maybe[1]**
B. kurtenbachii	**North America**	**Rodents**	***I. scapularis***	**Maybe[1]**
B. californiensis	**United States**	**Kangaroo rats** **Mule deer**	***I. pacificus*** ***(I. jellisonii)*** ***(I. spinipalpis)***	**No**
B. carolinensis	**United States**	**Rodents**	***(I. minor)***	**No**
B. chilensis	**Chile**	**Rice rats**	***(I. stilesi)***	**No**
B. afzelii	**Europe** **Asia**	**Rodents**	***I. ricinus*** ***I. persulcatus***	**Yes**
B. garinii	**Europe** **Asia**	**Birds** **Rodents**	***I. ricinus*** ***I. persulcatus***	**Yes**
B. bavariensis	**Europe** **Asia**	**Rodents**	***I. ricinus*** ***I. persulcatus***	**Yes**
B. spielmanii	**Europe**	**Rodents**	***I. ricinus***	**Yes**
B. valaisiana	**Europe** **Asia**	**Birds**	***I. ricinus*** ***(I. granulatus)***	**Yes**
B. lusitaniae	**Europe** **North Africa**	**Rodents**	***I. ricinus***	**Yes**
B. finlandensis	**Finland**	**Unknown**	***I. ricinus***	**No**
B. sinica	**China**	**Rodents**	***(I. ovatus)***	**No**
B. yangtzensis	**China** **Japan**	**Rodents**	***(Haemaphysalis longicornis)*** ***(I. granulatus)***	**No**
B. japonica	**Japan**	**Rodents**	***(I. ovatus)***	**No**
B. tanukii	**Japan**	**Unknown**	***(I. tanuki)***	**No**
B. turdi	**Japan**	**Birds**	***(I. turdus)***	**No**

Source: Adapted from Stone et al., 2017.

[1] The pathogenicity of these strains is not yet confirmed; however, they have been found in human samples [Clark et al., 2014; Clark et al., 2013].

The clinical manifestations due to the *Borrelia* genospecies that most commonly cause Lyme disease are presented in Table A2. The European strains of *B. burgdorferi* sensu stricto produce an infection that more closely resembles the infection produced by *B. afzelii* and *B.*

garinii than North American *B. burgdorferi* s.s. Further, the ability to disseminate varies from one genospecies to another: while the multisystem dissemination of North American strains of *B. burgdorferi* is common, *B. afzelii* typically persists at skin sites, and *B. garinii* is particularly neurotropic [Steere et al., 2016].

Table A2 Clinical manifestations of Lyme disease by causal bacterial genospecies

	United States	Europe	
	***B. burgdorferi* s.s.**	***B. garinii***	***B. afzelii***
Localized stage			
Skin manifestations	EM often accompanied by general symptoms[1] EM expands more rapidly than with other genospecies	EM accompanied by itching and a burning sensation EM expands more rapidly than with other European genospecies	EM usually with no other symptoms Borrelial lymphocytoma[2] (rare)
Early disseminated stage			
Skin manifestations	Multiple EM	N/A	Persistence at the site of the bite or other sites
Neurological manifestations	Lymphocytic meningitis with periodic headaches and slight cervical rigidity, cranial neuropathy[3] or radiculoneuritis Cerebellar ataxia and encephalomyelitis (rare)	Bannwarth's syndrome[4]	Non-specific clinical symptoms[5]
Cardiac manifestations	Varying degrees of fluctuation in the atrioventricular node Other less common manifestations[6]		
Late disseminated stage			
Lyme arthritis	Most common manifestation Intermittent painful joint swelling involving primarily the large joints	Less frequent and earlier in the progression of the disease than with the North American strain (3 months instead of 6 months)	
Skin manifestations	None	ACA (less frequent than with *B. afzelii*)	ACA
Neurological manifestations	Rare Controversial causality		

Source: Steere et al., 2016.

[1] Discomfort, fatigue, headaches, arthralgia, myalgia, fever, regional lymphadenopathy

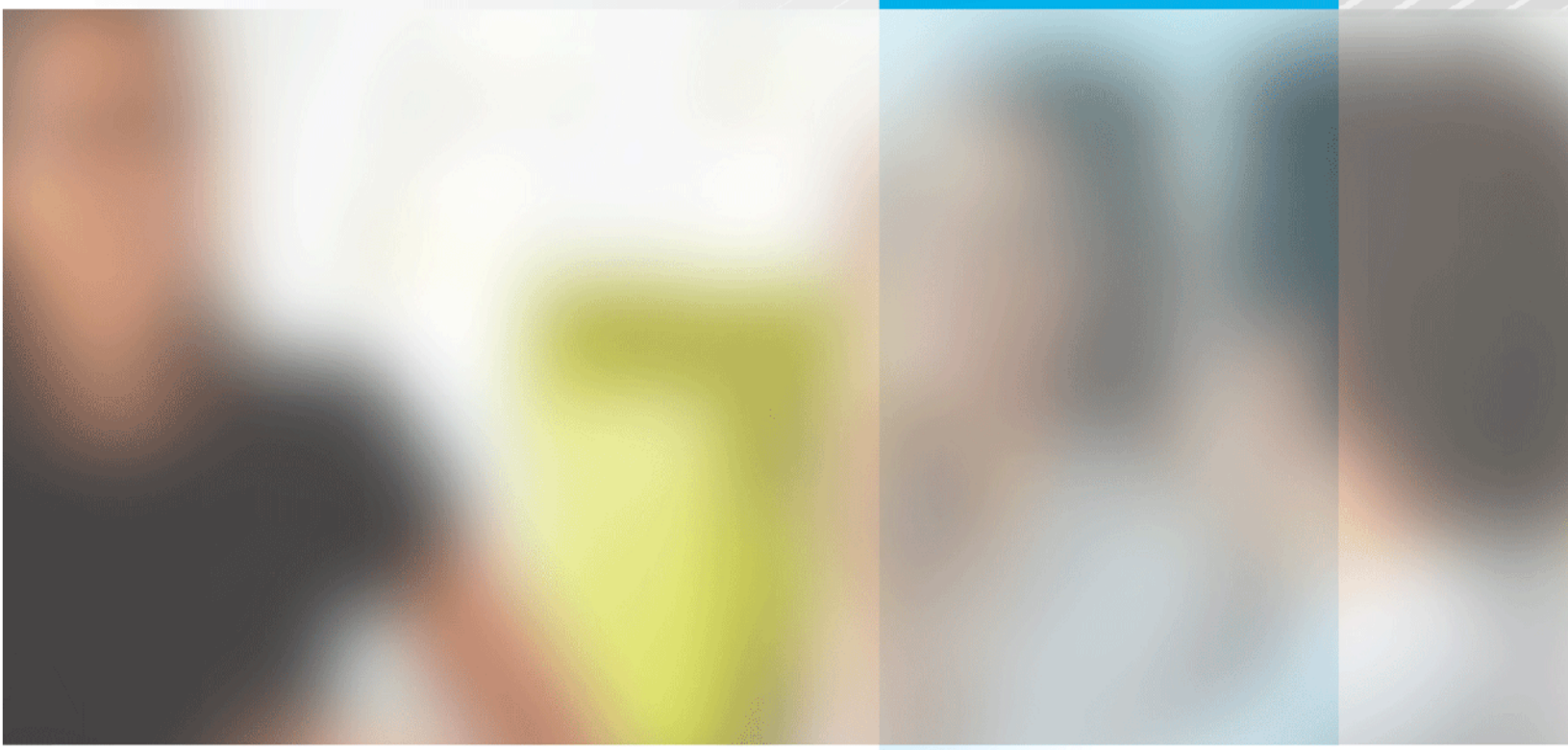
[2] Borrelial lymphocytoma is typically located on the earlobe in children and the nipple in adults.

[3] Particularly facial palsy

[4] Painful radiculoneuritis associated with lymphocytic meningitis (often without headaches) and sometimes followed by cranial neuropathy or partial palsy of the extremities

[5] Including headaches, dizziness, memory impairment, difficulty concentrating, and paresthesia

[6] Including acute myopericarditis and mild left ventricular dysfunction and, rarely, cardiomegaly or pancarditis



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