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Lyme Disease Training and Knowledge Translation Resources Available to Canadian Healthcare Professionals: A Gray Literature Review

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Abstract

Introduction: Lyme Disease (LD) is the most common tick-borne disease in North America. With the number of cases increasing yearly, Canadian healthcare professionals (HCP) rely on up-to-date and evidence-informed guidelines, instruction, and resources to effectively prevent, diagnose, and treat Lyme disease (LD). This review is the first of its kind to examine gray literature and analyze the diversity of recommendations provided to Canadian HCP about the prevention, diagnosis, and treatment of Lyme disease. **Methods:** A gray literature review consisting of 4 search strategies was conducted to retrieve materials targeted to Canadian HCP. Searches within targeted websites, targeted Google searches, and gray literature databases, and consultation with content experts were done to look for continuing medical education (CME) events, clinical flow charts, webinars, videos, and reference documents that discussed the prevention, diagnosis, and treatment of Lyme disease. **Results:** A total of 115 resources were included in this study. Recommendations surrounding prevention strategies were less varied between materials, whereas diagnosis and treatment recommendations were more varied. Our findings suggest that Canadian HCP are met with varying and sometimes contradictory recommendations for diagnosing and treating LD. **Conclusions:** Due to the increasing incidence of LD in Canada, there is a greater need for resource consistency. Providing this consistency may help mitigate LD burden, standardize approaches to prevention, diagnosis and treatment, and improve patient outcomes.

Keywords

diagnosis, gray literature, Lyme disease, medical education, treatment

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Introduction

Lyme disease (LD) is an infectious tick-borne disease caused by bacteria strains of *Borrelia burgdorferi* sensu lato complex. In North America, LD is commonly transmitted through infected ticks belonging to the *Ixodes scapularis* or *Ixodes pacificus* species.[1,2] The number of LD cases in Canada has increased 10-fold between 2009 and 2018.[3] The impact of LD has not been felt equally across Canada, with some provinces seeing much higher infection numbers than other provinces and/or territories.[3] However, all healthcare professionals need to have access to evidence-based protocols regardless of the LD infection rates in their area, due to travel-based infections.

Symptoms of LD are typically characterized with disease progression across 3 stages; early localized, early disseminated, and late disseminated.[4] The initial stage of the disease, early localized LD, is generally associated with symptoms such as headaches, fatigue, fevers, and muscle pain often with an erythema migrans rash.[5] Early disseminated LD symptoms can include multiple cutaneous rashes, joint pain, fatigue, cardiac (eg, palpitations, atrioventricular block) and neurological symptoms (eg, facial palsy, headache).[5,6] Late disseminated LD symptoms are often characterized as including worsening joint pain and/or arthritis, and cardiac and neurological symptoms (eg, encephalitis, chronic meningitis).[5,6] In some patients, those

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Table 1. Inclusion/Exclusion Criteria.

Inclusion criteria	Exclusion criteria
Workshop, webinar/video, podcast, reference document, clinical flow chart, CPD/CME event, guidelines, or training seminar (with/without accreditation) relating to Lyme disease.	Materials not available to Canadian HCPs.
Intended for healthcare professionals (HCPs) within the context of practice (preventing, diagnosing, and treating LD).	Conference presentations, research seminars, poster presentations, newsletters, abstracts.
Must be accessible to Canadians HCPs (eg, can be international source, if Canadian HCPs have access).	Intended solely for personal use and information (community facing messaging).
Within the last ten years (≥2010).	Training specific to students (medical, nursing, pharmacy) or residents.
English and/or French.	Primary research findings (eg, epidemiology of LD, microbiology/biochemistry of LD, surveillance of LD).
	Peer reviewed materials.
	Incomplete resources (eg, a syllabus).

disabling symptoms have been shown to persist after antibiotic treatment and this stage has been termed post-treatment LD syndrome (PTLDS).[7-9] There is another group of individuals who have been diagnosed or self-diagnosed with chronic Lyme disease (CLD). While there is no singularily agreed upon definition of chronic Lyme disease, these are individuals with real and debilitating symptoms that fit PTLD, but have not been previously diagnosed with LD.[10,11]

Current preventative practices for LD include personal protective behaviors as well as landscape preventative measures. Depending on the symptoms, LD is generally diagnosed using a combination of a clinical assessment, history of potential exposure to ticks, and/or serology testing.[12,13] Reducing the risk of LD disease progression requires prompt and accurate diagnosis and effective LD treatment. With the increasing burden of LD in certain regions of Canada, there is a need for consistent and evidence-based guidance for Canada healthcare professionals (HCP).

Public health units, professional organizations, and provincial and federal governments use their websites to share information and recommendations for the prevention, diagnosis, and treatment of various health conditions and public health concerns. Recently, 2 Canadian studies found varying information and recommendations presented on provincial public health websites[14] as well as patient groups, and provincial and federal government websites.[15] The present study extends the work of these studies.

This is the first to systematically collect national gray literature resources available to all HCP (including naturopathic practitioners) regarding LD prevention, diagnosis, and treatment. The goal of our work is to establish areas of HCP messaging consistency and inconsistency to inform ongoing research investigating the basis for HCP LD prevention, diagnosis, and treatment decision making.

Materials and Methods

Our preliminary gray literature review was completed in May 2020, and secondary revisions were conducted when policy resources were updated (until April 2021). Gray literature is defined as any literature that has not been published through traditional means (eg, academic journals) and is not controlled by commercial publishing.[16] Gray literature is produced by government, academic, and business sources and includes government reports, policy statements, theses, and conference proceedings.[16]

The scope of the review included all knowledge translation (KT) and educational resources and/or materials available to Canadian healthcare practitioners of any profession. The full inclusion and exclusion criteria can be found in Table 1. We chose to include a broad set of training materials/resources including workshops, webinars, podcasts, clinical guidelines, and continuing professional education or continuing medical education (CPD/CME) opportunities. We excluded materials specifically for non-healthcare professionals and clinical students (medicine, nursing, etc.). Although any resource or message could conceivably impact HCP, systematically searching these materials would be untenable. If a resource was published internationally, but available freely to Canadian HCP, it was included. Given the changing landscape of research into LD and resulting clinical recommendations, we chose to only include documents produced or updated subsequent to 2010.

The process for systematically collecting gray literature was divided into 4 steps based on a framework developed by Godin et al[17] and included: (1) targeted website searches, (2) Google searches, (3) targeted database searches, and (4) consultations with content experts (eg, LD patient advocates, clinical, patient and community, academic, and/or political members of the Canadian Lyme Disease Research Network). We used a broad set of search terms (Table 2) that were adapted for each website/database. The first 100 returned search results from each step were reviewed for relevancy. If a resource was incomplete (eg, a resource listed a date and time of a webinar, but not a recording of the webinar) a note was made to follow up and attempt to retrieve the missing materials. If materials could not be

Table 2. Search Terms.

Keywords	
Lyme	Lyme Canada
Lyme diagnosis	Lyme disease naturopathic doctor webinar
Lyme workshop	naturopathic Lyme disease training
Lyme treatment	Lyme disease naturopathic cpd
Lyme disease	Lyme nurse practitioner training
Lyme cpd	CME Lyme disease
Lyme professional development	Lyme training
Lyme disease continuing professional development	Lyme disease training pharmacists

acquired, the document was excluded from the study. All formal searches were conducted between May 14th, 2020 and May 19th, 2020.

We also contacted content experts to identify knowledge translation and or educational materials. Clinical, patient and community, academic, and/or political members of the Canadian Lyme Disease Research Network[18] were contacted with a survey asking them the following information: their profession, their experience with Lyme disease in their profession, their geographic location (within Canada), and any links to training materials they have used if applicable. The survey was created using Qualtrics and distributed via email. Each resource provided by content experts was reviewed for eligibility.

After duplicates were removed from within and across search strategies, each document/resource was reviewed by 2 blinded and independent reviewers (S.S., V.A.) for eligibility. Similar to a full systematic review each document was reviewed in full to assess eligibility. Discussion between the reviewers occurred when there was a disagreement or an "unclear" opinion regarding any of the documents. When required, a third reviewer was brought into discussions (A.C.B.).

Data Extraction

A deductive coding[19] approach was used to analyze the documents and was completed using NVivo.[20] Top and mid-level codes were pre-defined to address known themes: early localized LD, early disseminated LD, late LD, PTLD, CLD (top levels) and etiology, prevention, diagnosis, and treatment (mid-level codes). Subsequent level themes were developed with an iterative approach as coding progressed. Transcripts of webinars and other videos were obtained from YouTube's transcription option. If this was not possible, they were transcribed by our research team (V.A., S.S.). French language documents and webinars were translated into English.

Resources were characterized using Case Classifications in NVivo and included: country of publication, date of publication, province (where relevant), type of document (knowledge translation, continuing professional development, etc.), and estimates of LD activity based on case counts in the region where a document originated.[3] The estimates of LD infections were used to label regions of Canada into 4 groups: no cases, low endemic area (regions with small number of cases), moderate endemic area, and high endemic area (see Table 3). The number of LD cases was chosen over incidence rate (LD cases per unit of population) for 3 reasons: (1) provinces with large populations also have large urban areas that are less likely to be exposed to ticks, (2) some provinces with smaller populations can also have relatively higher densities of populations living within tick areas, and (3) the incidence of LD cases can be diluted in large populations living in urban areas. Documents retrieved from the Canadian federal government or other Canadian national organizations were labeled under "national" and those retrieved from international sources were labeled under "international", regardless of the level of LD within those countries. This approach to international documents was chosen as it is unclear how the information would influence the clinical decision making of doctors in different regions of Canada.

Table 3. Estimates of LD Activity.

LD activity	Provinces
No cases	Yukon, North West Territories, and Nunavut
Low cases	British Columbia, Alberta, Saskatchewan, New Brunswick, Prince Edward Island, and Newfoundland
Moderate cases	None
High cases	Nova Scotia, Quebec, and Ontario

Results

The initial search yielded 914 resources across all 4 search strategies (Figure 1). Duplicate resources were removed from within each search method, yielding a remaining 286 resources. Duplicates were then removed from between search strategies, yielding a remaining 242 materials. These 242 documents were then reviewed for eligibility and 127 materials were excluded at this stage. Reasons for exclusion included having inaccessible or incomplete materials,

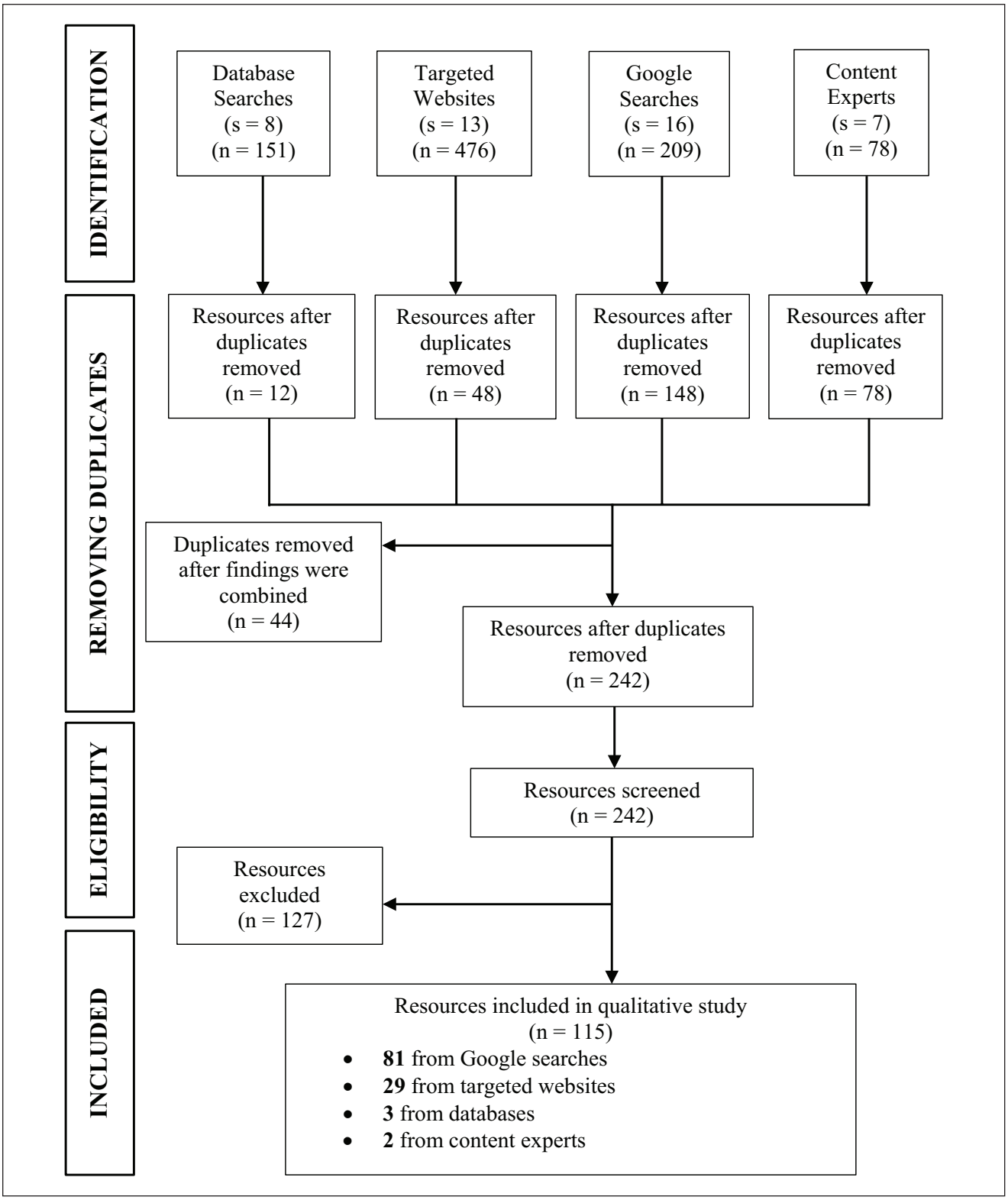

Figure 1. PRISMA diagram. The diagram outlines the flow of search findings from each of the 4 search strategies, removal of duplicates within and across search strategies, and retention of documents after screening.
s, refers to the number of databases, websites, etc. that were searched. n, refers to the number of documents returned.

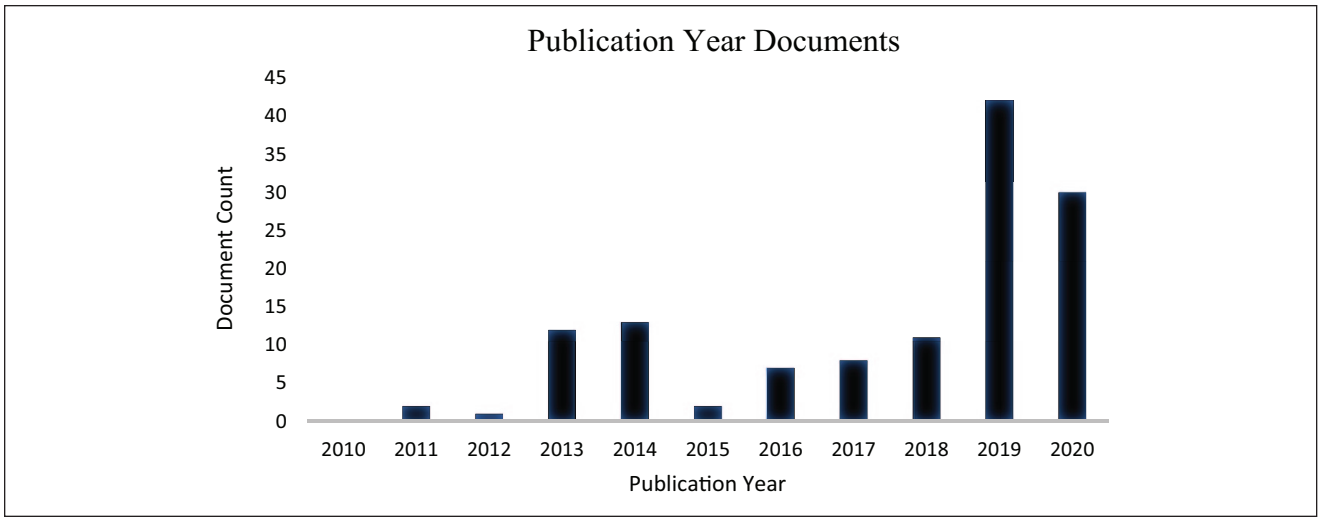

Figure 2. Publication Year of Documents.

materials were primarily for patients and/or families, or were published before 2010. In total, 115 resources were included in this review. A total of 128 documents were coded within the NVivo file because some resources had to be broken up and coded using multiple files (eg, a single website might have 2 webinars).

A total of 128 documents were identified and classified. Of the 128 documents, 86 documents were from different Canadian provinces, 10 from the Canadian national level, and 32 documents came from international sources. The largest number of provincial documents came from the province of Ontario (n = 25), followed by Quebec (n = 22). No documents were retrieved from the provinces of Saskatchewan, Prince Edward Island, Yukon, or Nanavut. Of the provincial documents, most (n = 82) came from high endemic regions, 3 from low endemic regions, and 1 from region with no reported cases. Additionally, the majority of documents (n = 72) were published within between 2019 and 2020 (see Figure 2).

Prevention

We examined the documents to see what strategies are recommended to prevent LD. Thirty-eight documents discussed some aspect of prevention. Discussed prevention strategies included personal protective measures (82%), proper removal of a tick (56%), landscape management (15%), checking pets (9%), and management of deer population (6%) (see Table 4). Personal protective measures included: avoiding tick infested areas, wearing long pants and sleeves, using bug repellent with DEET, wearing light colors, and removing ticks immediately. Documents recommending prevention strategies came from regions within Canada with no officially reported cases of LD, low and high numbers of cases, as well as from national and international sources. The largest number of documents (50%) came from high-endemic areas and the fewest came from regions with no cases (3%). Most resources (61%) were published in the 2019 and 2020.

Twenty-six documents included details on the attachment time needed for a tick to transmit LD causing bacteria to its human (Table 5). Twelve (46%) of those documents reported that it took a minimum of 24 h after a tick bites its host for LD causing bacteria to be transmitted. Six (23%) of the documents reported less that 24 h and another 6 (23%) reported that it took a minimum of 36 to 48 h. Most of the documents came from high endemic regions of Canada. The publication dates ranged from 2013 to 2020.

Thirty-one documents reported clinical criteria for offering a patient antibiotic prophylaxis treatment for a tick bite (Table 6). Fifteen documents (48%) reported that patients must meet 4 criteria: the tick was a black legged tick, the tick was removed $<$72 h ago, the patient must have been bitten in a high endemic area, and the tick was attached for $>$36 h. Eight documents (26%) reported the same 3 initial criteria, but that the tick was attached for $>$24 h.

Diagnosis

Twenty-nine documents provided a reference for the incubation period after a tick bite. All 29 documents referenced overlapping windows of time of between 1 and 32 days (data not shown).

Symptoms of early localized LD. Sixty documents discussed the symptoms of early localized (EL) Lyme disease (see Table 7). Six categories of symptoms were reported for early localized LD: cutaneous, joint pain/arthritis, myalgia,

Table 4. Recommended Prevention Strategies (n = 38 documents).

Mechanism	Prevention document count	Endemic level	Region	Publication date	
Personal protective measures*	32	No cases = 1 Low = 1 High = 15	Natl = 5 Intl = 10	2013 = 1 2014 = 5 2016 = 3 2017 = 3	2018 = 3 2019 = 7 2020 = 10
Checking pets to protect humans	3	No cases = 1 High = 2	No data	2017 = 1 2019 = 1	2020 = 1
Landscape management	4	High = 2	Natl = 1 Intl = 1	2013 = 1 2018 = 1	2020 = 2
Management of deer population	2	High = 1	Intl = 1	2020 = 2	
Proper removal of a tick	23	Low = 1 High = 8	Natl = 4 Intl = 10	2013 = 1 2017 = 1 2018 = 5	2019 = 7 2020 = 9

*Avoid tick infested areas (eg, wooded areas), wear long pants/sleeves, wear light colors (to help spot ticks), use bug repellent with DEET, remove ticks immediately.

Table 5. Attachment Time Needed for Bacteria to Move From Tick to Host (n = 26 documents).

Time frame	Document count	Endemic level	Region	Date	
Less than 24 h	6	High = 5	Intl = 1	2013 = 2 2019 = 2	2020 = 2
A minimum of 24 h	12	High = 8	Natl = 1 Intl = 2	2016 = 1 2017 = 1	2019 = 5 2020 = 4
A minimum of 24-48 h	3	High = 2	Intl = 1	2016 = 1 2019 = 1	2020 = 1
A minimum of 36-48 h	6	High = 5	Natl = 1	2013 = 2 2017 = 1	2018 = 1 2019 = 2
A minimum of 36-72 h	1	Low = 1	No data	2018 = 1	
A minimum of 48 h	2	High = 2	No data	2013 = 1	2014 = 1

Table 6. Clinical Criteria for Offering Prophylaxis Antibiotic Treatment (n = 31 documents).

Criteria	Document count	Endemic level	Region	Date	
Must meet four criteria: tick was a black legged tick, was removed less than 72 h ago, patient must have been bitten in high endemic area, *AND tick was attached for 24-36 h.*	2	High = 2	No data	2017 = 1	2019 = 1
Must meet four criteria: black legged tick, tick was removed less than 72 h ago, patient must have been bitten in high endemic area, *AND tick attached for MORE than 24 h.*	8	High = 7	Natl = 1	2014 = 2 2019 = 4	2020 = 2
Must meet four criteria: black legged tick, tick was removed less than 72 h ago, patient must have been bitten in high endemic area, *AND tick attached for more than 36 h.*	15	Low = 1 High = 7	Natl = 2 Intl = 5	2013 = 1 2014 = 1 2016 = 2 2017 = 2	2018 = 2 2019 = 2 2020 = 5
Anyone with black legged tick bite	1	No data	Intl = 1	2020 = 1	
Based on prevalence of LD in area	2	High = 2	No data	2016 = 1	2019 = 1
Routine Prophylaxis not recommended.	9	High = 5	Natl = 2 Intl = 2	2013 = 1 2014 = 1 2016 = 1	2018 = 1 2019 = 1 2020 = 4

Table 7. Symptoms Associated With Early Localized and Early Disseminated Stages of LD.

		Symptoms							
Stage		Cardiac	Cognitive	Cutaneous	Joint pain/ arthritis	Myalgias	Neuro- logical	Ocular	Systemic
Early localized (n = 60 documents about EL symptoms)	Document count	No data	No data	56 (93%)	27 (45%)	22 (37%)	4 (7%)	1 (2%)	39 (65%)
	Regional endemic level	No data	No data	No cases = 1 Low = 3 High = 37	No cases = 1 Low = 2 High = 13	No cases = 1 Low = 2 High = 11	N/A	N/A	No cases = 1 Low = 2 High = 20
	National or international sources	No data	No data	Natl = 8 Intl = 7	Natl = 4 Intl = 7	Natl = 3 Intl = 5	Intl = 4	Intl = 1	Natl = 6 Intl = 10
	Date	No data	No data	2013 = 2 2014 = 4 2015 = 2 2016 = 4 2017 = 5 2018 = 4 2019 = 20 2020 = 15	2014 = 1 2015 = 1 2016 = 2 2017 = 2 2018 = 2 2019 = 9 2020 = 10	2014 = 1 2015 = 1 2016 = 2 2017 = 2 2018 = 2 2019 = 6 2020 = 8	2018 = 1 2019 = 2 2020 = 1	2020 = 1	2014 = 3 2015 = 2 2016 = 2 2017 = 3 2018 = 4 2019 = 12 2020 = 13
Early disseminated (n = 46 documents about ED symptoms)	Document count	39 (85%)	3 (7%)	35 (76%)	28 (61%)	8 (17%)	40 (87%)	10 (22%)	20 (43%)
	Regional endemic level	No cases = 1 Low = 1 High = 27	N/A	No cases = 1 Low = 1 High = 24	No cases = 1 Low = 1 High = 17	High = 6	No cases = 1 Low = 1 High = 26	Low = 1 High = 5	No Cases = 1 Low = 1 High = 13
	Natl or international sources	Natl = 6 Intl = 4	Natl = 2 Intl = 1	Natl = 5 Intl = 4	Natl = 4 Intl = 5	Intl = 2	Natl = 6 Intl = 6	Natl = 1 Intl = 3	Natl = 1 Intl = 4
	Date	2013 = 1 2014 = 5 2015 = 1 2016 = 4 2017 = 2 2018 = 3 2019 = 14 2020 = 9	2014 = 1 2020 = 2	2013 = 1 2014 = 4 2015 = 1 2016 = 4 2017 = 1 2018 = 2 2019 = 13 2020 = 9	2013 = 2 2014 = 4 2015 = 1 2016 = 2 2017 = 2 2018 = 3 2019 = 6 2020 = 8	2013 = 1 2018 = 1 2019 = 3 2020 = 3	2013 = 1 2014 = 4 2015 = 1 2016 = 3 2017 = 2 2018 = 4 2019 = 14 2020 = 10	2018 = 1 2019 = 2 2020 = 7	2014 = 1 2017 = 1 2018 = 1 2019 = 9 2020 = 8

neurological, ocular, and systemic symptoms. These categories of symptoms were based on the individual symptoms listed within and across documents (see Supplemental Appendix 1 for a complete list of reported EL symptoms).

Systemic (65%), cutaneous (59%), and joint pain/arthritis symptoms (45%) were the most commonly reported symptoms in early localized LD. Most documents were published in high endemic regions and were published as of 2019.

Symptoms of early disseminated LD. Forty-six documents discussed the symptoms of early disseminated (ED) Lyme disease (see Table 7). Eight categories of symptoms were reported for early disseminated LD: cardiac, cognitive, cutaneous, joint pain/arthritis, musculoskeletal (MSK), neurological, ocular, and systemic symptoms. These categories of symptoms were based on the individual symptoms listed within and across documents (see Supplemental Appendix 2 for a complete list of reported ED symptoms).

Neurological (87%), cardiac (85%), and cutaneous symptoms (76%) were most commonly reported, followed by joint pain/arthritis (61%) and systemic symptoms (43%). Most documents were published in high endemic areas. These documents were published between 2013 and 2020, with most documents being published in recent years.

Symptoms of late disseminated LD. Forty-four documents discussed the symptoms of late disseminated (LD) Lyme Disease (see Table 8). Eight categories of symptoms were reported for late LD: cardiac, cognitive, cutaneous, joint pain/arthritis, myalgias, neurological, ocular, and systemic symptoms. These categories of symptoms were based on the individual symptoms listed within and across documents (see Supplemental Appendix 3 for a complete list of reported LD symptoms).

Joint pain/arthritis (98%) and neurological symptoms (82%) were most commonly reported, and most documents were published in high endemic areas. These documents were published between 2013 and 2020, which most document being published in the later years.

Symptoms of post treatment Lyme disease. Nineteen documents discussed the symptoms of Post Treatment Lyme Disease (PTLD) (see Table 8). Seven categories of symptoms were reported for PTLD: cardiac, cognitive, joint pain/arthritis, musculoskeletal (MSK), neurological, ocular, and systemic symptoms. These categories of symptoms were based on the individual symptoms listed within and across documents (see Supplemental Appendix 4 for a complete list of reported PTLD symptoms).

Systemic symptoms (89%) and cognitive (79%) symptoms were most commonly reported however, 1 resource published in 2019 in a high endemic region also listed gastrointestinal and reproductive symptoms as symptoms of PTLD. Most documents were published in high endemic areas, between 2013 and 2020.

Diagnostic criteria of early localized. Thirty-eight documents discussed the diagnostic criteria for early localized Lyme disease (see Table 9). The reported criteria included: '*diagnosis is clinical*', '*diagnosis is clinical supported by potential exposure*', '*diagnosis is based on clinical presentation and supported by serology*', and '*serology is not recommended*'. The criteria '*serology is not recommended*' was most commonly mentioned (66%), and most documents were published in high endemic areas. The documents were published between 2013 and 2020, with most published in recent years.

Diagnostic criteria of early disseminated. Twenty-two documents discussed the diagnostic criteria for early disseminated Lyme Disease (see Table 9). The reported criteria included: some conditions should prompt questions about potential tick exposure (18%) and diagnosis is based on clinical presentation and positive serology (86%). The documents were published between 2013 and 2020, with most of them being published in recent years.

Diagnostic criteria of late disseminated Lyme disease. Twenty-two documents discussed the diagnostic criteria for late disseminated Lyme Disease (see Table 9). The reported criteria included: some conditions should prompt questions about potential tick exposure (9%) and diagnosis is based on clinical presentation and positive serology (91%). Diagnosis is based on clinical presentation and positive serology, and serology is effective were mentioned the most, and most documents were published in high endemics areas. The documents were published between 2013 and 2020

Average onset of late disseminated LD. Twenty documents provided estimates of the average onset of late disseminated LD after initial tick bit (see Table 10). These estimates ranged from "less than 3 months," through to "months to years" post tick bite. The most common estimate was "months to years" (40%), followed by "weeks to months" (30%). The majority of these documents were published between 2018 and 2020.

Average onset of PTLD. Eight documents provided an estimated prevalence of PTLD (see Table 11). The estimated prevalence ranges included: 10% to 20%, 10% to 15%, and 10% of individuals who have received treatment for LD. Only documents published in high endemic areas and at the national level included estimates of PTLD prevalence. The documents were published between 2014 and 2020.

Eight documents provided the reported prevalence of PTLD (See Table 12). The reported prevalence included: months to years after initial treatment and 6 months after

Table 8. Symptoms Associated With Late Disseminated and PTLD.

Stage		Symptoms							
		Cardiac	Cognitive	Cutaneous	Joint pain/ arthritis	Myalgias	Neurological	Ocular	Systemic
Late disseminated Lyme disease (n = 44 documents about LD symptoms)	Document count	23 (52%)	26 (59%)	4 (9%)	43 (98%)	2 (5%)	36 (82%)	2 (5%)	6 (14%)
	Regional endemic level	No cases = 1 Low = 2 High = 10	Low = 2 High = 18	Low = 1	No cases = 1 Low = 2 High = 28	High = 1	No cases = 1 Low = 2 High = 22	High = 2	Low = 1 High = 3
	Natl or international sources	Natl = 4 Intl = 6	Natl = 3 Intl = 3	Intl = 3	Natl = 6 Intl = 6	Intl = 1	Natl = 5 Intl = 6	N/A	Intl = 2
	Date	2014 = 2 2015 = 1 2016 = 2 2017 = 2 2018 = 2 2019 = 4 2020 = 10	2013 = 1 2014 = 3 2015 = 1 2016 = 1 2017 = 2 2018 = 3 2019 = 8 2020 = 7	2018 = 1 2020 = 3	2013 = 1 2014 = 4 2015 = 1 2016 = 3 2017 = 3 2018 = 3 2019 = 16 2020 = 12	2016 = 1 2019 = 1	2013 = 1 2014 = 3 2015 = 1 2016 = 2 2017 = 3 2018 = 3 2019 = 11 2020 = 12	2019 = 1 2020 = 1	2018 = 2 2019 = 3 2020 = 1
Post treatment Lyme disease* (n = 19 documents about PTLD symptoms)	Document count	1 (5%)	15 (79%)	No data	11 (58%)	8 (42%)	10 (53%)	1 (5%)	17 (89%)
	Regional endemic level	High = 1	No cases = 1 Low = 1 High = 11	No data	No cases = 1 High = 6	No cases = 1 Low = 1 High = 5	Low = 1 High = 3	High = 1	No cases = 1 Low = 1 High = 10
	Natl or international sources	N/A	Natl = 1 Intl = 2	No Data	Intl = 4	Natl = 1	Intl = 6	N/A	Natl = 1 Intl = 4
	Date	2019 = 1	2013 = 1 2014 = 2 2016 = 2 2017 = 1 2018 = 2 2019 = 4 2020 = 3	No Data	2016 = 1 2017 = 4 2018 = 1 2019 = 2 2020 = 3	2014 = 2 2017 = 1 2018 = 1 2019 = 3 2020 = 1	2016 = 1 2017 = 2 2018 = 2 2019 = 1 2020 = 4	2019 = 1	2013 = 1 2014 = 2 2016 = 2 2017 = 3 2018 = 2 2019 = 4 2020 = 3

*One document from a high endemic region and published in 2019 also listed reproductive and gastrointestinal symptoms as symptoms of PTLD.

Table 9. Diagnostic Criteria for Early Localized, Early Disseminated, and Late Disseminated Lyme Disease.

		Diagnostic criteria									
Stage	Metric	Diagnosis is clinical		Diagnosis is clinical supported by potential exposure		Some conditions should prompt questions about potential tick exposure	Diagnosis is based on clinical presentation and supported by serology		Serology is NOT recommended	
Early localized Lyme disease (n = 38 documents)	Document count	11 (29%)		10 (26%)		No data	11 (29%)		25 (66%)	
	Endemic level	High = 5		Low = 1 High = 5		No data	Low = 1 High = 9		Low = 1 High = 13	
	Natl or Intl	Natl = 2 Intl = 4		Natl = 2 Intl = 2		No data	Intl = 1		Natl = 6 Intl = 5	
	Date	2014 = 1 2016 = 2 2017 = 1	2018 = 1 2019 = 5 2020 = 1	2016 = 2 2017 = 1 2018 = 1	2019 = 2 2020 = 4	No data	2013 = 3 2016 = 1 2017 = 1	2018 = 1 2019 = 3 2020 = 2	2013 = 1 2014 = 3 2015 = 1 2016 = 1	2017 = 2 2018 = 3 2019 = 6 2020 = 7
Early disseminated Lyme disease (n = 22 documents)	Document count	No data		No data		4 (18%)	19 (86%)		No data	
	Endemic level	No data		No data		High = 2	Low = 1 High = 11		No data	
	Natl or Intl	No data		No data		Intl = 2	Natl = 3 Intl = 4		No data	
	Date	No data		No data		2017 = 1 2019 = 3	2013 = 1 2014 = 1 2016 = 4 2017 = 1	2018 = 1 2019 = 5 2020 = 6	No data	
Late disseminated Lyme disease (n = 22 documents)	Document count	No data		No data		2 (9%)	20 (91%)		No data	
	Endemic level	No data		No data		No data	Low = 1 High = 13		No data	
	Natl or Intl	No data		No data		Intl = 2	Natl = 4 Intl = 2		No data	
	Date	No data		No data		2019 = 2	2013 = 1 2014 = 2 2016 = 3 2017 = 2	2018 = 1 2019 = 5 2020 = 6	No data	

Table 10. Average Onset of Late Disseminated LD (n = 20).

Average Onset	Document count (%)	Endemic level	Region	Date	
More than 4 to 6 weeks, but less than 3 months	1 (5)	No data	Natl = 1	2015 = 1	
>3 months	4 (20)	High = 2	Natl = 1	2019 = 1	2020 = 3
Weeks to months	6 (30)	Low = 1 High = 5	No data	2018 = 1	2019 = 5
6 months	2 (10)	Low = 1 High = 1	No data	2018 = 1	2019 = 1
Months to years	8 (40)	High = 1	Intl = 1	2013 = 1 2014 = 2	2019 = 3 2020 = 2

Table 11. Reported Prevalence of PTLD (n = 8).

Estimated prevalence	Document count (%)	Endemic level	Region	Date	
10%-20%	5 (63)	High = 4	Natl = 1	2014 = 2 2017 = 1	2019 = 1 2020 = 1
10%-15%	2 (25)	High = 1	Natl = 1	2015 = 1	2019 = 1
10%	1 (13)	High = 1	No data	2019 = 1	

Table 12. Average Onset Time of Symptoms of PTLD (n = 8).

Onset of symptoms	Document count (%)	Endemic level	Region	Date	
Months to years after initial treatment	5 (6)	Low = 1 High = 2	Natl = 2	2015 = 1 2017 = 1	2018 = 1 2020 = 2
6 months after initial treatment	3 (38)	High = 3	No data	2014 = 1	2019 = 2

treatment. Most documents published in high endemic areas and at the national level included the average onset time of symptoms of PTLD. The documents were published between 2014 and 2020.

Whereas there were thirteen documents that described the symptoms associated with PTLD (Table 8), only a few discussed how PTLD is diagnosed. One document from a high endemic area described how a PTLD diagnosis requires a previous confirmed diagnosis of Lyme disease that was treated properly.[21] Other documents from high endemic and a national source described the need for prolonged and debilitating symptoms.[10]

Treatment

Prophylactic treatment. Twenty nine documents included specific details on what antibiotics should be used as prophylactic treatment (Table 13). Most documents (79%) recommended a single, 200 mg dose of doxycycline while only 2 documents (7%) recommended a 20-day course of doxycycline. None of the documents published in Canada recommended a 20-day course. Canadian documents recommending a single dose of doxycycline came from low and high endemic areas as well as at the national level. Canadian documents were published between 2013 and 2020, with most published between 2018 and 2020.

Treatment during pregnancy. Fourteen documents discussed antibiotic options during pregnancy (Table 14). Most documents (86%) reported that Doxycycline was contraindicated during pregnancy, while 3 documents from high endemic areas reported that a single dose of Doxycycline was safe during pregnancy. Five documents recommended other antibiotic options for treating LD.

Treatment recommendations based on symptoms. Adult antibiotic treatment recommendations were also examined (Table 15). Antibiotic treatment recommendations were generally made based on the symptoms of the presenting patient. Across early localized, early disseminated, and late disseminated LD, we found that symptoms for treatment were categorized into "Arthritis or Joint Pain," "Cardiac," "Cutaneous," and "Neurological." Oral antibiotic options generally included: Doxycycline, Amoxicillin, and Cefuroxime and intravenous (IV) antibiotic options included: Ceftriaxone, Cefotaxime, and Penicillin. A list

Table 13. Prophylaxis Antibiotic Treatments (n = 29).

Treatment recommendations	Document count (%)	Endemic level	Region	Date	
20 days of doxycycline	2 (7)	No data	Intl = 2	2020 = 2	
Single dose of doxycycline (200 mg for adults)	23 (79)	Low = 1 High = 15	Natl = 2 Intl = 5	2013 = 1 2014 = 2 2016 = 2 2017 = 2	2018 = 2 2019 = 9 2020 = 5
2 weeks of doxycycline	1 (3)	No data	Intl = 1	2020 = 1	
Routine prophylaxis is not recommended.	9 (31)	High = 5	Natl = 2 Intl = 2	2013 = 1 2014 = 1 2016 = 1	2018 = 1 2019 = 1 2020 = 4

Table 14. Treatment Options During Pregnancy (n = 14).

Recommendation	Document count (%)	Endemic Level	Region	Date	
Doxycycline is contraindicated during pregnancy	12 (86)	Low = 1 High = 5	Natl = 3 Intl = 2	2013 = 1 2018 = 1	2019 = 5 2020 = 5
Single dose doxycycline (200 mg—prophylaxis) for pregnant women	3 (21)	High = 3	No data	2014 = 1	2019 = 2
Amoxicillin or cefuroxime instead of doxycycline	3 (21)	High = 2	Natl = 1	2013 = 1 2019 = 1	2020 = 1
Tetracycline HCl (acromycin, and others) instead of doxycycline	2 (14)	High = 1	Intl = 1	2019 = 1	2020 = 1

or grouping of antibiotic recommendations means that documents included 2 or more of those options in their recommendations.

Treatment recommendations for children. Twenty-two documents provided antibiotic treatment recommendations for children diagnosed with LD (Table 16). Thirteen of those documents (59%) recommended against the use of Doxycycline in young children (<8 years of age), whereas 8 (36%) indicated that Doxycycline is safe in children of all ages. Additionally, 3 documents (14%) indicated that Doxycycline was safe for short durations in young children. All documents indicating that Doxycycline is safe in young children (or at least in short durations) were published since 2019, whereas documents indicating that it is not safe were published between 2013 and 2020.

Discussion

We found recommendations for the prevention, diagnosis, and treatment of all stages of LD that varyied by specificity and consistency. When analyzing the recommendations for the prevention of LD, the recommendations were generally consistent across documents and provinces. Out of the 38 documents that mentioned a preventive measure, 84% discussed personal protective measures including avoiding tick infested areas, wearing long and light-colored clothes, and using insect repellant with DEET. However, we found that the recommendations for diagnosis and treatment were often inconsistent and at times lacked specificity. For example, recommendations regarding the diagnosis of LD varied across resources and there was conflicting advice regarding the usefulness of serology. Additionally, treatment recommendations across documents were at times conflicting. For example, while the majority of Canadian documents indicated that Doxycycline is contraindicated during pregnancy, 3 resources from high endemic areas indicated that a single dose of Doxycycline was safe during pregnancy.

There are conflicting perspectives and mounting tensions and conflict amongst physicians and patients. Such experiences have prompted some patients to pursue alternative medicine in Canada or receive treatment outside of the country.[22] Patients have expressed a desire for change within the healthcare system (eg, more open communication and better physician-patient relations),[23] and physicians must stay abreast of the latest clinical recommendations.

Patient frustration is not unique to Canada. Drew and Hewitt[24] reported negative experiences associated with LD care in the US, including frustrations with having to visit multiple physicians, prolonged diagnosis process, financial stress, and the need for self-advocacy if experiencing unresolved symptoms after treatment. Similar experiences were documented over a decade later, where patients continued to report experiences of strained physician-patient relationships and dissatisfaction with their care.[23]

Inconsistent information could impede healthcare professionals' ability to effectively diagnosis and treat LD. A

Table 15. Adult Antibiotic Recommendations Based on Symptoms.

Symptoms	Antibiotic choices	Document count	Endemic level	Region	Date	
Arthritis (n = ?)						
Uncomplicated arthritis	Treat with oral doxycycline or amoxicillin or cefuroxime	7	High = 4	Intl = 3	2013 = 1 2017 = 1	2019 = 2 2020 = 3
Arthritis and neurological symptoms	Treat with IV ceftriaxone, cefotaxime, or penicillin	1	High = 1	No data	2017 = 1	
Recurrent or persistent arthritis	Treat with another course of oral antibiotics.	2	No data	Intl = 2	2020 = 2	
	Treat with IV if showed no improvements with oral	2	High = 1	Intl = 1	2016 = 1	2020 = 1
	Treat with another course or oral, or IV.	4	High = 4	No data	2013 = 1 2017 = 1	2019 = 2
More serious arthritis	Treat with IV ceftriaxone or penicillin	1	No data	Intl = 1		2020 = 1
Cardiac						
Cardiac disease in early Lyme	Treat with oral antibiotics*	2	High = 1	Intl = 1	2013 = 1	2020 = 1
First degree AV Block	Treat with oral antibiotics*	4	High = 3	Intl = 1	2017 = 1 2019 = 2	2020 = 1
More serious cardiac symptoms^	Treat with IV antibiotics**	4	High = 1	Intl = 3	2017 = 1	2020 = 3
Treat myocarditis or pericarditis	Treat with IV antibiotics**	1	High = 1	No data	2019 = 1	
Cutaneous						
Erythma Migrans Rash	Treat with doxycycline	1	No data	Intl = 1	2017 = 1	
	Treat with oral antibiotics*	6	High = 4	Intl = 2	2013 = 1 2017 = 1	2019 = 1 2020 = 3
Neurological						
Mild neurological symptoms	Treat with oral antibiotics*	3	High = 3	No data	2013 = 1	2017 = 1
More serious neurological symptoms	Treat with IV antibiotics**	9	High = 7	Intl = 2	2013 = 1 2017 = 1	2019 = 4 2020 = 3
Neurological symptoms generally	Treat with IV antibiotics**	3	High = 2	Intl = 1	2016 = 1	2020 = 2
Peripheral nervous symptoms (including facial palsy)	Treat with oral antibiotics*	7	High = 5	Intl = 2	2019 = 4	2020 = 3

*Oral antibiotic options typically included doxycycline, amoxicillin, or cefuroxime.
**IV antibiotic options typically included ceftriaxone, cefotaxime, or penicillin.
^First degree AV block with PR interval >300 ms, or second or third degree AV blocks.

Table 16. Treatment Recommendations for Children With EL (n = 22).

Antibiotic options	Document count (%)	Endemic level	Region	Date	
Doxycycline contraindicative in young children (<8 years of age)	13 (59)	Low = 1 High = 7	Natl = 2 Intl = 3	2013 = 2 2014 = 1 2016 = 1 2017 = 1	2018 = 2 2019 = 1 2020 = 5
Doxycycline is safe to use in young children.	8 (36)	High = 3	Natl = 2 Intl = 3	2019 = 2	2020 = 6
Doxycycline is safe in young children for short periods	3 (14)	High = 2	Natl = 1	2019 = 2	2020 = 1

recent systematic review examining the impacts of educational interventions on the knowledge, attitudes, and behaviors of LD found a dearth of studies related to training initiatives for HCP.[25] Additionally, inconsistent information can influence the emergence and persistence of controversies within a healthcare system, leading to subsequent consequences on individual health.[26] Consistent education for healthcare professionals is an important step to reduce this knowledge gap. Multiple studies have shown how continuing medical education (CME) improves a HCP's performance to effectively treat patients, leading to better patient health outcomes.[27] For example, when studying the impact of a CME-certified series on addressing patients with multiple chronic comorbidities, participants demonstrated significant knowledge gains and were more likely to engage in actions leading to better patient outcomes (ie, referrals to specialists).[28]

It is important to highlight that clinical recommendations and guidelines presented to HCP are also reflective of the ongoing and evolving understanding of LD. The goal of this study was to examine the recommendations made to Canadian HCP to highlight areas of consistent and inconsistent recommendations that might inform basic science research in LD prevention, diagnosis, and treatment.

This study has limitations that should be considered when interpreting the results. First, not all material available to HCP was analyzed as they could not be obtained. For example, workshop materials were sometimes not obtained if permission was not granted from the organizers. Additionally, it is likely that some included materials may have been updated or removed after we conducted these searches, and these changes were not accounted for. Thirdly, other forms of gray literature (such as blogs, news articles, and more) were not considered, despite their increase in popularity. It is possible that these materials can provide valuable information to HCP[29] and warrant further research. Lastly, no formal metric was established to measure the degree of variability between the materials. Nonetheless, this study is the first of its kind and highlights the variability in LD resources available to Canadian HCP for the prevention, diagnosis, and treatment of Lyme disease.

Conclusions

This analysis of 115 materials discussing the prevention, diagnosis, and treatment of Lyme disease for healthcare professionals revealed that recommendations vary in specificity and consistency. Recommendations surrounding prevention strategies were less varied between materials, whereas diagnosis and treatment recommendations were more varied across the different stages of Lyme disease. Knowledge translation tools must acknowledge the diversity of literature available to HCPs, patients, and fundamental scientists, as a lack of consistency may lead to contentious approaches to diagnosis and treatment.

The Canadian Lyme Disease Research Network has been funded to co-develop a publicly accessible and comprehensive database of stage-dependent LD research, as well as research that may narrow the variations in diagnosis and treatment recommendations. This gray literature review will help inform the development of the database. This database will be collaboratively developed by, and translated to, patient partners, fundamental scientists, and clinicians. This initiative may render the complexity of diagnosis and treatment more transparent and accessible to all invested parties.

Additional research is also needed to understand how this variability in information affects healthcare professionals and their knowledge, beliefs, and practices regarding Lyme disease. Also, we need to understand what interventions are most effective for disseminating information needed to improve the prevention, diagnosis, and treatment of Lyme disease in Canada. Doing so can help healthcare professionals make timely, informed clinical decisions which have a profound effect on patient outcomes, and mitigate the burden that Lyme disease imposes on the Canadian healthcare system.

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Supplemental Material

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References

1. Eisen L, Dolan MC. Evidence for personal protective measures to reduce human contact with blacklegged ticks and for environmentally based control methods to suppress host-seeking blacklegged ticks and reduce infection with Lyme disease spirochetes in tick vectors and rodent reservoirs. *J Med Entomol*. 2016;53(5):1063-1092. doi:10.1093/jme/tjw103
2. Steere AC, Strle F, Wormser GP, et al. Lyme borreliosis. *Nat Rev Dis Primers*. 2016;2(1):16090. doi:10.1038/nrdp.2016.90
3. Government of Canada. Surveillance of Lyme disease. 2020. Accessed November 17, 2020. https://www.canada.ca/en/public-health/services/diseases/lyme-disease/surveillance-lyme-disease.html
4. Murray TS, Shapiro ED. Lyme disease. *Clin Lab Med*. 2010;30(1):311-328. doi:10.1016/j.cll.2010.01.003
5. Government of Canada. For health professionals: Lyme disease. 2018. Accessed December 14, 2020. https://www.canada.ca/en/public-health/services/diseases/lyme-disease/health-professionals-lyme-disease.html
6. Cardenas-de la Garza JA, De la Cruz-Valadez E, Ocampo-Candiani J, Welsh O. Clinical spectrum of Lyme disease. *Eur J Clin Microbiol Infect Dis*. 2019;38(2):201-208. doi:10.1007/s10096-018-3417-1
7. Cairns V, Godwin J. Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. *Int J Epidemiol*. 2005;34(6):1340-1345. doi:10.1093/ije/dyi129
8. Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med*. 2001;345(2):85-92. doi:10.1056/NEJM200107123450202
9. Ścieszka J, Dąbek J, Cieślik P. Post-Lyme disease syndrome. *Reumatologia*. 2015;53(1):46-48. doi:10.5114/reum.2015.50557
10. BC Women's Hospital + Health Centre. *Clinical protocol: "Chronic Lyme disease" or "post-Lyme syndrome"*. BC Women's Hospital + Health Centre. 2020. Accessed February 5, 2021.
11. International Lyme and Associated Diseases Society. Controversies and challenges. ILADS. 2020. Accessed December 11, 2020. https://www.ilads.org/research-literature/controversies-challenges/
12. Centre for Effective Practice. Early Lyme Disease Management in Primary Care. 2020. Accessed July 12, 2021. https://cep.health/media/uploaded/CEP_EarlyLymeDisease_Provider_2020.pdf
13. Morrow G, Karam F. Lyme Disease, From Diagnosis to Treatment, at the Localized and Disseminated Stages. Report in Support of Knowledge Transfer Tools for Diagnosis and Treatment. Institut national d'excellence en santé et an services sociaux (INESS); 2019. Accessed July 12, 2021. https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Biologie_medicale/Lyme_Diag-traitement/inesss_report-lyme-rx-dx.pdf
14. Irving K, Galway L. An evaluation of tick and Lyme disease information on health unit websites in Ontario. *Environ Health Rev*. 2019;62(1):20-27. doi:10.5864/d2019-006
15. Journault A-A, Richard L, Aenishaenslin C. Lyme disease prevention: a content analysis of Canadian patient group and government websites. *Zoonoses Public Health*. 2020;67(2):177-185. doi:10.1111/zph.12669
16. Library of University of Toronto. Grey literature – searching the literature: a guide to comprehensive searching in the health sciences. 2019. Accessed September 15, 2019. https://guides.library.utoronto.ca/c.php?g=577919&p=4123572
17. Godin K, Stapleton J, Kirkpatrick SI, Hanning RM, Leatherdale ST. Applying systematic review search methods to the grey literature: a case study examining guidelines for school-based breakfast programs in Canada. *Syst Rev*. 2015;4(1):138.
18. CLyDRN. Canadian Lyme disease research network | About the network. 2019. Accessed January 22, 2021. https://www.clydrn.ca/about-the-network/
19. Bowen GA. Document analysis as a qualitative research method. *Qual Res J*. 2009;9(2):27-40. doi:10.3316/QRJ0902027
20. NVivo. Learn more about data analysis software. 2021. Accessed January 23, 2021. https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/about/nvivo
21. Hatchette TF. The diagnosis and management of Lyme disease in Nova Scotia. 2019. Accessed December 14, 2020. https://cdn.dal.ca/content/dam/dalhousie/pdf/faculty/medicine/departments/core-units/cpd/CHP/Lyme.pdf
22. Boudreau CR, Lloyd VK, Gould ON. Motivations and experiences of Canadians seeking treatment for Lyme disease outside of the conventional Canadian health-care system. *J Patient Exp*. 2018;5(2):120-126. doi:10.1177/2374373517736385
23. Ali A, Vitulano L, Lee R, Weiss TR, Colson ER. Experiences of patients identifying with chronic Lyme disease in the healthcare system: a qualitative study. *BMC Fam Pract*. 2014;15(1):79. doi:10.1186/1471-2296-15-79
24. Drew D, Hewitt H. A qualitative approach to understanding patients' diagnosis of Lyme disease. *Public Health Nurs*. 2006;23(1):20-26. doi:10.1111/j.0737-1209.2006.230104.x
25. Coderre-Ball AM, Robertson M, Matzinger E, Durando P, Egan R. Training initiatives that enhance knowledge, attitudes, and practices regarding the prevention, diagnosis and

treatment of Lyme disease: a systematic review. *Int J Health Promot Educ*. Published online May 5, 2021. doi:10.1080/14635240.2021.1920045

26. Wu JT, McCormick JB. Why health professionals should speak out against false beliefs on the Internet. *AMA J Ethics*. 2018;20(11):E1052-E1058. doi:10.1001/amajethics.2018.1052
27. Cervero RM, Gaines JK. The impact of CME on physician performance and patient health outcomes: an updated synthesis of systematic reviews. *J Contin Educ Health Prof*. 2015;35(2):131-138. doi:10.1002/chp.21290
28. Andolsek K, Rosenberg MT, Abdolrasulnia M, Stowell SA, Gardner AJ. Complex cases in primary care: report of a CME-certified series addressing patients with multiple comorbidities. *Int J Clin Pract*. 2013;67(9):911-917. doi:10.1111/ijcp.12175
29. Ventola CL. Social media and health care professionals: benefits, risks, and best practices. *Pharmacol Ther*. 2014;39(7):491-520.