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Technical report: Update on Lyme disease prevention and control

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Contents

Introduction

This report is an update to PHO's 2012 publication *Technical report: Update on Lyme disease prevention and control* (*Technical Report*).[1] Since 2012, the science surrounding the surveillance of blacklegged ticks and Lyme disease in Ontario has evolved. In order to provide the latest, evidence-based advice on surveillance, PHO performed systematic reviews of the surveillance of blacklegged ticks and Lyme disease: *Blacklegged tick surveillance in Ontario: A systematic review* and *Lyme disease human surveillance in Ontario: A systematic review*. The *Tick Surveillance* and *Human Disease Surveillance* chapters in this document have been updated based upon these systematic reviews.

The updated chapters provide guidance on several aspects of blacklegged tick and Lyme disease surveillance:

1. When PHO published the initial technical report, passive tick surveillance was used to identify priority areas for active tick dragging, followed by prioritization of areas for small mammal trapping. PHO now identifies Lyme disease risk areas based on active tick surveillance, in the absence of small mammal trapping. This allows for the timeliest identification of new risk areas and more effective monitoring of expanding risk areas.

2. In 2015, PHO and the Ministry of Health and Long-Term Care (MOHLTC) updated the surveillance case definitions for Lyme disease (*Ontario Infectious Disease Protocols*).[2] Risk areas were added to the updated surveillance case definitions, a location where one *I. scapularis* was found during three person-hours of drag sampling, with two sampling events from May through October. In addition, the updated surveillance case definitions provide clarity concerning the pathognomonic nature of erythema migrans (EM); that is, clinical presentation with EM alone provides the necessary clinical evidence for confirmed and probable cases.

3. PHO, in conjunction with MOHLTC, Public Health Agency of Canada (PHAC) and public health units (PHUs) developed the Ontario Lyme disease case management tool to improve human disease surveillance in the province.[3] This tool enhances and standardizes the collection of exposure data for human cases by local PHUs, thus allowing PHUs and PHO to better analyze exposure data. These data will be a key source of information to identify new and emerging Lyme disease risk areas, permitting effective and targeted tick surveillance and public health intervention activities.

The Infectious Diseases Society of America (IDSA) produces guidelines on the symptoms, diagnosis and testing of Lyme disease. These guidelines are endorsed by the Association of Medical Microbiology and Infectious Disease Canada (AMMI), and followed by PHAC and PHO. The IDSA, in partnership with the American Academy of Neurology and the American College of Rheumatology, is currently working on updating these guidelines. As this process is still ongoing, the *Clinical Signs and Symptoms* and *Diagnosis and Testing* chapters of this report will not be updated until the new IDSA guidelines are released.

Background

Lyme disease is a bacterial spirochete infection caused by *Borrelia burgdorferi* and transmitted to humans through the bite of an infectious blacklegged tick, *Ixodes scapularis*. Lyme disease is the most common vector-borne disease in North America, with an estimated 300,000 cases annually in the US alone.[4-6] Lyme disease was first recognized in 1975, when it was initially described as a cluster of juvenile rheumatoid arthritis cases in several towns in Connecticut, US.[7] Soon after the description of Lyme disease in the early 1980s, the blacklegged tick was identified as the vector of *B. burgdorferi* in New York, US.[8,9] Lyme disease is found throughout eastern North America, including southern portions of Canada, wherever blacklegged ticks are present. Disease rates are highest, however, in the Northeast and Upper Midwestern US states.[10]

In Canada, *I. scapularis* distribution is limited primarily to the southern portions of Manitoba, Ontario, Quebec, New Brunswick and Nova Scotia.[11,12] In the early 1970s, the first population of blacklegged ticks in Canada was identified at Long Point Provincial Park, Ontario, along the northern shore of Lake Erie.[13] Beginning in the mid-1990s and through the 2000s, additional established populations of blacklegged ticks were detected along the northern shores of Lake Erie (Point Pelee National Park, Rondeau Provincial Park, Turkey Point Provincial Park and the Wainfleet Bog Conservation Area), Lake Ontario (Prince Edward Point National Wildlife Area) and the St. Lawrence River (St. Lawrence Islands National Park), Northwest Ontario (Rainy River), Southwest Ontario (Pinery Provincial Park) and urban-suburban parks (Rouge Valley).[14-17] Since 1988, the majority of Ontario-acquired human cases have originated from Southern Ontario, especially in areas of Southeastern Ontario where blacklegged tick populations are expanding.

Multiple variables are responsible for the expansion of blacklegged ticks in Ontario. A driving force behind the recent expansion in Ontario and other areas is climate change, specifically the increase in the mean annual degree days above 0°C.[18,19] Other factors contributing to blacklegged tick advances include land use changes (farmland to forest; encroaching human populations; forest fragmentation) and changes in the range of the main hosts for ticks (i.e., white-footed mouse *Peromyscus leucopus*, white-tailed deer *Odocoileus virginianus*). All tick surveillance indicators suggest that the current geographic range of blacklegged tick populations is expanding in southern Ontario and will likely continue to do so as available habitat permits.[20]

Blacklegged tick populations can occur sporadically over a wide geographic range in Canada due to larvae and nymphs readily attaching themselves to migratory birds.[21] Consequently, birds help transport blacklegged ticks from areas in the US and Canada to disparate locales across Canada. Bird-borne (adventitious) ticks create the possibility of infectious tick bites almost anywhere in Ontario. Human cases of Lyme disease may occur outside of known Ontario risk areas; however, the risk of exposure is considerably less than in identified risk areas. The risk of Lyme disease is usually greater in tick-established areas because of a greater probability of bites from infectious ticks compared to areas where blacklegged ticks are not established.[14]

With expanding *I. scapularis* populations and increased public and health care clinician awareness, the incidence of Lyme disease has increased in Ontario since it became a reportable disease in the province in 1988. The first isolation of *B. burgdorferi* from a blacklegged tick in Ontario occurred in 1993, when a tick

removed from a dog in Kenora (Northwestern Health Unit) tested positive for the agent of Lyme disease.[22] In 2014, Ontario reported 220 confirmed and probable human cases of Lyme disease (incidence rate of 1.6 cases per 100,000 population).[23] Overall, the incidence of Lyme disease in Ontario has increased steadily since 2002. In Ontario, approximately 70% of all reported cases are reported in June, July and August. This peak in cases during the summer months is similar to other Lyme disease regions in the US and Canada, and coincides with both greater participation in outdoor activities and increased presence of infectious nymphs in the environment. Compared to adult blacklegged ticks, blood-feeding nymphs are much more difficult to detect and are more likely to go unnoticed, allowing them to feed longer, leading to a greater risk of *B. burgdorferi* infection. Blacklegged ticks are three-host ticks with larvae and nymphs that blood feed on small rodents (e.g. white-footed mouse) and passerine birds, and adults that feed on large mammals (white-tailed deer, humans). Blood feeding is the tick's sole source of nutrition and is needed for molting from one stage to the next and for developing eggs. Blacklegged tick larvae and nymphs are most active in the summer, while adults are most active in the spring and the fall.

Incidence rates for Lyme disease are higher in specific PHUs, including Eastern Ontario (EOH); Hastings and Prince Edward Counties (HPE); Kingston, Frontenac and Lennox & Addington (KFL); Leeds, Grenville and Lanark District (LGL); Ottawa (OTT); and Renfrew (REN). This trend of higher incidence of cases in the Eastern Region (EOH, HPE, KFL, LGL, OTT, REN) correlates with areas reporting larger numbers of blacklegged ticks submitted through passive surveillance.[23]

Tick Surveillance

PHO's systematic review, and its assessment of the available blacklegged tick active surveillance methods, has identified tick dragging as the best option, supplemented by small mammal trapping where specified. Currently, there is no evidence to support changing Ontario's passive tick surveillance program in Ontario, except where indicated by a PHU's historical surveillance.

This chapter provides the methods and best practices for both passive and active methods for the monitoring of blacklegged ticks, based on the assessment of the systematic review, focusing on 1) the objectives of Ontario's surveillance program; 2) the identification of risk areas in Ontario; and 3) recommendations for tick surveillance based upon PHU blacklegged tick population levels. The goal of this chapter is to:

- provide support to assess a PHU's blacklegged tick populations;
- provide support to detect new or emerging Lyme disease risk areas in PHUs, which may require confirmation through active blacklegged tick surveillance methods; and
- provide support to determine the best tick surveillance option for specific PHUs based on historical blacklegged tick collections.

Background

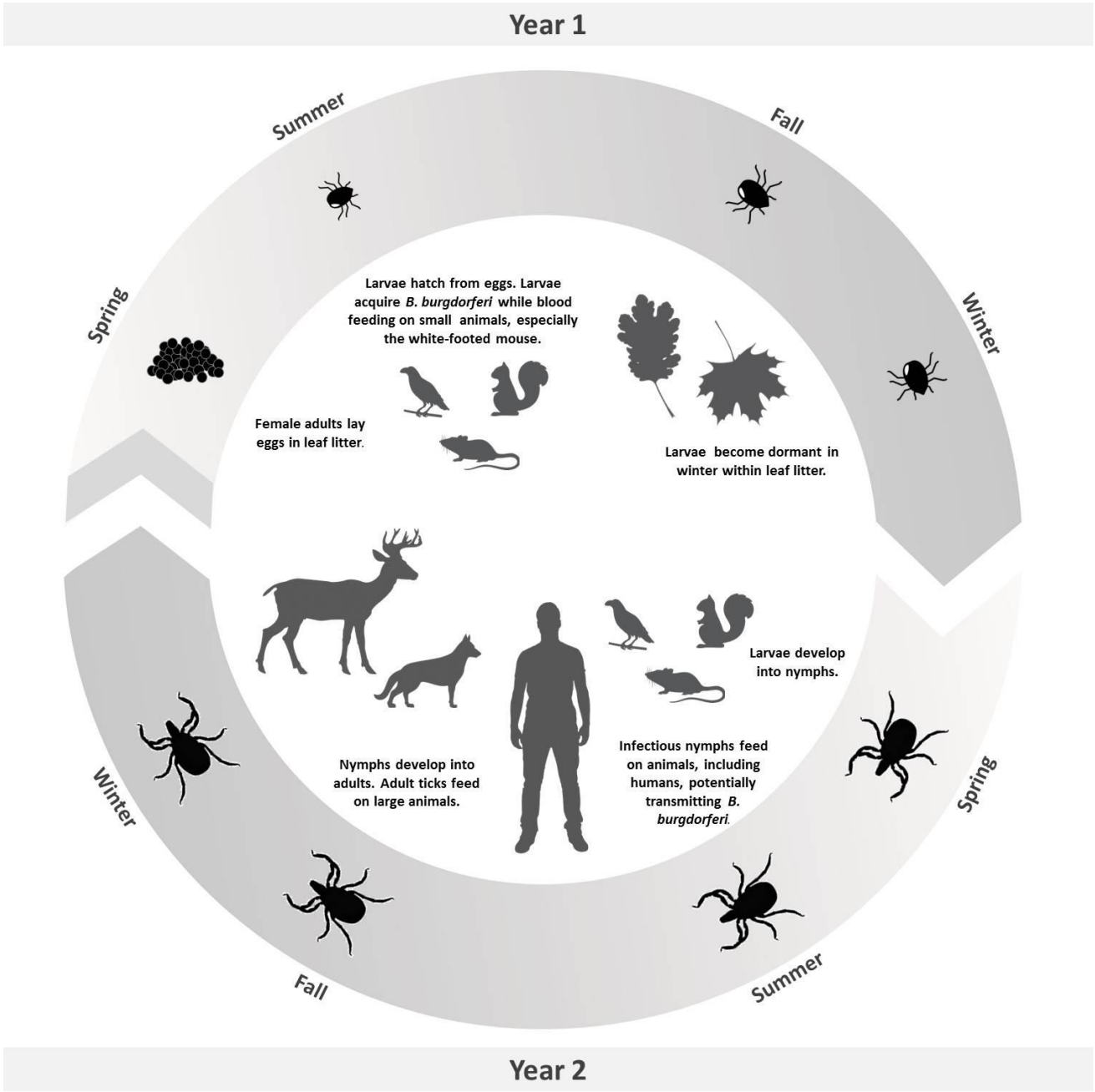
Tick surveillance determines the level of establishment of *I. scapularis* populations within an area and assesses the possible risk of human *B. burgdorferi* infection. Tick surveillance may be passive (examining ticks the public brings into health professional or PHU offices), or it may be active (collecting ticks from their natural habitat through tick dragging). Passive tick surveillance is used to prioritize areas where active tick surveillance should be performed. While different in their approaches, both are beneficial to help determine the level of Lyme disease risk in the local community.

The passive tick surveillance system in Ontario has a number of core elements. First, healthcare providers and PHUs submit ticks on behalf of the public to the Public Health Ontario Laboratory (PHOL). PHOL then performs tick species identifications on the submitted ticks. The ticks that are identified by PHOL as *I. scapularis* are forwarded to Canada's National Microbiological Laboratory (NML, PHAC; Winnipeg, Manitoba) for pathogen detection (*B. burgdorferi* and *Anaplasma phagocytophilum*).

A risk area is a location where at least one *I. scapularis* is collected during spring and fall sampling events (from May through October; a sampling event is defined as at least three person-hours of drag sampling). Collections are made in the spring and fall because this is when adult blacklegged ticks are more active and easier to detect when dragging (Figure 1). Since 2015, risk area is a term used to describe locations in Southern Ontario where there is an increased risk of Lyme disease. This is based on the PHAC publication describing risk through tick dragging as the sole active surveillance method.[24] For PHUs in which there are known Lyme disease risk areas, PHO has encouraged a shift from passive tick surveillance to active tick surveillance (tick dragging), with no need to perform small mammal trapping (see Category 1: PHUs with

known risk areas and/or high numbers of tick submissions and Category 2: PHUs with known risk areas and/or moderate numbers of tick submissions).[14] PHO developed the *Active tick dragging: Standard operating procedure* to support PHUs in the field collection of blacklegged ticks; this active surveillance will continue to track the expansion of blacklegged tick populations and the increasing prevalence of *B. burgdorferi*. As the science of tick surveillance advances, PHO will continue to re-assesses existing advice to ensure that Ontario is at the forefront of blacklegged tick surveillance methods.

Figure 1. Life cycle of the blacklegged tick (*Ixodes scapularis*).



Objectives of Passive and Active Tick Surveillance

The objective of passive tick surveillance is to understand and assess the possible risk of Lyme disease infection across the province. Information gathered through passive surveillance can help identify new areas where active surveillance is warranted. An updated tick requisition form is now available on PHO's Lyme disease webpage. The objective of active surveillance, like passive surveillance, is to identify established blacklegged tick populations and to determine Lyme disease risk areas. Active surveillance is a targeted approach to identifying risk areas where passive surveillance methods (tick submissions, human case exposure histories) have indicated the potential presence of blacklegged tick populations. Unlike passive surveillance, active surveillance involves the collection of blacklegged ticks in the field through tick dragging and small mammal trapping.

PHO's Ontario Lyme disease estimated risk areas map: 2016 assists clinicians in the diagnosis and/or treatment of Lyme disease, with potential exposures or tick bites in the risk areas delineated on the map indicating greater concern as to the risks of Lyme disease.[14] In addition, public health professionals can use the risk areas defined on the map to determine if reported case exposure locations represent known or possible new/emerging risk areas, thus helping to inform public health messages aiming to raise awareness of Lyme disease risk areas in Ontario. PHU staff can also use the map during Lyme disease case investigations when determining the most likely exposure locations. The estimated risk areas are a 20-km radius from the center of a location where blacklegged ticks were found through drag sampling. The risk map development is based on work done by the Nova Scotia Department of Health and Wellness and adopted by PHAC for its national Lyme disease risk mapping.

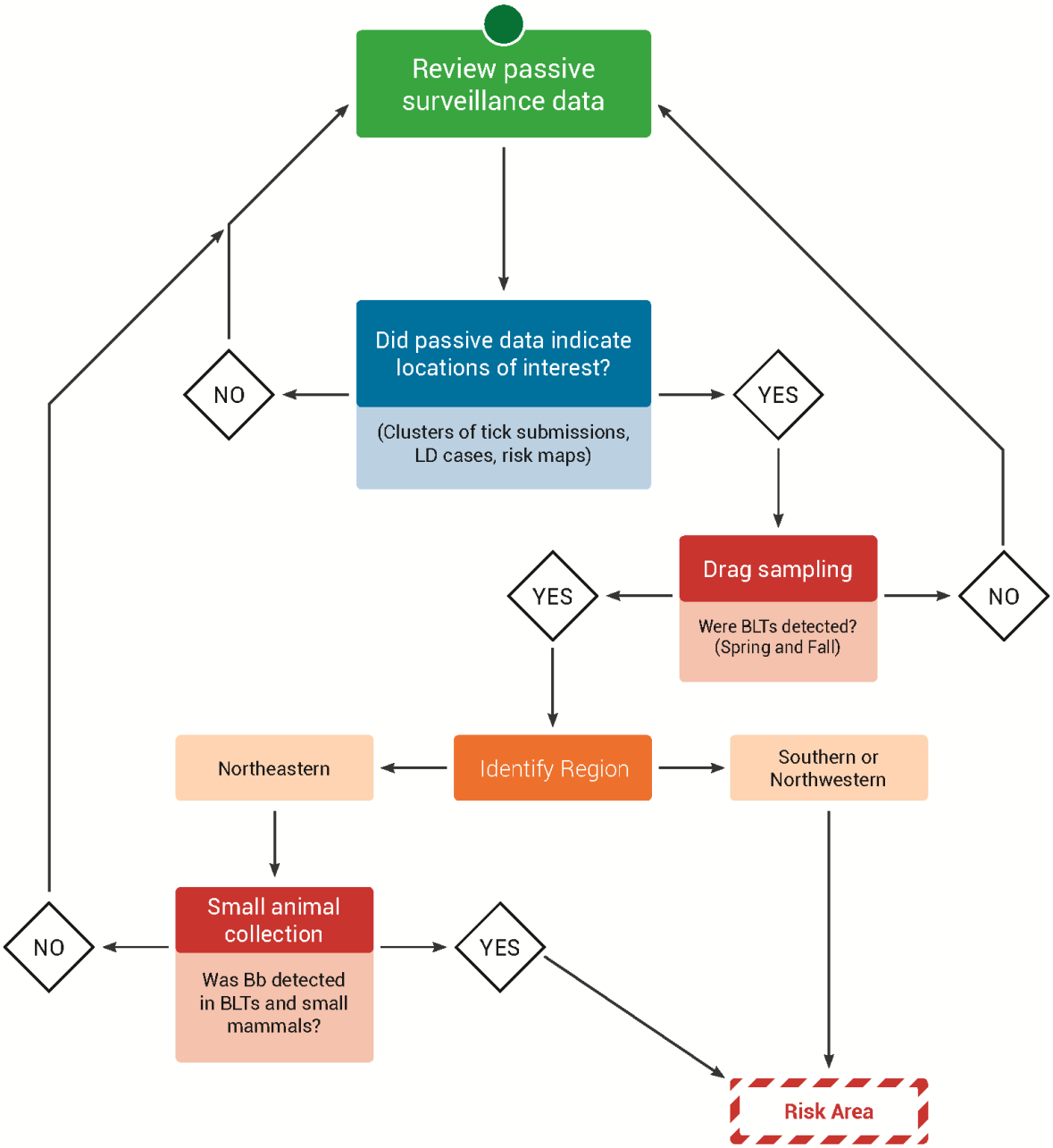
In Ontario, blacklegged ticks are found primarily in rural areas along the north shores of Lake Erie, Lake Ontario and St. Lawrence River. These areas have the most suitable habitat and climate for tick populations to become established. The estimated risk areas for Lyme disease in Ontario are centered in Long Point Provincial Park, Pinery Provincial Park, Point Pelee National Park, Prince Edward Point National Wildlife Area, Rainy River, Rouge Valley, St. Lawrence Islands National Park, Turkey Point Provincial Park, Rondeau Provincial Park and the Wainfleet Bog Conservation Area. The precise boundaries of established tick populations are difficult to define and certain populations continue to expand into neighbouring areas (several locations in eastern Ontario).

Tick Surveillance Recommendations

Our systematic review has identified that several methods exist for active monitoring of blacklegged tick populations. Little empirical evidence supports the use of one active method over another and method selection has to take into account several factors besides efficacy. Taking into account an active method's costs, ease of use, ability to detect various stages and repeatability, tick dragging is the preferred method, with small mammal trapping where indicated. From the studies reviewed, passive tick surveillance is not a common practice in areas where Lyme disease has been present for some time; however, passive surveillance offers important information in regions with newly established and/or expanding blacklegged tick populations.

It is important that *I. scapularis* surveillance data address the evolving ecology and epidemiology of Lyme disease in Ontario. Tick surveillance needs vary in different parts of Ontario depending on existing tick surveillance data (numbers of ticks submitted through passive tick submissions). To date, the data collected shows that several PHUs have high numbers of *I*. *scapularis* with expanding populations; others have no significant tick populations; while others have primarily non-blacklegged tick populations (i.e., *Dermacentor variabilis*, *Ixodes cookei*).[20] There are also PHUs that have focal blacklegged tick populations, but little evidence of expansion outside of those risk areas (e.g., Rondeau Provincial Park in Chatham Kent). Having a blacklegged tick surveillance program will allow public health professionals to apply the most appropriate surveillance methods for assessing tick populations in their respective PHUs. In 2014, PHAC noted that an area may be considered a Lyme disease risk area if one blacklegged tick was found during three person-hours of drag sampling at that location, during two dragging events (once in spring and again in the fall; from May through October).[24] Based on the current information on blacklegged ticks and human cases of Lyme disease, this revised surveillance method is recommended for jurisdictions in southern and northwestern Ontario. In the Northeast Region (i.e., Category 3: Algoma, ALG; North Bay Parry Sound District, NPS; Porcupine, PQP; Timiskaming), small mammal trapping is still needed to determine risk, where there are low historical numbers of blacklegged ticks submitted through passive surveillance and where indicated by active tick dragging. PHO, with PHAC, has developed a decision tree for determining if an area of concern is a Lyme disease risk area (Figure). Note this process can take over two years to determine if there is a risk area.

Figure 2. Decision tree for determining if a location is a Lyme disease risk area.



Based on the *Ontario Infectious Diseases Protocols*, a PHU is required to develop a vector-borne disease management strategy based on a local risk assessment, including a Lyme disease management strategy.[2] This local risk assessment aids public health professionals in determining target areas for active tick surveillance. The following three categories are recommended tick surveillance methods that PHUs should consider in their region.

Category 1: PHUs with known risk areas and/or high numbers of tick submissions

PHUs in this category historically submit more than 250-blacklegged ticks per year and have a known risk area (Table 1; Figure). PHO recommends that these PHUs move to active tick surveillance only and submit these ticks directly to NML for identification and testing. As evidenced in the systematic review and with the high volume of tick submissions in these regions, the value of continued passive tick submissions is negligible and regular tick dragging becomes more important in these PHUs. In this category, PHO strongly encourages the PHU and local physicians to stop collecting and/or submitting ticks. Tick dragging, within the risk areas, will allow these PHUs to track the prevalence of *B. burgdorferi* in blacklegged ticks and monitor for the possible emergence of other blacklegged tick-borne pathogens. In addition, these PHUs may want to conduct tick dragging outside of known risk areas to examine the extent of expansion and to determine baseline counts of blacklegged ticks in areas with little data.

Table 1. Comparison of blacklegged tick surveillance categories for public health units

Category	Average number blacklegged ticks submitted per year*	Known risk area(s) present**	Passive tick surveillance (via physicians)	Passive tick surveillance (PHU via public)	Active tick surveillance (tick dragging)†	Active tick surveillance (small mammal trapping)
1	>250	Yes	No	Not recommended	Yes	No
2	10≤n<250	Yes	Outside of risk areas	Outside of risk areas	Yes	No
3	<10	No	Yes	Yes	If indicated by passive surveillance	If indicated by passive surveillance and tick dragging

*Average number of blacklegged ticks submitted per year through passive surveillance, last 3 years
**Risk areas as identified in PHO's *Map of Lyme disease risk areas*
†Perform tick dragging twice a year, once in spring and again in fall

Category 2. PHUs with known risk areas and/or moderate numbers of tick submissions

PHUs in this category include those that submit less than 250, but greater than ten, blacklegged ticks per year (Table 1; Figure). For these PHUs, passive tick surveillance is unlikely to provide additional useful information related to known risk areas. PHUs may want to carry out semi-annual tick dragging in the known risk areas to monitor the prevalence of *B*. *burgdorferi*, and testing for other pathogens associated with blacklegged ticks where indicated. When trying to determine if a new risk area exists, PHUs should conduct tick dragging in the spring and the fall. To consider a new area a risk area, PHUs must find at least one blacklegged tick per three-person hours of dragging in the spring and fall. Passive tick surveillance should continue in the remaining parts of the PHUs. PHO strongly encourages the PHU and local physicians to stop collecting and/or submitting ticks via passive surveillance from known risk areas.

Category 3. Other PHUs with no risk areas and low numbers of tick submissions

PHUs in this category submit less than ten blacklegged ticks per year (Table 1; Figure). In this category, passive tick surveillance provides a low-cost mechanism to detect early indications of blacklegged tick establishment in these PHUs. PHO will continue to accept ticks through the passive surveillance system for these PHUs. These PHUs have low rates of tick submissions and therefore, any data gathered is beneficial, allowing public health officials to monitor the emergence of blacklegged tick populations in new areas as well as in determining the prevalence of *B*. *burgdorferi*. If an established blacklegged tick population is suspected in PHUs located in the Northeast Region (i.e., ALG, NPS, PQP, TSK), PHUs may still want to consider small mammal trapping, as there is little evidence of blacklegged ticks in this area and confirmation would be needed. The systematic review indicates that small mammal trapping is the preferred method for determining the presence of immature blacklegged ticks and the presence of *B. burgdorferi* in areas with low tick numbers.

Human Disease Surveillance

Where Lyme disease is a reportable disease, the systematic review has identified that reportable disease systems (e.g., iPHIS) are the backbone for Lyme disease surveillance; however, several additional methods are available for the surveillance of Lyme disease. PHO's *Ontario Lyme disease case management tool* is intended to improve the Lyme disease data captured in iPHIS, leading to improved epidemiological analyses and the timely identification of populations at risk. The literature supports that administrative claims and laboratory databases provide effective, accessory methods for validating or enhancing reportable disease data.

This section provides methods and best practices for the surveillance of Lyme disease in Ontario, focusing on 1) the new standardized *Ontario Lyme disease case management tool*; and 2) updates to the Ontario Lyme disease case definition. The purpose of this human disease surveillance section is to:

- provide support for assessing the burden of illness associated with Lyme disease;
- provide support for the public health management of Lyme disease; and
- provide support for monitoring locations where increased numbers of Lyme disease cases may be occurring, using this to guide to inform public messaging or site interventions that may help to reduce transmission.

Background

Ontario's human Lyme disease surveillance program is legislated under Ontario Regulation 559/91 of the Health Protection and Promotion Act and the Ontario Public Health Standards. Human cases are reported via the Integrated Public Health Information system (iPHIS), the standard surveillance reporting method for all Ontario reportable diseases and conditions. Lyme disease is a reportable disease in Ontario, with a provincial surveillance case definition[2] similar to the national surveillance case definition[25] as well as the US's Centers for Disease Control and Prevention's (CDC) case definition.[26] Underscoring the purpose of a surveillance case definition, the CDC states "case definitions are intended to establish uniform criteria for disease reporting; they should not be used as sole criteria for establishing clinical diagnoses, determining the standard of care necessary for a particular patient, setting guidelines for quality assurance, providing standards for reimbursement, or initiating public health actions. Use of additional clinical, epidemiologic and laboratory data may enable a physician to diagnose a disease even though the surveillance case definition may not be met."

Physicians make the diagnosis of Lyme disease based on a patient's signs and symptoms, the presence or absence of confirmatory laboratory results and, to a certain extent, the patient's response to antibiotic treatment (depending on stage of illness: early localized, early disseminated, late disseminated). Physician diagnosis should not be dependent on the patient having visited or resided in a risk area, given the potential for a bird-transported, infectious tick to be distributed anywhere in Ontario. Similar to other reportable diseases, there is likely under-reporting of Lyme disease. For example, under-reporting could arise when a

physician makes a clinical diagnosis such as EM without ordering serological testing or with negative serology, and not reporting the case to their PHU(s). While reportable disease databases (e.g., iPHIS) represent the primary method for determining the spatiotemporal dynamics of Lyme disease and determining populations at risk, accessory methods (administrative claims and laboratory databases) are able to verify epidemiological data or enhance case detection. As accessory methods are developed, PHO will continue to evaluate methods to improve our understanding of Lyme disease epidemiology in Ontario.

Ontario Lyme disease case management tool

A working group consisting of members from PHO, PHUs and PHAC developed the *Ontario Lyme disease case management tool* in early 2015.[27] The investigation tool is designed for administration by telephone; however, PHUs can also use it for in-person investigations. The *Lyme Disease case management tool companion guide* was also developed to provide instructions on how to use the standardized tool and to explain the rationale for each section.[3] The investigation tool's purpose is to:

- identify exposure location;
- improve case and contact management;
- provide case counseling;
- assist with disease management;
- obtain required data elements under the *Health Protection and Promotion Act* pertaining to the case; and
- facilitate investigation documentation.

Ontario Lyme disease case definition

Ontario updated the surveillance case definition in 2015 to give clarity to risk areas and the pathognomonic nature of EM. Please refer to the *Ontario Infectious Disease Protocols* for complete details and for any updates to the case definition.

Confirmed case:

- clinician-confirmed EM greater than 5 cm in diameter with a history of residence in, or visit to, a Lyme disease risk area; OR
- clinical evidence of Lyme disease with laboratory confirmation by polymerase chain reaction (PCR) or culture; OR
- clinical evidence of Lyme disease with laboratory support by serological methods, and a history of residence in, or visit to, a risk area.

Probable case:

- clinical evidence of Lyme disease with laboratory support by serological methods, but with no history of residence in, or visit to a risk area, OR
- clinician-confirmed EM greater than 5 cm in diameter but with no history of residence in, or visit to a risk area.

Clinical Signs and Symptoms

Note: The Infectious Diseases Society of America (IDSA) produces guidelines on the symptoms, diagnosis and testing of Lyme disease. These guidelines are endorsed by the Association of Medical Microbiology and Infectious Disease Canada (AMMI), and followed by PHAC and PHO. The IDSA, in partnership with the American Academy of Neurology and the American College of Rheumatology, is currently working on updating these guidelines. As this process is still ongoing, this section will not be updated until the new IDSA guidelines are released.

Symptoms usually begin within three days to one month after being bitten by an infected tick. An infected tick must attach and feed on a human for 24 to 36 hours before the agent of Lyme disease is transmitted. This is the amount of time required for the bacteria to migrate from the tick's gut to its salivary glands where the bacteria are injected into the host. Therefore, if people conduct a thorough check of themselves after being outdoors and promptly remove any attached ticks, even bites from infected ticks will not result in an infection. The first sign of infection is usually a circular rash called erythema migrans (EM), commonly known as the "bull's-eye" rash. This rash typically occurs in 70 to 80 percent of those infected and it varies in shape and size.

During the initial stage of infection, symptoms may include: fatigue, chills, fever, headache, muscle and joint pain, and swollen lymph nodes. If left untreated, the patient may progress to the second stage that can last several months. The symptoms for the second stage may include: multiple skin rashes, heart palpitations, arthritis and arthritic symptoms, extreme fatigue and general weakness, and central and peripheral nervous system disorders. The third stage may last for months or years with recurring neurological problems and arthritis. For more information about the clinical signs and symptoms, see Wormser.[5]

Diagnosis and Testing

Note: The Infectious Diseases Society of America (IDSA) produces guidelines on the symptoms, diagnosis and testing of Lyme disease. These guidelines are endorsed by the Association of Medical Microbiology and Infectious Disease Canada (AMMI), and followed by PHAC and PHO. The IDSA, in partnership with the American Academy of Neurology and the American College of Rheumatology, is currently working on updating these guidelines. As this process is still ongoing, this section will not be updated until the new IDSA guidelines are released.

The diagnosis of Lyme disease, particularly the early stage of Lyme disease, is primarily based on clinical symptoms associated with Lyme disease and epidemiological risk factors. Within this context, laboratory testing plays a supporting role in diagnosis of Lyme disease. Currently, based on surveillance data, the province of Ontario, except for a few regions, is considered low or non-endemic for Lyme disease.

Despite the low risk, physicians appear to be considering Lyme disease in the differential diagnosis and the number of requests for serological testing submitted by physicians has increased. In 2010, over 13,000 specimens were submitted to Public Health Ontario Laboratories (PHOL) for Lyme disease antibody testing, which is significantly higher than 4,000 or so specimens submitted to PHL in 2003. Blood tests are the most commonly used laboratory tests to supplement clinical information about possible Lyme disease and most labs use either Indirect immunofluorescent-antibody assays (IFA), Enzyme-linked immunosorbant assay (ELISA), or western blot (WB) as their front-line serological assays. Other laboratory-based detection methods are available such as bacterial culture and polymerase chain reaction (PCR) assays but these tests are much less frequently used. Each of these assays has advantages and disadvantages that are influenced by factors such as the duration of disease, specimen type and prevalence of diseases.

B. burgdorferi sensu lato can be recovered from various tissues and body fluids of patients with Lyme disease, including biopsy from EM skin lesions, cerebrospinal fluid and blood specimens.[4] The sensitivity of culture method from skin biopsy of EM lesion from untreated patients is shown to be from 57% to 86%.[5] The bacterium usually cannot be recovered from EM lesions of patients who have already received appropriate antibiotic treatment.[4] Culture method is highly labour intensive requiring up to 12 weeks of incubation and lacks readily available culture media. In addition, it is generally useful only for untreated patients as culture positivity rapidly decreases in treated patients. Furthermore, it is highly insensitive in patients with extra cutaneous manifestation of Lyme disease, thus it is not commonly used in routine clinical diagnostic settings. Culture method is generally used in research settings as it allows researchers to better understand pathogenesis of Lyme disease as well as biology of the bacterium.

Content on this page will be reviewed after the publication of the ISDA guidelines which are currently being updated.

Similarly, various PCR-based protocols have been developed over the years to detect *B. burgdorferi* DNA from clinical specimens. The median sensitivity of PCR varies from 18% in blood specimens, 64% in biopsy specimen from EM lesions to 73% from cerebrospinal fluid (CSF) specimens.[28] Similar to culture method, PCR method has not been widely used in routine clinical settings as the sensitivity is low in blood and CSF specimens. The use of PCR method in patients with EM is rarely used as physicians usually make a diagnosis of Lyme disease based on clinical presentations with the presence of characteristics EM lesions.

As mentioned above, many clinical laboratories throughout the world uses serological methods to detect antibodies developed in patients infected with *B. burgdorferi*. The immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies appear two to four weeks and four to six weeks, respectively, after the onset of EM. It has been shown that IgM may be elevated for more than six months after the infection, whereas IgG antibodies persist for years. The sensitivity of serology assays is reported to be only between 33 – 49% during acute stage of disease.[28] Therefore, patients with early stage Lyme disease are primarily diagnosed based on clinical presentations compatible with Lyme disease and epidemiological risk factors, as serological testing at this stage of the disease is often negative. The laboratory testing becomes particularly useful during late stages where clinical symptoms are non-specific and there has been adequate time for antibodies to develop. The sensitivity increases significantly as the disease progresses from acute to convalescent to late-stage Lyme arthritis (Table 2).[28] In addition, it is important to note that approximately 15% of patients treated with antibiotics early in the infection will have either delayed or no antibody response. It has been reported that negative serological testing in patients with prolonged non-specific symptoms essentially rules out Lyme disease, and physicians should pursue other clinical and laboratory investigations to establish cause of these symptoms.[29]

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Testing Algorithm

Currently, *B. burgdorferi* sensu stricto*, B. garinii* and *B. afzelii* are the only species known to infect humans. All three species are found in Europe, whereas *B. burgdorferi* is the only species identified in North America that is known to cause disease in humans. The PHL perform serological testing to detect antibodies against *B. burgdorferi*. If a patient was exposed to other species of *Borrelia* such as those that occur in Europe, the physician can state travel history to Europe and request testing for European Lyme disease. The specimens from these patients are sent to the National Microbiology Laboratory for antibody testing.

Table 2. PERFORMANCE CHARACTERISTICS OF SEROLOGICAL ASSAY IN PATIENTS WITH Lyme disease. (ADAPTED FROM AGUERO-ROSENFELyme disease[1])

Test	% Reactivity in patients with			
	EM, acute	EM, convalescent*	Neurological involvement	Arthritis
Whole-cell ELISA	33-49	75-86	79 (IgG only)	100 (IgG only)
IgM WB	43-44	75-84	8 0	1 6
IgG WB	0-13	15-21	64-72	96-100
Two-tier testing	29-40	29-78	8 7	9 7

* Sera obtained after antibiotic treatment

% Reactivity in the above table refers to the frequency that the different serological assays will be positive depending of the stage of the Lyme disease infection

PHL follows guidelines published by the Canadian Public Health Laboratory Network (CPHLN).[30] These guidelines are consistent with guidelines published by other organizations including CDC, IDSA, British Infection Association, and German Association of Hygiene and Medical Microbiology.[31-33]

The PHL testing algorithm follows two-tier serological testing: initially, the patient sera are tested using ELISA to detect total IgM and IgG antibodies against *B. burgdorferi*. If results from ELISA are either positive or indeterminate, 2nd tier (i.e. supplemental testing) using WB is performed. This test is comprised of separate IgM and IgG immunoblots to detect antibodies against *B. burgdorferi*. The test result is interpreted as per manufacturer's instructions. Both ELISA and WB assays in two-tier system are considered complementary rather than independent tests to improve accuracy of the laboratory results.

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ELISA testing is highly sensitive but not specific, and therefore serves as an ideal screening test to detect antibodies to *B. burgdorferi*. Since it has lower specificity, it can produce false-positive results and may cross-react with antibodies that are produced as a result of other infections including those caused by other spirochetes. In addition, patients with autoimmune disorders and inflammatory conditions may also yield positive ELISA results. The WB, especially IgM, can also yield false-positive results if not interpreted correctly in the context of clinical disease presentation. An IgM only reactive result in a patient with persisting non-specific symptoms for more than two months will most likely represent a false-positive result. Many studies have shown that patients with other infections either acute or past infections caused by spirochetes (syphilis), viruses (cytomegalovirus, Epstein–Barr virus, Hepatitis B virus, Hepatitis C virus, Parvovirus) or bacteria may have circulating antibodies that cross-react with *B. burgdorferi* antigens on WB assay, thus producing positive results.

Both ELISA and WB assays used at PHL in Ontario are approved by the Medical Devices Branch of Health Canada. To ensure that accurate laboratory results are reported to physicians, PHL has established an internal quality assurance (QA) system. In addition, the laboratory participates in an external QA program and uses a proficiency panel obtained from the College of American Pathology (CAP) to ensure that test kits and laboratory procedures are providing accurate results.

Controversies in Laboratory Testing

A number of private laboratories in the United States offer testing for Lyme disease that does not follow the same testing protocols and recommendations used by accredited Canadian or American laboratories. Such private testing facilities have been known to use testing methods that have not been validated, and results from these labs must be interpreted with caution. Results of serological tests provide supportive evidence, not the sole evidence, for a diagnosis of Lyme disease.[34] In 2005 the CDC placed a notice in their **Morbidity and Mortality Weekly Report (MMWR)**[35] cautioning about using these private laboratories. The results from laboratories that are not using validated tests can lead to misdiagnoses that can be harmful to patients, to the extent that appropriate diagnoses and treatment can be delayed or precluded. The WB interpretations used by these laboratories, based on their own internal validation studies, are much more liberal than interpretations recommended based on CDC guidelines. As has been noted in the CDC advisory referenced above, labs using unvalidated Lyme disease IgG and IgM WB testing will use a more limited number of bands in their determination of what constitutes a positive test. Given that these tests are most usually undertaken in individuals who purport to have chronic Lyme disease (see below), the important consideration is the WB IgG interpretation. CDC has made recommendations about the number of bands as well as which bands to use to interpret WB results. These recommendations are based on validated scientific studies that are peer-reviewed and accepted by the scientific community. On the other hand, private labs' interpretation of WB results may place additional weight on specific bands that are not validated and peer-reviewed by the scientific community.

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Treatment Issues

As stated earlier, Lyme disease is mainly diagnosed through clinical symptoms and signs along with a history of appropriate exposure to ticks, which happens most frequently via residence in/travel to established areas endemic for Lyme disease. A clinical diagnosis of Lyme disease can be made regardless of the outcomes of diagnostic testing. Currently Canadian specialty bodies such as AMMI and the Canadian Pediatrics Society (CPS) recommend use of the IDSA's clinical practice guidelines that cover assessment, treatment, and prevention of Lyme disease, which can be accessed via:
http://www.journals.uchicago.edu/doi/abs/10.1086/508667

As noted in the IDSA guidelines, there are controlled clinical trials that provide the basis for the treatment of early Lyme disease, especially erythema migrans and acute disseminated non-neurologic infection, but limited if no controlled clinical trials for acute neurological and cardiac presentations or for the late manifestations of Lyme disease, especially neurologic (encephalomyelitis, encephalopathy, neuropathies) and arthritic presentations. It is also clear from the clinical studies and case series that, while recommended treatments are highly effective in early Lyme disease, treatment of late forms of Lyme disease can be associated with persistence of a wide variety of symptoms beyond the treatment period, especially arthralgia, pain, fatigue, weakness, malaise and cognitive disturbances (e.g. memory, concentration). While this may infrequently be due to concurrent infection with other tick-borne pathogens, especially *Babesia*, in areas where both are endemic, there are other, more probable explanations. As noted in the 2006 IDSA Guidelines: "…it can be expected that a minority of patients with Lyme disease will be symptomatic following a recommended course of antibiotic treatment as a result of the slow resolution of symptoms over the course of weeks to months, or as the result of a variety of other factors, such as the high frequency of identical complaints in the general population."

The IDSA 2006 Guidelines noted that there was general confusion as to the reality of post Lyme disease syndromes and a broader conception of "chronic Lyme disease" held by a number of patients, Lyme disease advocacy groups and physicians who considered themselves Lyme disease-literate (Lyme-literate MDs, or LLMDs). The IDSA 2006 Guidelines, in an attempt to address these issues, proposed a case definition of post-Lyme disease syndrome (PLDS) that defined the nature and timing of persistent non-specific symptoms, included exclusion criteria to address other potential or proven causes of PLDS and required objective evidence of previous Lyme disease diagnosis, through either clinical or preferably laboratory results as well as access to and compliance with recommended treatment regimens. On the basis of this proposed case definition, the IDSA reviewed and summarized in its 2006 Guidelines the clinical trial evidence addressing longer-term antibiotic therapy for PLDS, and concluded that it should not be recommended, given the absence of evidence of benefit and the clear evidence of harms (especially related to infectious complications from intravenous catheters).

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The development and dissemination of the IDSA 2006 Guidelines was not without controversy, given the existence of a variety of Lyme disease advocacy organizations and LLMDs in disagreement with the IDSA Guidelines. This led to an anti-trust action instituted by the then Connecticut Attorney-General against the IDSA, alleging conflict-of-interest in the development of the IDSA 2006 Guidelines. Through an agreed-upon resolution, the IDSA convened in 2009 a review panel, carefully assessed by an independent adjudicator for conflicts-of- interest, which reviewed the evolving science and clinical studies relevant to the prevention, assessment and treatment of all forms of Lyme disease. The IDSA 2009 review panel was not constituted to update the IDSA 2006 Guidelines but to assess the status of the recommendations contained therein. Following extensive consultations and review of evidence the review panel supported all of the Guideline recommendations, including those related to the contentious issues involved in the case definition and treatment of PLDS. The following section of this technical report is taken verbatim from the IDSA 2010 Review Panel Report[36]:

Post Lyme Syndromes

2006 Recommendation
There is no well-accepted definition of post–Lyme disease syndrome. This has contributed to confusion and controversy and to a lack of firm data on its incidence, prevalence, and pathogenesis. In an attempt to provide a framework for future research on this subject and to reduce diagnostic ambiguity in study populations, a definition for post–Lyme disease syndrome is proposed in these guidelines. Whatever definition is eventually adopted, having once had objective evidence of *B. burgdorferi* infection must be a condition sine qua non. Furthermore, when laboratory testing is done to support the original diagnosis of Lyme disease, it is essential that it be performed by well-qualified and reputable laboratories that use recommended and appropriately validated testing methods and interpretive criteria. Unvalidated test methods (such as urine antigen tests or blood microscopy for *Borrelia* species) should not be used.

2006 Recommendation
To date, there is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease.

> When the 2006 Lyme Guidelines are next updated, the Review Panel suggests that consideration be given to changing the phrase “no convincing biologic evidence” to something more specific, such as “Reports purporting to show the persistence of viable *B. burgdorferi* organisms after treatment with recommended regimens for Lyme disease have not been conclusive or corroborated by controlled studies.” It has been proposed by some that there are hardy, drug-tolerant reservoirs of *B. burgdorferi*, including intracellular cystic forms. To date, this has not been shown to correlate with symptom persistence, nor has eradication of these forms been shown to correlate with symptom improvement.

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2006 Recommendation

Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (>6 months) subjective symptoms after recommended treatment regimens for Lyme disease (E-I).

The Review Panel reviewed numerous sources of evidence for this contentious topic. These included but were not limited to: 1) a large volume of case reports and case series submitted by representatives of the International Lyme and Associated Diseases Society(ILADS) and referenced by that society's published guidelines; 2) case reports cited by representatives of ILADS and patient representatives in oral presentations to the Panel during the Hearing on July 30, 2009; 3) journal correspondence published in response to several Lyme disease practice guidelines, editorials, and clinical trials; 4) patient testimony; and 5) the available placebo-controlled randomized clinical trials of long term antibiotic therapy for symptoms attributed to Lyme disease.

Upon reviewing this abundance of material, and after lengthy discussions among the Review Panel members, the Review Panel reached the following conclusions:

1. **The prospective, controlled clinical trials for extended antibiotic treatment of Lyme disease have demonstrated considerable risk of harm, including potentially life- threatening adverse events.** Such events include intravenouscatheter infection, including septicemia (line sepsis), venous thromboembolism, drug hypersensitivity reactions, and drug-induced cholecystitis. Minor adverse events, such as diarrhea and candidiasis, were also more common in antibiotic treated patients. In a recent cohort of 200 patients, catheter-associated adverse events such as thrombosis and infection occurred on average 81 days into therapy, underscoring the cumulative risk of adverse events with increasing time.

   In clinical trials evaluating prolonged IV antibiotics for Lyme disease, there has been a lower rate of line sepsis in patients receiving IV ceftriaxone than those receiving IV placebo. It must be emphasized however, this adverse event is directly related to the intravenous access device. As ceftriaxone is intrinsically inactive against many common causes of line sepsis, including *Enterococcus, Candida, methicillin resistant Staphylococcus aureus* (MRSA), and coagulase-negative *Staphylococci*, it should not be seen as mitigating the potential risk of septicemia due to long term intravenous lines.

2. **Prospective, controlled clinical trials have demonstrated little benefit from prolonged antibiotic therapy**. Nearly all primary outcome measures have failed to demonstrate a benefit to prolonged antibiotic therapy. Statistically significant improvements in treatment groups were not demonstrated across studies, were nonspecific, were of unclear clinical importance, and in one case, not sustained at the end of the trial.

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3. **The risk/benefit ratio from prolonged antibiotic therapy strongly discourages prolonged antibiotic courses for Lyme disease.** Several presenters in the July 30th hearing argued that patients with symptoms attributed to chronic Lyme disease confer considerable societal cost. This argument, however, was not accompanied by quantitative evidence from controlled trials that prolonged antibiotic therapy could even partly reduce this cost. The Panel concluded that a societal benefit was at best hypothetical based on current evidence.

> It has been argued that prolonged parenteral antibiotics are considered sufficiently safe for their routine use in such infections as osteomyelitis and endocarditis. The Panel does not agree with this comparison, however, because in these conditions clinical trials have decisively shown a clinical and mortality benefit. On the other hand, in the case of Lyme disease, there has yet to be a single high quality clinical study that demonstrates comparable benefit to prolonging antibiotic therapy beyond one month. Therefore, the Review Panel concluded that *in the case of Lyme disease* inherent risks of long-term antibiotic therapy were not justified by clinical benefit.

This conclusion was reached despite the large volume of case reports, case series, anecdotes, and patient testimonials reviewed that attested to perceived clinical improvement during antibiotic therapy. Such evidence is by its nature uncontrolled and highly subject to selection and reporting biases. In many published case reports patients did not receive initial Lyme disease therapy consistent with the current standard of care, so it was impossible to be sure that shorter duration therapy had failed. In some cases the diagnosis of Lyme disease was doubtful based on clinical presentations consistent with other illnesses. Some patients were abnormal hosts and not representative of the general population. Many reports included patients whose diagnosis was made before the implementation of the CDC recommendation for 2-tier serological testing, and were therefore based on less stringent criteria. Finally, caution should be used in extrapolating results from European studies to North American patients, due to the well- established microbiological and clinical distinctions in Lyme borreliosis on the two continents.

In the end, such sources of evidence were felt to be fertile material for hypothesis generation, but intrinsically incapable of hypothesis-testing. By contrast, the prospective, randomized, controlled trials were formal hypothesis tests with strict recruitment criteria, prospectively defined outcome measures, and independent oversight. The Panel's conclusions, which are consistent with those reached by guidelines panels from the IDSA as well as other societies, represent the state of medical science at the time of writing. Only high-quality, prospective, controlled clinical trial data demonstrating both benefit and safety will be sufficient to change the current recommendations."

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Future Directions

Based on the current scientific literature for the surveillance of Lyme disease cases, this report provides PHUs with up-to-date, evidence-based methods and best practices for performing human disease surveillance in Ontario. The sections that cover the *Clinical Signs and Symptoms*, and *Diagnosis and Testing* follow the guidance provided by the IDSA and CPHLN. The IDSA is currently in the process undertaking a systematic review and developing guidelines on the treatment of Lyme disease. As this process is still ongoing, these sections will not be updated until the release of the new IDSA guidelines. Once those guidelines have been released, PHO will review them, in consultation with the CPHLN and AMMI, and determine if changes are needed to relevant sections of this document.

Periodic re-assessment of the methods and best practices for the surveillance of Lyme disease cases, based on the current evidence base, will be required to ensure Ontario remains at the forefront of Lyme disease surveillance in Canada. PHUs should continue to conduct local risk assessments, with support from PHO, to identify and communicate risk areas to the public. Over time, there exists the possibility of other pathogens entering the blacklegged tick populations in Ontario. The introduction of new tick-borne pathogens into Ontario or significant changes in Lyme disease risk and epidemiology may necessitate further revisions to this report.

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