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Changes to Serological Testing of Lyme Disease

Samir Patel, Chief, Microbiology and Laboratory Sciences, Public Health Ontario

Richard Mather, Public Health Physician, Public Health Ontario

April 13, 2023

Public Health Ontario Rounds

Learning Objectives

By the end of this session, participants will be able to:

- Describe the epidemiology of Lyme disease in Ontario
- Identify the new Lyme disease testing method and how it compares to previous testing methods
- Interpret laboratory results using the new modified two-tier testing (MTTT) for detection of Lyme disease

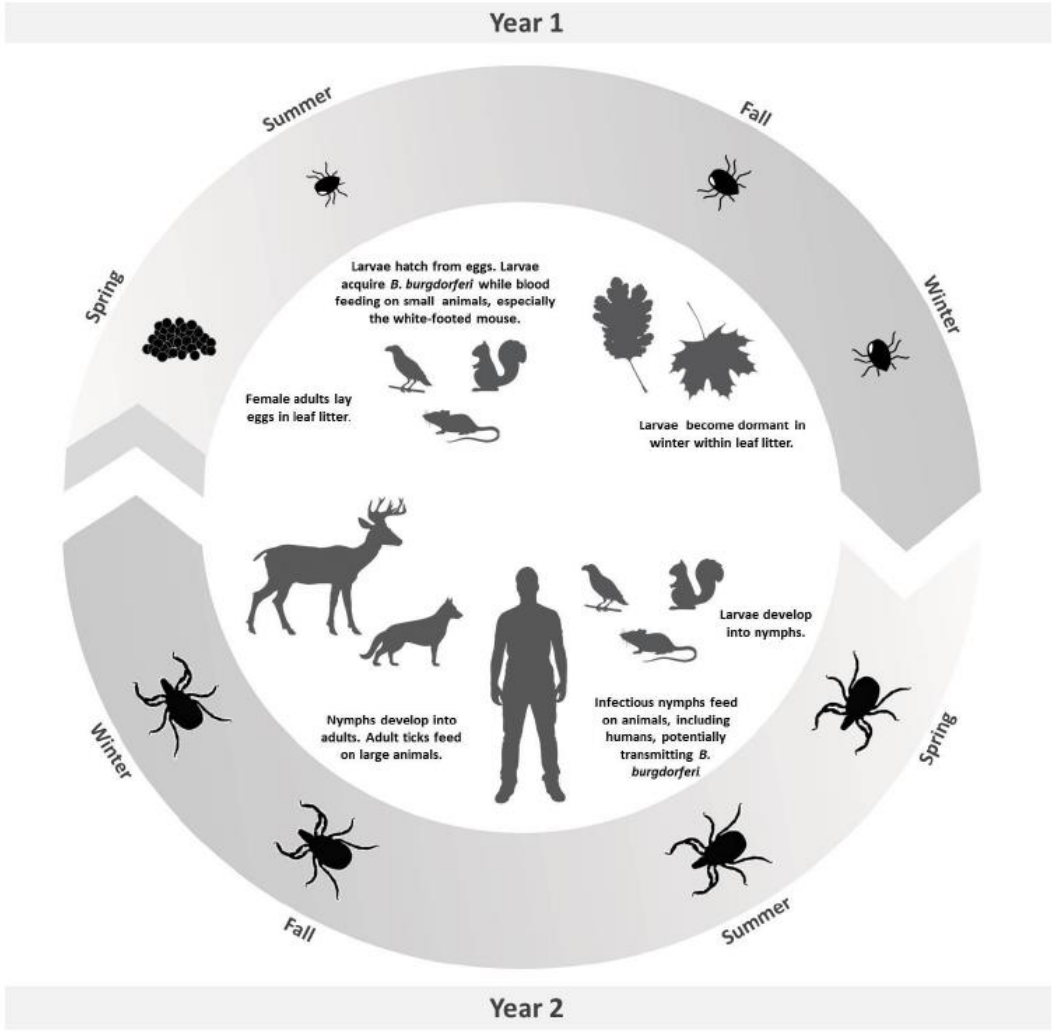
Outline

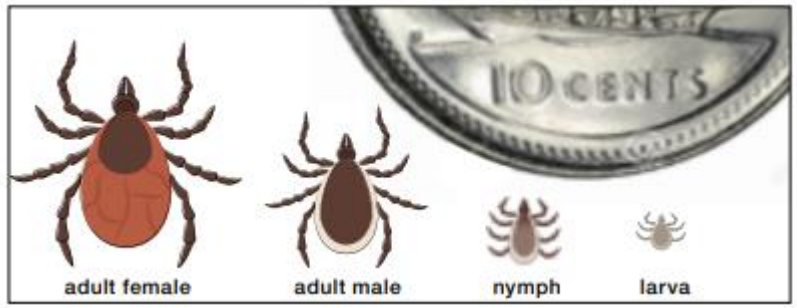
- Epidemiology of Lyme disease in Ontario
- Clinical stages of Lyme disease
- Diagnostic testing for Lyme disease and changes to serological testing
- Implications for practice
- Case studies

Lyme Disease Overview

- Lyme disease is the most common tick-borne infection in Canada
- Vector-borne disease caused by infection with the spirochete bacteria *Borrelia burgdorferi* (in North America)
- *B. burgdorferi* is transmitted to humans in Ontario through the bite of an infected blacklegged tick (*Ixodes scapularis*) that has been attached for >24 hours

Blacklegged Tick Life-Cycle





Source: Ontario Agency for Health Protection and Promotion (Public Health Ontario). Technical report: Update on Lyme disease prevention and control. Second edition. Toronto, ON: Queen's Printer for Ontario; 2016. Available from:

Source: Source: Health Quality Ontario. Clinical guidance document: management of tick bites and investigation of early localized Lyme disease. Toronto, ON: King's Printer for Ontario; 2023. Available from:

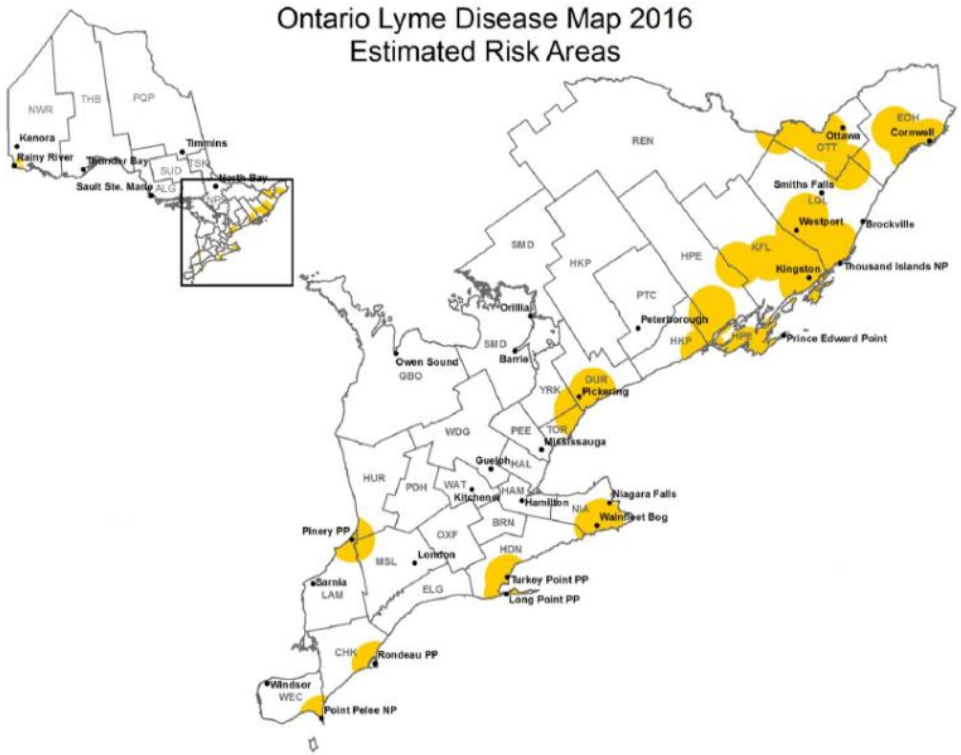
Lyme Disease Transmission

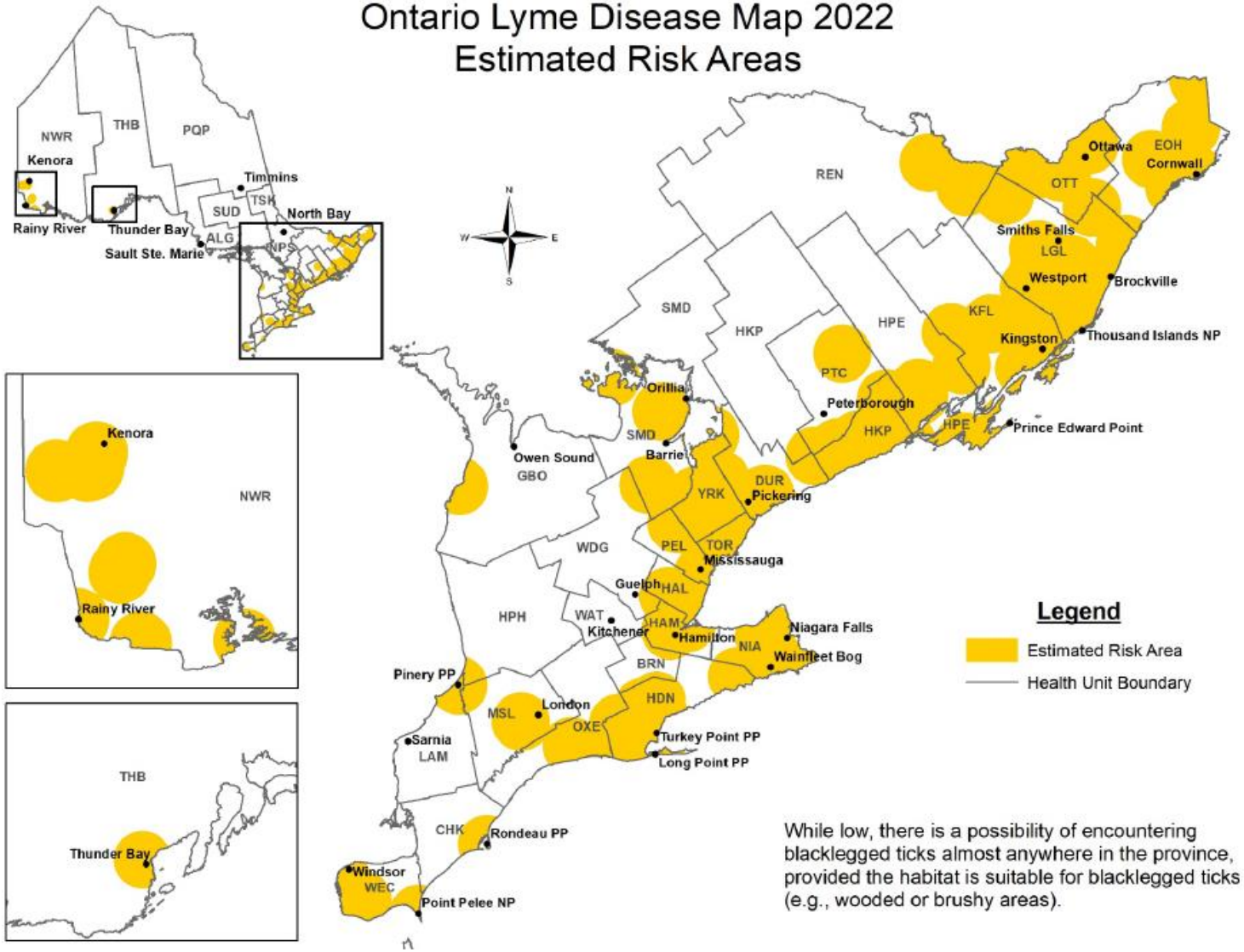
- Nymphal ticks are most likely to transmit *B. burgdorferi*:
  - Active in late spring + summer when humans are most often in areas where ticks live
  - Small in size so harder to detect when attached to a person

Source: Health Canada. Blacklegged (deer) ticks [Internet]. Ottawa, ON: Government of Canada; 2015 [cited 2023 Apr 13]. Figure 3; Figure 4. Available from:

Steere AC, Strle F, Wormser GP, Hu LT, Branda JA, Hovius JW, Li X, Mead PS. Lyme borreliosis. Nat Rev Dis Primers. 2016;2:16090. Available from:

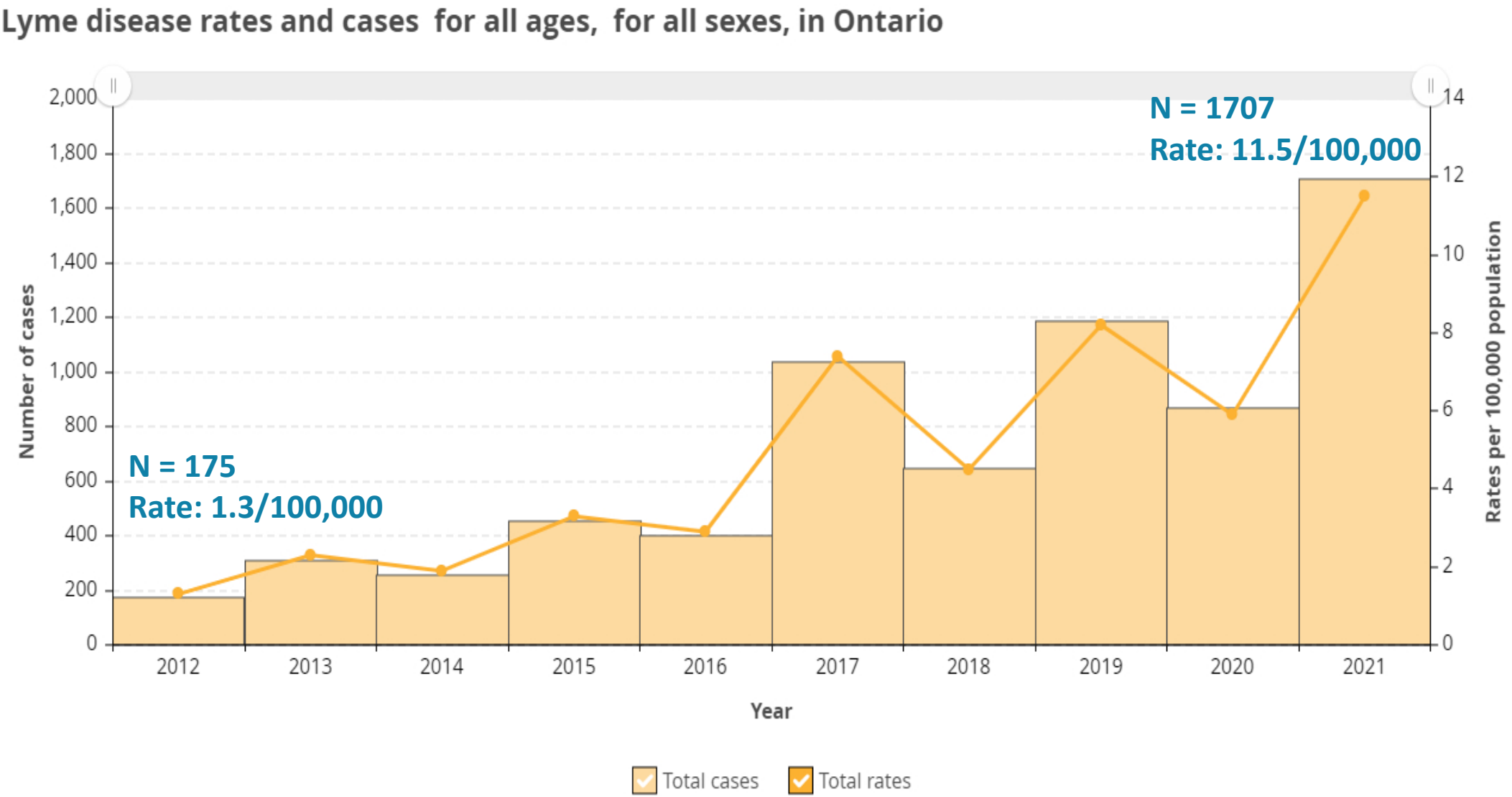
Blacklegged Ticks in Ontario





Source: Ontario Agency for Health Protection and Promotion (Public Health Ontario). Ontario Lyme disease map 2022 estimated risk areas [Internet]. Toronto, ON: Queen's Printer for Ontario; 2022 [cited 2023 Apr 06]. Available from:

Lyme Disease Cases in Ontario



Source: Ontario Agency for Health Protection and Promotion (Public Health Ontario). Infectious disease trends in Ontario [Internet]. Toronto, ON: King's Printer for Ontario; 2022 [cited 2023 Apr 6]. Available from:

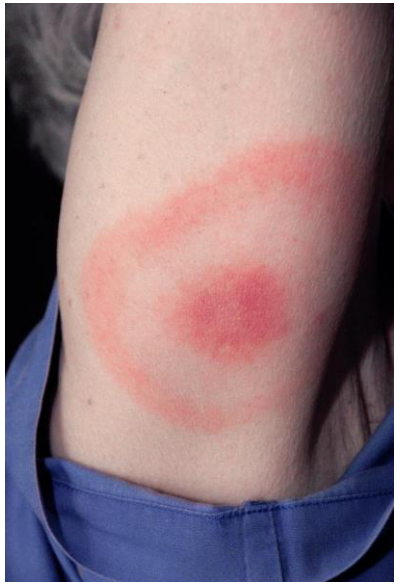
Lyme Disease Clinical Manifestations

- Early localized
  - **3 to 30 days** after an infected tick bite
- Early disseminated
  - **1-3 months** after an infected tick bite
- Late disseminated
  - **>3 months** after an infected tick bite

Source: Government of Canada. Lyme disease: for health professionals [Internet]. Ottawa, ON: Government of Canada; 2022 [cited 2023 Apr 13]. Available from:

Early Localized Lyme Disease

- 3 to 30 days after tick bite (usually 7-14 days)
- Erythema migrans rash
  - Expanding rash >5 cm, occurs in 70-80% of infected patients
- Other potential signs + symptoms:
  - Fever, generalized arthralgia and myalgia, headache, lymphadenopathy



Source: Public Health Agency of Canada. Lyme disease: symptoms and treatment [Internet]. Ottawa, ON: Government of Canada; 2022 [cited 2023 Apr 13]. Available from:

Early Disseminated Lyme Disease

- Weeks to months after tick bite
- Fatigue and general weakness
- Multiple erythema migrans lesions
- Peripheral/central nervous system
  - Cranial nerve palsies (often 7th)
  - Meningitis or encephalitis
  - Subtle cognitive difficulties
- Cardiac symptoms
  - Atrioventricular (AV) node block
  - Atrial fibrillation
  - Myocarditis, pericarditis or endocarditis

Public Health Agency of Canada. Lyme disease: for health professionals [Internet]. Ottawa, ON: Government of Canada; 2022 [cited 2023 Apr 13]. Available from:

Late Disseminated Lyme Disease

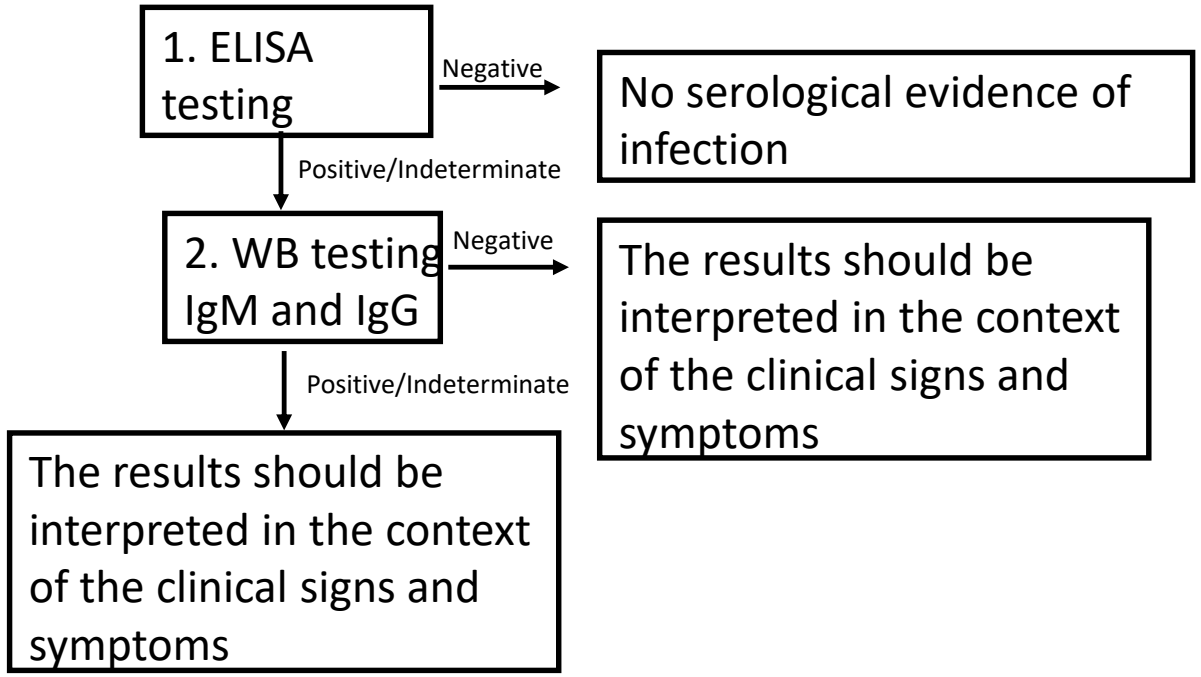
- Weeks to months after the initial infection, late symptoms can occur if untreated, including:
- Musculoskeletal
  - Arthritis - often monoarticular, usually involves large joints, especially the knee
  - Baker’s cyst
- Neurological
  - Meningitis
  - Subacute mild encephalopathy, affecting memory + concentration
  - Polyneuropathy

Public Health Agency of Canada. Lyme disease: for health professionals [Internet]. Ottawa, ON: Government of Canada; 2022 [cited 2023 Apr 13]. Available from:

Lyme Disease Serological Testing

Current Testing Approach in Ontario

2-tier testing (Recommended by IDSA/CDC and CPHLN)



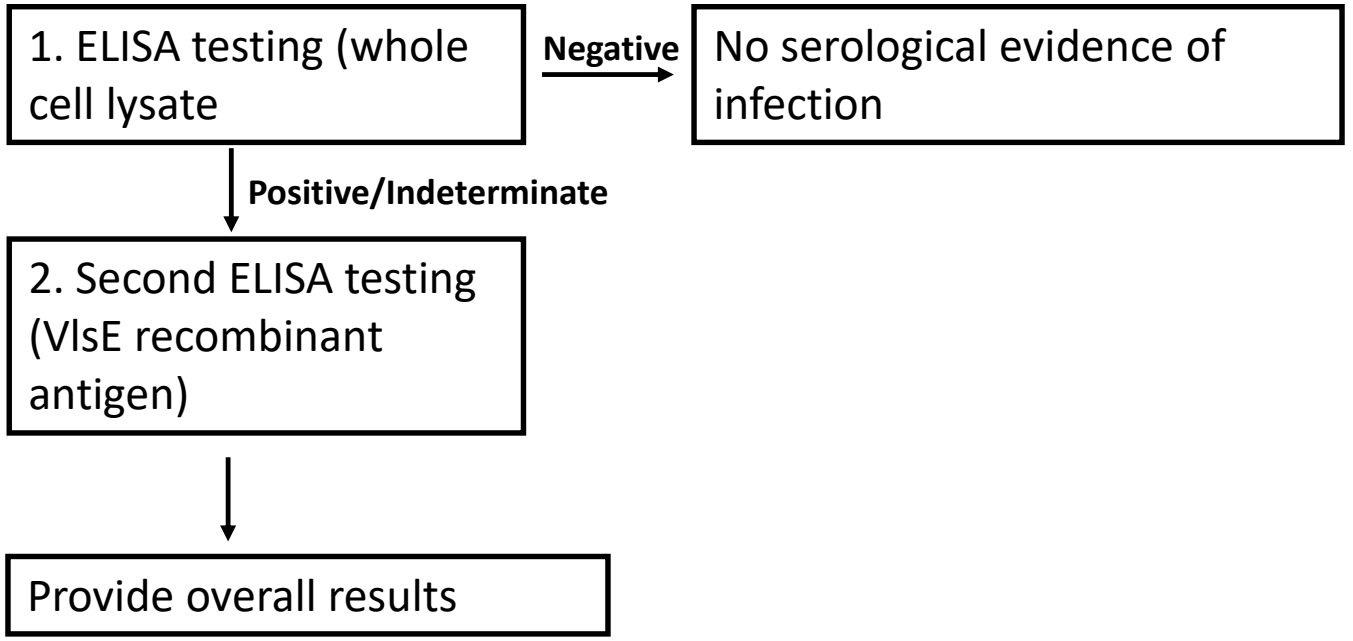
Sensitivity of two-tier testing

Erythema migrans, acute phase (early localized disease)	29–40%
Erythema migrans, convalescence phase‡ (early localized disease)	29–78%
Neurological involvement (early disseminated disease)	87%
Arthritis (late disseminated disease)	97%

IDSA: Infectious Disease Society of America
CDC: Centers for Disease Control
CPHLN: Canadian Public Health Laboratory Network

Is there an alternative method that can be used to improve sensitivity or workflow?

Modified-two Tier-testing (MTTT)



Evaluation of Modified Two-Tiered Testing Algorithms for Lyme Disease Laboratory Diagnosis Using Well-Characterized Serum Samples

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Adoracion Pegalajar-Jurado,[a*] Martin E. Schriefer,[a] Ryan J. Welch,[b] Marc R. Couturier,[b,c] Tiffany MacKenzie,[d*]
Rebecca J. Clark,[a*] Laura V. Ashton,[a] Mark J. Delorey,[a] Claudia R. Molins[a]

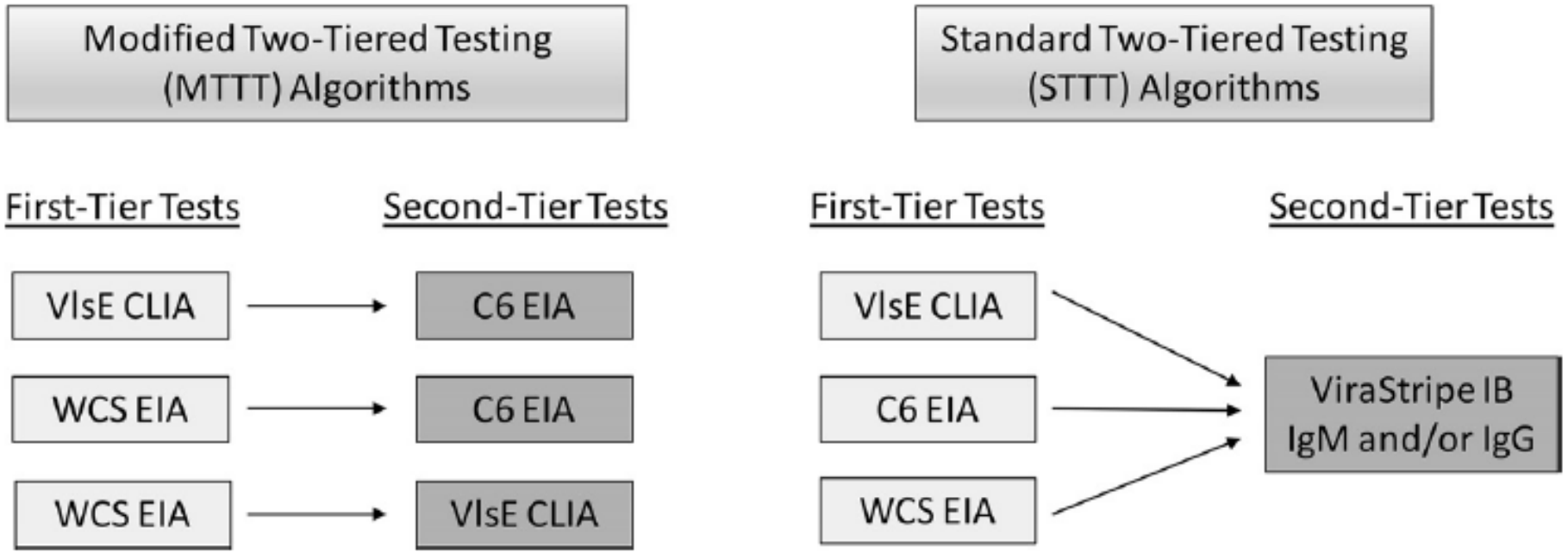

FIG 1 MTTT and STTT algorithms evaluated in this study.

Evaluation of Modified Two-Tiered Testing Algorithms for Lyme Disease Laboratory Diagnosis Using Well-Characterized Serum Samples

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TABLE 1 Results of first-tier tests, MTTTs, and STTTs

Sample type	No. of samples	Test result[a] (no. of positives [%])								
		First-tier test			MTTT algorithm			STTT algorithm[b]		
		VlsE	C6	WCS	VlsE/C6	WCS/C6	WCS/VlsE	VlsE/ ViraStripe	C6/ ViraStripe	WCS/ ViraStripe
Lyme disease	124									
Early Lyme disease with EM[c]										
Acute phase	40	23 (58)	23 (58)	29 (73)	20 (50)	22 (55)	23 (58)	17 (43)	17 (43)	20 (50)
Convalescent phase	38	30 (79)	32 (84)	35 (92)	29 (76)	30 (79)	29 (76)	23 (61)	23 (61)	24 (63)
Early Lyme neuroborreliosis or Lyme carditis										
Lyme neuroborreliosis	10	10 (100)	10 (100)	10 (100)	10 (100)	10 (100)	10 (100)	9 (90)	9 (90)	9 (90)
Lyme carditis	7	5 (71)	6 (86)	7 (100)	5 (71)	6 (86)	5 (71)	5 (71)	6 (86)	7 (100)
Late Lyme disease										
Lyme arthritis	29	29 (100)	29 (100)	29 (100)	29 (100)	29 (100)	29 (100)	28 (97)	28 (97)	28 (97)
Total for Lyme disease		97 (78)	100 (81)	110 (89)	93 (75)	97 (78)	96 (77)	82 (66)	83 (67)	88 (71)
Controls	347									
Other diseases	144									
Fibromyalgia	31	0 (0)	0 (0)	9 (29)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Severe periodontitis	20	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Rheumatoid arthritis	21	0 (0)	0 (0)	9 (43)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Syphilis	20	2 (10)	2 (10)	18 (90)	0 (0)	2 (10)	2 (10)	0 (0)	1 (5)	0 (0)
Multiple sclerosis	22	0 (0)	1 (5)	8 (36)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Infectious mononucleosis	30	1 (3)	4 (13)	19 (63)	0 (0)	2 (7)	1 (3)	0 (0)	1 (3)	9 (30)
Total for other diseases		3 (2)	7 (5)	64 (44)	0 (0)	5 (3)	3 (2)	0 (0)	2 (1)	9 (6)
Healthy controls	203									
Region of endemicity	101	3 (3)	1 (1)	24 (24)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	5 (5)
Region of nonendemicity	102	1 (1)	4 (4)	23 (23)	1 (1)	2 (2)	0 (0)	0 (0)	1 (1)	1 (1)
Total for healthy controls		4 (2)	5 (2)	47 (23)	2 (1)	3 (1)	1 (0)	1 (0)	2 (1)	6 (3)
Total for negative controls		7 (2)	12 (3)	111 (32)	2 (1)	8 (2)	4 (1)	1 (0)[d]	4 (1)	15 (4)

Performance of a Modified Two-Tiered Testing Enzyme Immunoassay Algorithm for Serologic Diagnosis of Lyme Disease in Nova Scotia

Ian R. C. Davis,[a,b,c] Shelly A. McNeil,[a,b,c] Wanda Allen,[b] Donna MacKinnon-Cameron,[b] L. Robbin Lindsay,[d] Katarina Bernat,[d] Antonia Dibernardo,[d] Jason J. LeBlanc,[a,b,c] Todd F. Hatchette[a,b,c]

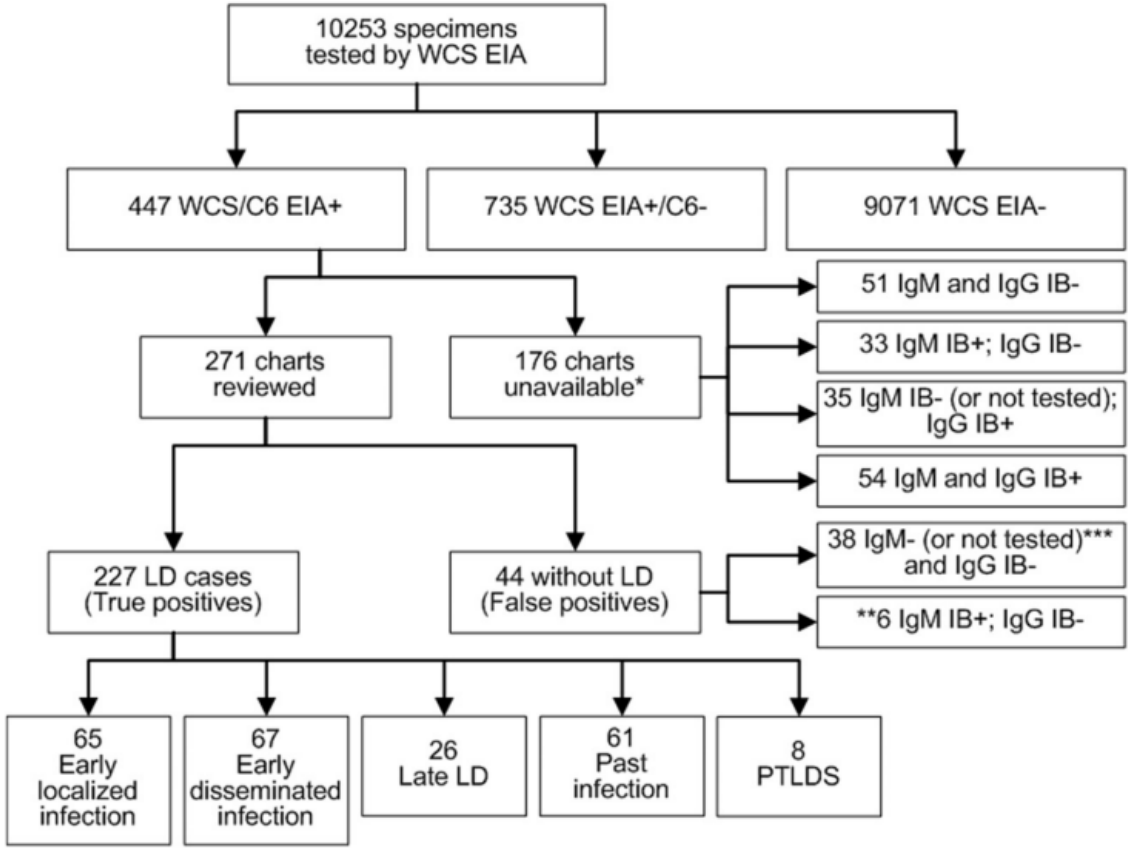


FIG 1 Breakdown of LD serological testing and chart review results. PTLDS, posttreatment Lyme disease syndrome. *, three charts had no IB results. **, of the six individuals who had a positive IgM immunoblot but a negative IgG immunoblot, for two symptoms were ongoing for >30 days and one was diagnosed with optic neuritis and ultimately multiple sclerosis, all consistent with false-positive IgM results; of the remaining three, one patient had 3 days of chest pain and no other symptoms (not a typical presentation for LD), one patient had no clinical data associated with the sample, and one patient had 1 week of subjective fever without documentation of temperature but with no other symptoms. ***, two patients with negative IgG IBs did not have IgM tested, as symptoms were ongoing for >30 days.

- Between 2011-2014, 10253 patients were tested using STTT method
- Samples that were WCS EIA positive were also tested for C6 EIA.
- 271 patients with WCS/C6 positive had their charts reviewed
- Patient charts with WCS neg were NOT reviewed – thus can't determine true sensitivity
- MTTT detected 25% more early localized cases than STTT
- Specificity was comparable

Estimation of MTTT specificity in Nova Scotia patients of whom charts were reviewed

Stage	Published performance of MTTT				Modeled performance of MTTT*		
	EIA methods	Sn (%)	Sp (%)	Ref.	FN**	TN**	Sp (%) [95% CI]
Early localized	WCS; C6	53	99.5	18	56	9750	99.6 [99.4 to 99.7]
	WCS; C6	38	99.5		103	9703	99.5 [99.4 to 99.7]
	WCS; VlsE	36	99.5		112	9694	99.5 [99.4 to 99.7]
	VlsE; C6	54	99.3	19	54	9752	99.6 [99.4 to 99.7]
	WCS; C6	50	98		63	9743	99.6 [99.4 to 99.7]
	VlsE; C6	48	98		68	9738	99.6 [99.4 to 99.7]
	WCS; C6	55	98		52	9754	99.6 [99.4 to 99.7]
	WCS; VlsE	58	99	23	46	9760	99.6 [99.4 to 99.7]
	VlsE; C6	50	99		63	9743	99.6 [99.4 to 99.7]
	VlsE/C10; WCS	73	98.9	16	23	9783	99.6 [99.4 to 99.7]
Early disseminated	WCS; C6	100	99.5	18	0	9806	99.6 [99.4 to 99.7]
	WCS; C6	88	98	28	8	9798	99.6 [99.4 to 99.7]
	VlsE; C6	88	98		8	9798	99.6 [99.4 to 99.7]
	WCS; C6	100	98		0	9806	99.6 [99.4 to 99.7]
	WCS; VlsE	100	99	23	0	9806	99.6 [99.4 to 99.7]
	VlsE; C6	100	99		0	9806	99.6 [99.4 to 99.7]
	VlsE/C10; WCS	66.1	98.9	16	31	9775	99.6 [99.4 to 99.7]
Late disseminated	WCS; C6	100	99.5	18	0	9806	99.6 [99.4 to 99.7]
	WCS; C6	100	98	28	0	9806	99.6 [99.4 to 99.7]
	VlsE; C6	100	98		0	9806	99.6 [99.4 to 99.7]
	WCS; C6	100	98		0	9806	99.6 [99.4 to 99.7]
	WCS; VlsE	100	99	23	0	9806	99.6 [99.4 to 99.7]
	VlsE; C6	100	99		0	9806	99.6 [99.4 to 99.7]
	VlsE/C10; WCS	100	98.9	16	0	9806	99.6 [99.4 to 99.7]
All patients combined	WCS; C6	68	99.5	18	107	9699	99.5 [99.4 to 99.7]
	WCS; C6	76	98	28	72	9734	99.6 [99.4 to 99.7]
	VlsE; C6	73	98		84	9722	99.6 [99.4 to 99.7]
	WCS/C6	78	98		64	9742	99.6 [99.4 to 99.7]
	WCS/VlsE	77	99	23	68	9738	99.6 [99.4 to 99.7]
	VlsE/C6	75	99		76	9730	99.6 [99.4 to 99.7]
	VlsE/C10; WCS	81	98.9	16	53	9753	99.6 [99.4 to 99.7]

Table 2. Sensitivity of standard and modified serological testing for Lyme disease in patients with LD

Reference (sample size)	Disease manifestations[1]	2 EIAs combinations used[2]	STTT sensitivity (CI)[4]	MTTT[5] sensitivity % (CI)
Branda et al. 2011 (140)	EM, ENB, LC	WCS f/b C6	48 (40-56)	61 (53-69)
Branda et al. 2018 (318)	EM, ENB	WCS f/b C6	41 (36-46)	60 (55-66)
Branda et al. 2017 (55)	Acute EM	WCS f/b C6; WCS f/b VlsE CFLIA; VlsE FLIA f/b C6	25	38; 36; 54
Branda et al. 2017 (47)	Convalescent EM	WCS f/b C6; WCS f/b VlsE CFLIA; VlsE FLIA f/b C6	55	72; 66; 72
Molins et al. 2016 (95)	EM, ENB, LC	Vidas f/b C6 or VlsE[3]	60.2 (56.8-64.2)*	66.8 (65.2-68.4)[3]
Lipsett et al. 2016 (114)	All disease stages combined	WCS f/b C6	81.6 (73-88)	79.8 (71.1-86.5)
Pegalajar-Jurado et al. 2018 (40)	Acute EM	VlsE f/b C6; WCS f/b C6; WCS f/b VlsE	43; 43; 50**	50; 55; 58
Pegalajar-Jurado et al. 2018 (38)	Convalescent EM	VlsE f/b C6; WCS f/b C6; WCS f/b VlsE	61; 61; 63	76; 79; 76
Pegalajar-Jurado et al. 2018 (124)	All disease stages combined	VlsE f/b C6; WCS f/b C6; WCS f/b VlsE	66, 67; 71	75: 78: 77
Zweitzig et al. 2019 (30)	Acute EM	VlsE /PEPC10 f/b WCS	50	73.3
Zweitzig et al. 2019 (30)	Convalescent EM	VlsE /PEPC10 f/b WCS	76.7	83.3
Zweitzig et al. 2019 (56)	Early disseminated disease-stage 2	VlsE /PEPC10 f/b WCS	60.7	66.1
Branda et al. 2011 (29)	LA, LNB	WCS f/b C6	100 (86-100)	100 (86-100)
Branda et al. 2018 (122)	LA, LNB	WCS f/b C6	96 (91-98)	98 (93-99)
Molins et al. 2016 (29)	LA	Vidas f/b C6 or VlsE[3]	98.9 (97-100)	100
Zweitzig et al. 2019 (50)	Late disseminated disease-stage 3	VlsE /PEPC10 f/b WCS	100	100

Adapted from: Hatchette T, Robbin L; Lyme Disease Diagnostics Working Group. Modified two-tiered testing algorithm for Lyme disease serology: the Canadian context. Can Commun Dis Rep. 2020;46(5):125-31. Available from: https://doi.org/10.14745/ccdr.v46i05a05

Table 3. Specificity of standard and modified serological testing for Lyme disease in control subjects

Reference (sample size)	Patient cohort	2 EIAs combinations used[1]	MTTT specificity % (CI)
Overall controls			
Branda et al. 2011 (1300)	Healthy and symptomatic controls	WCS f/b C6	99.5 (98.9-99.8)
Branda et al. 2018 (2208)	Healthy controls & patients with other diseases	WCS f/b C6	99.5 (99.1-99.8)
Molins et al. 2016 (347)	Healthy controls & patients with other diseases	Vidas f/b C6 or VlsE2	98.3 (96.2-99.3)
Lipsett et al. 2016 (931)	Healthy and symptomatic controls	WCS f/b C6	96.5 (94.6-97.6)**
Pegalajar-Jurado et al. 2018 (347)	Healthy controls & patients with other diseases	VlsE f/b C6; WCS f/b C6; WCS f/b VlsE	99.4; 97.7; 98.8
Zweitzig et al. 2019 (190)	Healthy controls & patients with other diseases	VlsE /PEPC10 f/b WCS	98.9
Unhealthy controls only			
Branda et al. 2011 (54)	Symptomatic controls	WCS f/b C6	100
Branda et al. 2017 (50)	Patients with other diseases	WCS f/b C6; WCS f/b VlsE CLIA; VlsE CLIAf/b C6	98
Molins et al. 2016 (144)	Patients with other diseases	Vidas f/b C6 or VlsE2	98.2 (96.5 -100)**
Lipsett et al. 2016 (830)	Symptomatic controls	WCS f/b C6	96.5 (94.6-97.6)**
Pegalajar-Jurado et al. 2018 (144)	Patients with other diseases	VlsE f/b C6; WCS f/b C6; WCS f/b VlsE	100; 96.5; 98
Zweitzig et al. 2019 (90)	Patients with other diseases	VlsE /PEPC10 f/b WCS	97.8

“Science rarely advances by revolution. Science is an activity carried out by hundreds of thousands of researchers all contributing to the general picture that eventually emerges.”

Eric Scerii

Historian

U of California at Los Angeles

From New York Times

Advantages and Disadvantages of the MTTT Compared to STTT

Advantages

- Improved sensitivity for the detection of early infection (>25% improvement)
- Less costly
- Less laborious
- Less subjectivity
- Faster TAT

Disadvantages

- Cannot be used to rule out early localized disease (sen: <90%)
- Similar to STTT, MTTT cannot differentiate between recent and past infection or re-infections
- May provide lower specificity in low prevalence area (data unclear)

Recommendations by CDC AND CPHLN

- *"When cleared by FDA for this purpose, serologic assays that utilize EIA rather than western immunoblot assay in a two-test format are acceptable alternatives for the laboratory diagnosis of Lyme disease."*
  - **Mead P, Petersen J, Hinckley A.** Updated CDC recommendation for serologic diagnosis of Lyme disease. MMWR Morb Mortal Wkly Rep. 2019;68:703. Available from:

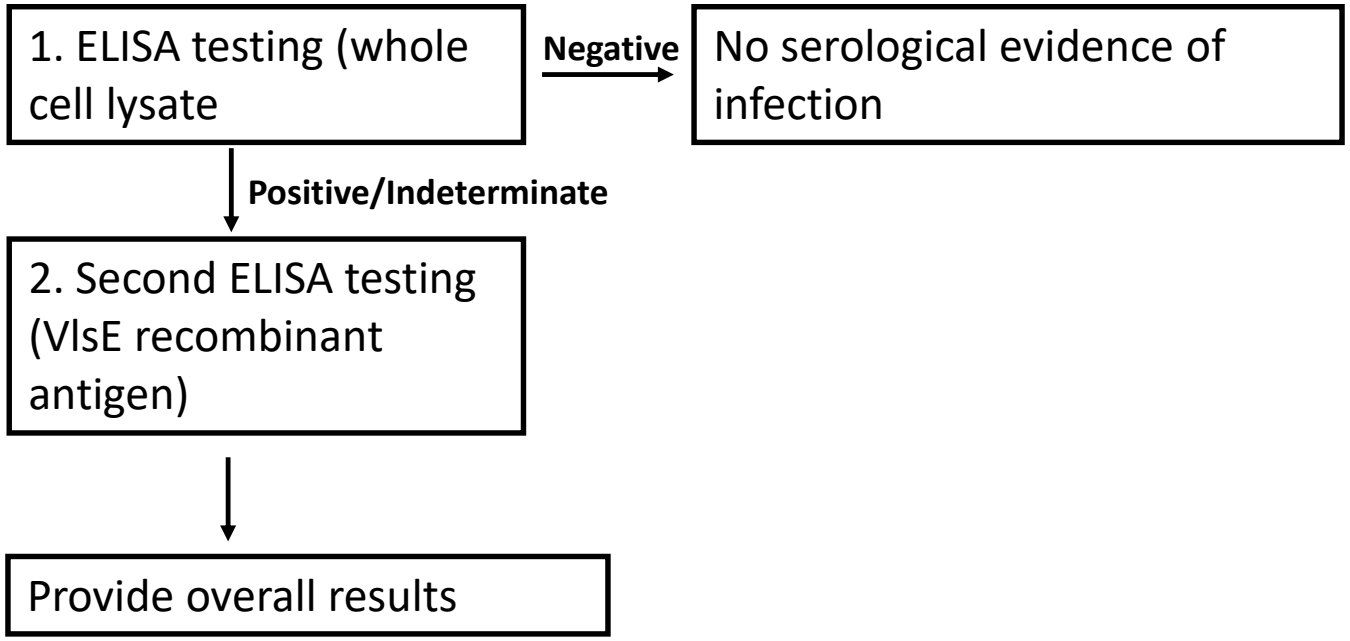
- *"Our working group agrees with the recommendation by the United States Centers for Disease Control that serological testing for LD using MTTT is an acceptable alternative to STTT."*
  - **Hachette T, Lindsay R; Lyme Disease Diagnostics Working Group.** Modified two-tiered testing algorithm for Lyme disease serology: the Canadian context. Can Comm Dis Rep. 2020;46(5):125-31. Available from:

IDSA draft statement: https://www.idsociety.org/practice-guideline/lyme-disease/

- Serological testing for Lyme Disease
  - *"Serum antibody tests should be performed using clinically validated assays in a conventional 2-tiered testing protocol, in which an enzyme immunoassay (EIA) or indirect fluorescent antibody test (IFA) is followed by immunoglobulin M (IgM) and IgG immunoblots, or in a modified 2-tiered testing protocol, in which 2 different EIAs are performed sequentially or concurrently without the use of immunoblots [23–27]."*

Lantos PM, Rumbaugh J, Bockenstedt LK, Falck-Ytter YT, Aguero-Rosenfeld ME, Auwaerter PG, et al. Clinical practice guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 guidelines for the prevention, diagnosis and treatment of Lyme disease. Clin Infect Dis. 2021;72(1):e1-48. Available from:

As of April 1, 2023, PHO is Implementing Modified-two Tier-testing (MTTT)



Testing Indications

- Serological testing of asymptomatic patients, including individuals following a tick bite, is **not recommended.**
- Serological testing for individuals with Erythema migrans, acute phase (seasonal occurrence and exposure in an endemic/risk area) is **generally not recommended.**
- **Serological testing is useful for individuals in the absence of a rash, presenting with non-specific symptoms where Lyme disease is suspected.** An acute and convalescent specimen (2-4 weeks apart) may be required for laboratory confirmation of Lyme disease.
- Serological tests should **not** be used to assess treatment response.
- When European Lyme is suspected, **European Lyme serology should be specifically stated on the requisition along with exposure to tick bite and RECENT travel history (≤ 12 months) including location and dates**

Lyme Disease Test Result Interpretation

Lyme Tier 1 EIA	Lyme Tier 2 EIA	*Borrelia burgdorferi* (Lyme disease) serology interpretation
Non- Reactive	Not tested	Non- Reactive Advise follow-up specimen (2-4 weeks apart) if clinically indicated.
Indeterminate	Non- Reactive	Non- Reactive The results should be interpreted within the clinical context. Advise follow-up specimen (2-4 weeks apart) if clinically indicated.
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Lyme Disease Serological Testing Changes: Implications for Practice

Testing Changes: Implications for Practice

- Potential for more early cases identified
- Diagnosis of early localized Lyme disease is still a clinical diagnosis
- Minimal changes to interpretation of results
  - Lyme disease test information sheet: results interpretation
- Minimal changes to iPHIS case entry
  - Updated Lyme disease Ontario Investigation Tool (OIT)
- Updated Ontario Health Clinical Guidance Document
  - Management of Tick Bites and Investigation of Early Localized Lyme Disease
- Updated Ministry of Health Appendix 1: Lyme Disease

Ontario Investigation Tool Updates

OLD

Human Lab Testing Information							
Requisition #	**Test Date**	**Sample Type (serum)**	**Collection Date**	**EIA/ELISA Result IgM/IgG**	**Western Blot IgM**	**Western Blot IgG**	**Results**
	YYYY-MM-DD		YYYY-MM-DD				☐ Reactive ☐ Non-Reactive ☐ Indeterminate

NEW

Human Lab Testing Information						
Requisition #	**Test Date**	**Sample Type (serum)**	**Collection Date**	**EIA/ELISA Tier 1 Result IgM/IgG**	**EIA/ELISA Tier 2 Result IgM/IgG**	**Results**
	YYYY-MM-DD		YYYY-MM-DD			☐ Reactive ☐ Non-Reactive ☐ Indeterminate

European Human Lab Testing Information							
Travel to Europe	☐ NO	☐ YES, if yes please fill out the following information					
Requisition #	**Test Date**	**Sample Type (serum)**	**Collection Date**	**EIA/ELISA Tier 1 Result IgM/IgG**	**Western Blot IgM**	**Western Blot IgG**	**Results**

Source: Ontario Agency for Health Protection and Promotion (Public Health Ontario). Lyme disease investigation tool [Internet]. Toronto, ON: King's Printer for Ontario; 2023 [cited 2023 Apr 13]. Available from:

CLINICAL GUIDANCE DOCUMENT

Management of Tick Bites and Investigation of Early Localized Lyme Disease

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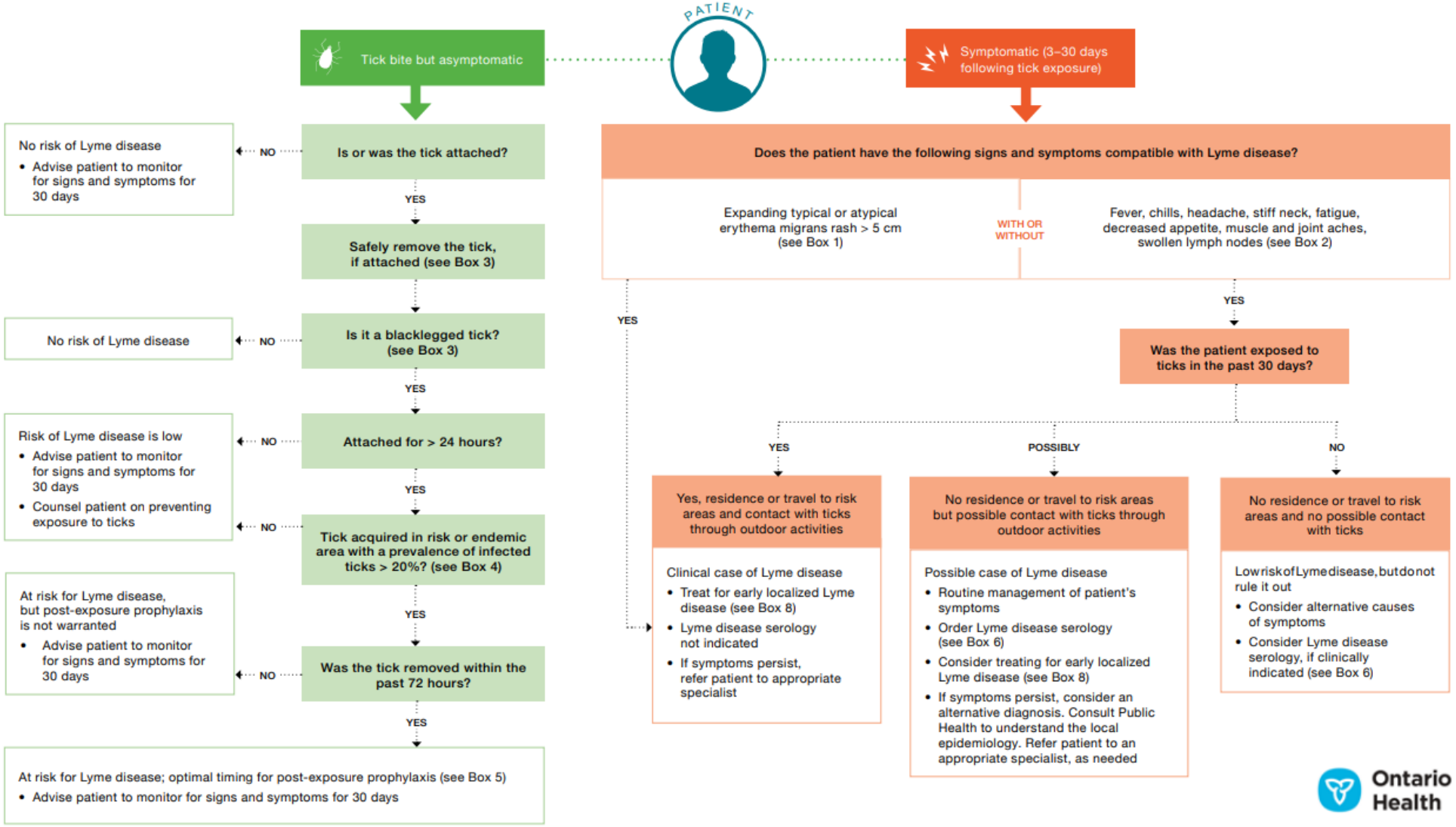
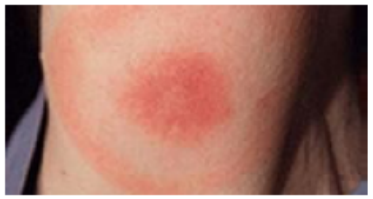
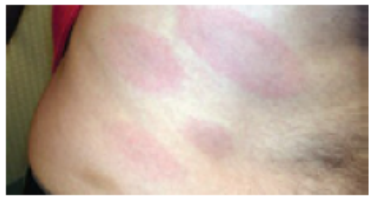


Source: Health Quality Ontario. Clinical guidance document: management of tick bites and investigation of early localized Lyme disease. Toronto, ON: King's Printer for Ontario; 2023. Available from:

Box 1. Clinical Manifestations of Early Localized Lyme Disease: Erythema Migrans Rashes





Additional images of typical and atypical rashes are available on Health Canada's website; under "Clinical manifestations," please see "Erythema migrans rash."

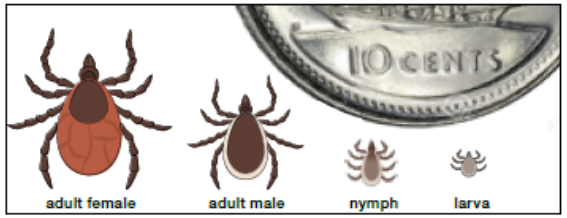
Note: People with darker skin tones may present with a bruise-like rash.

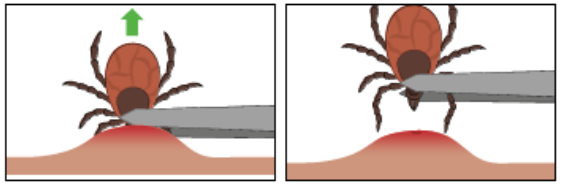
Box 2. Prevalence of Symptoms in Patients Presenting With Possible Early Localized Lyme Disease[‡]

- Erythema migrans rash (typical or atypical) ~70%
- Fatigue 54%
- Myalgia 44%
- Headache 42%
- Fever/chills 39%
- Stiff neck 35%
- Decreased appetite 26%

[‡]As a disease of public health significance, Lyme disease is reportable in Ontario under the *Health Protection and Promotion Act*, R.S.O. 1990, c. H.7.

Box 3. Blacklegged Ticks at Various Stages and Safe Tick Removal





Box 4. Areas of Risk for Lyme Disease

- The risk of acquiring Lyme disease varies across geographical regions. Please click to see the risks in Ontario, Canada, and the United States
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Box 5. Post-Exposure Prophylaxis

The risk of developing Lyme disease following a tick bite by an infected tick is between 1% and 3%. In Ontario, the prevalence of infected ticks varies by geographic region. In many instances, it is reasonable to adopt the "wait and see" approach and treat patients if they develop symptoms compatible with Lyme disease. **Counsel patients to watch for the development of early signs and symptoms for 30 days, and advise patients that other tick-borne infections may result in signs or symptoms too.**

Based on the best available evidence, post-exposure prophylaxis can be considered if these four criteria are met:

1. The tick was attached > 24 hours
2. The tick was removed within the past 72 hours
3. The tick was acquired in an area with a prevalence of ticks infected with *Borrelia burgdorferi* > 20% (e.g., Rouge National Urban Park and Morningside Park in the Greater Toronto Area, Brighton, Kingston and surrounding areas, Thousand Islands, Brockville, Perth-Smiths Falls and surrounding areas, Ottawa and surrounding areas, Rondeau Provincial Park in Morpeth, and Pinery Provincial Park in Grand Bend*)
4. Doxycycline is not contraindicated. (Doxycycline is contraindicated for pregnant or lactating people and those with an allergy. There is insufficient evidence for the prophylactic use of other medications, such as amoxicillin)

Recommended treatment for post-exposure prophylaxis:

Adults: 1 dose of doxycycline 200 mg, by mouth

Children < 18 years of age: 1 dose of doxycycline 200 mg dose or 4 mg/kg (up to a maximum dose of 200mg), by mouth

*Note: This is not a comprehensive list of higher-risk areas in Ontario. Infectivity rate is not uniformly collected and updated, and therefore post-exposure prophylaxis decisions are sometimes made based on risk-benefit discussions with patients.

For more information, please refer to the Ontario Lyme Disease Map.

Box 6. Laboratory Testing

- Laboratory testing is generally not indicated for asymptomatic patients
- Serological testing may not yield positive results during early localized Lyme disease, so management should not be based on serological testing results during this phase
- Antibiotic treatment in early disease may reduce seroconversion; testing should not be used to monitor treatment outcome
- Following exposure to *Borrelia burgdorferi*, immunoglobulin M (IgM) antibodies are detected within 2–4 weeks, and IgG antibodies within 4–6 weeks
- As of April 1, 2023, Public Health Ontario uses a modified two-tiered testing (MTTT) algorithm to maximize sensitivity and specificity (see Box 7)
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Box 7. Sensitivity of Serological (Modified Two-Tier) Testing[†] in Patients With Lyme Disease[6,7]

Erythema migrans, acute phase (early localized disease)	58%
Erythema migrans, convalescence phase[‡] (early localized disease)	76%
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[‡]Following antibiotic treatment.

Box 8. Recommendations for Treatment of Patients With Early Localized Lyme Disease

Drugs	Dosage for Adults	Dosage for Children
Preferred		
Doxycycline*	100 mg twice a day for 10–21 days[†] Contraindicated for pregnant or lactating people	For children < 18 years of age: 4 mg/kg, orally divided into 2 doses (maximum 200 mg/day) for 10–21 days[†]
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Cefuroxime	500 mg twice per day for 14–21 days	For children > 8 years of age: 30 mg/kg/day divided in 2 doses (maximum 500 mg/dose) for 14–21 days
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Source: Health Quality Ontario. Clinical guidance document: management of tick bites and investigation of early localized Lyme disease. Toronto, ON: King's Printer for Ontario; 2023. Available from:

Summary

- Effective Apr 1, 2023 PHO implemented modified two-tier testing (MTTT) for detection of antibodies against *B. burgdorferi* (Lyme Disease)
- The MTTT algorithm has been endorsed by the Centers for Disease Control and Prevention (CDC) as well as the Canadian Public Health Laboratory Network (CPHLN) as an acceptable alternative method to the standard two-tier testing (STTT)
- Sensitivity of MTTT is higher (15-25%) than STTT in detecting antibodies during early-localized Lyme disease
- PHO has updated iPHIS and the Lyme disease OIT to meet the new testing updates

Links

- Lyme Disease Ontario Investigation Tool
- Lyme Disease Test Information Sheet
- Ontario Lyme Disease Estimated Risk Areas Map
- Ontario Health Clinical Guidance Document: Management of Tick Bites and Investigation of Early Localized Lyme Disease
- Ministry of Health Appendix 1: Lyme Disease

Cases

Case #1

- 68-year-old retired nurse living in **Ottawa area** was **bitten by a tick** while gardening
- She took the tick to her local public health unit, but the tick was not sent to the laboratory at Public Health Ontario for identification
- A few days later she developed a rash and “flu-like” symptoms
- Upon examination – **erythematous rash** at the site of the bite **measuring 8 cm**
- Treated with doxycycline for two weeks
- Doctor did not test her for Lyme disease antibodies

Case #1 Questions

- What evidence supports the diagnosis of early localized Lyme disease?
- Should the physician have ordered serology?
- Patient returns and insists on getting tested for Lyme disease. How would you counsel her?

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- **What evidence supports the diagnosis of early localized Lyme disease?**
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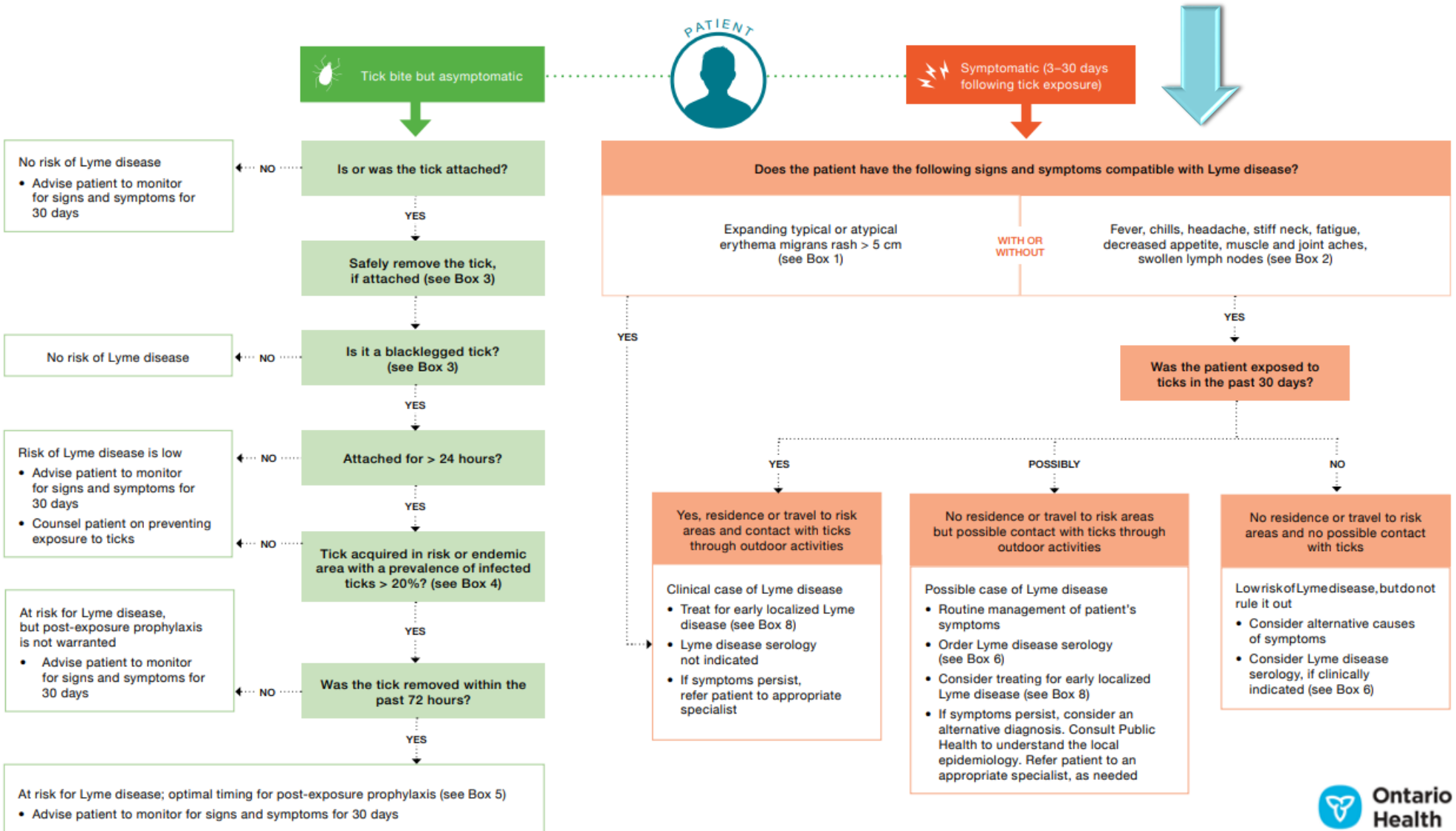

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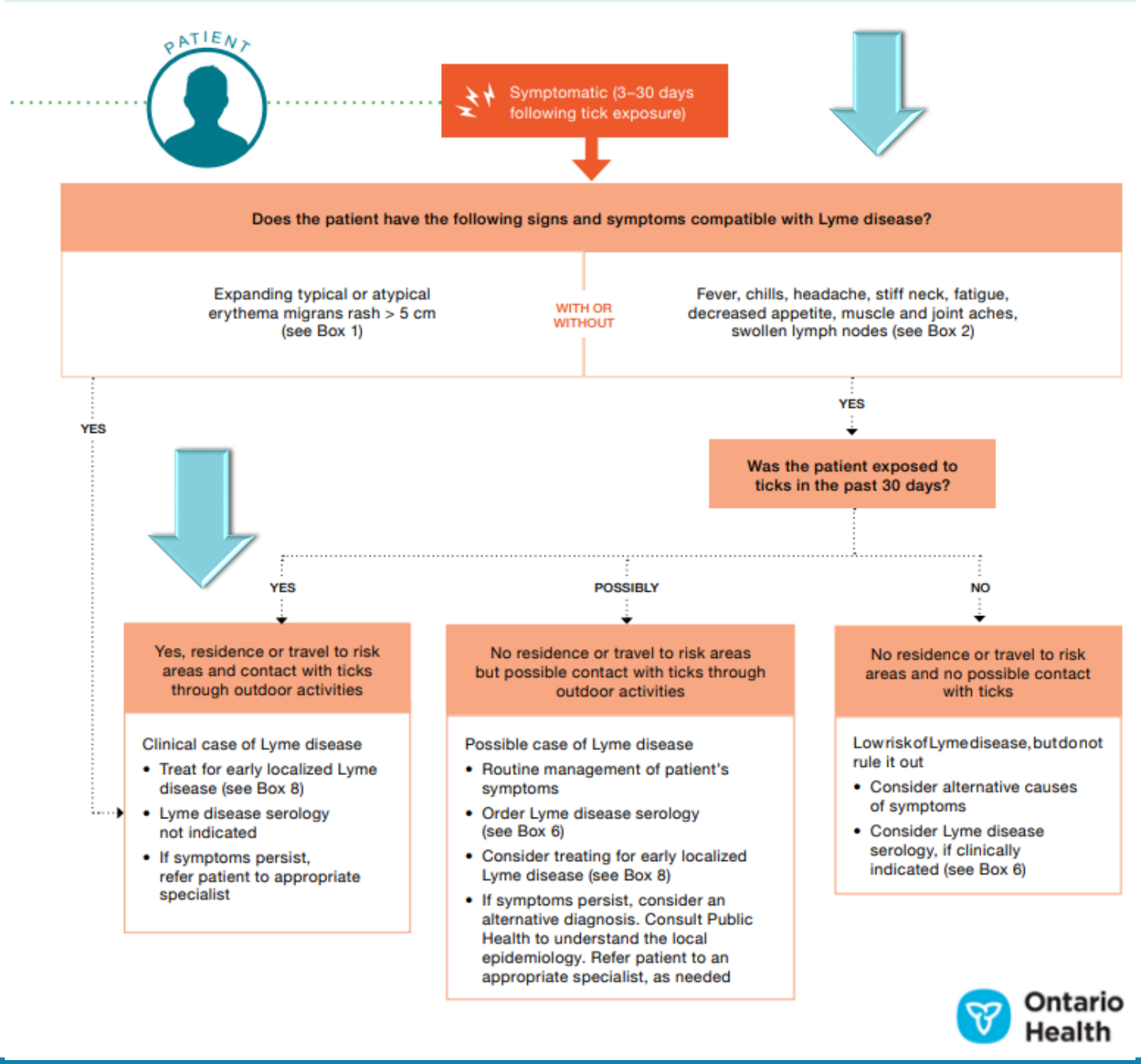

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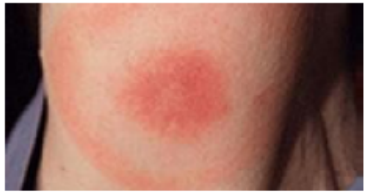

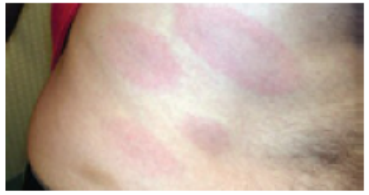

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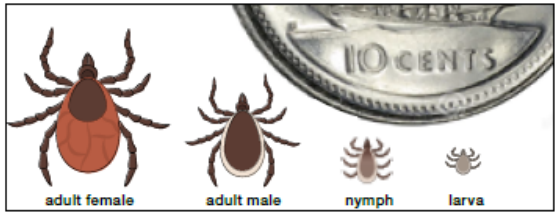

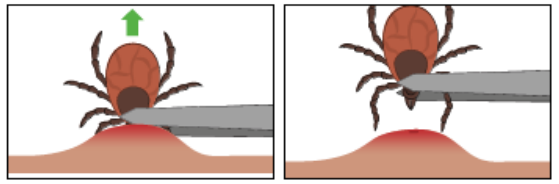

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Source: Source: Health Quality Ontario. Clinical guidance document: management of tick bites and investigation of early localized Lyme disease. Toronto, ON: King's Printer for Ontario; 2023. Available from:

Case #2

- 19 year old student lives in **Kitchener**
- Presented to a doctor with a 1 week history of rash (circular erythematous patch)
- General “flu-like” symptoms (i.e., fatigue, chills, fever, headache, muscle and joint aches, and swollen lymph nodes)
- No travel history **to risk areas and no possible contact with ticks** in past month
- Initial thoughts and work-up?

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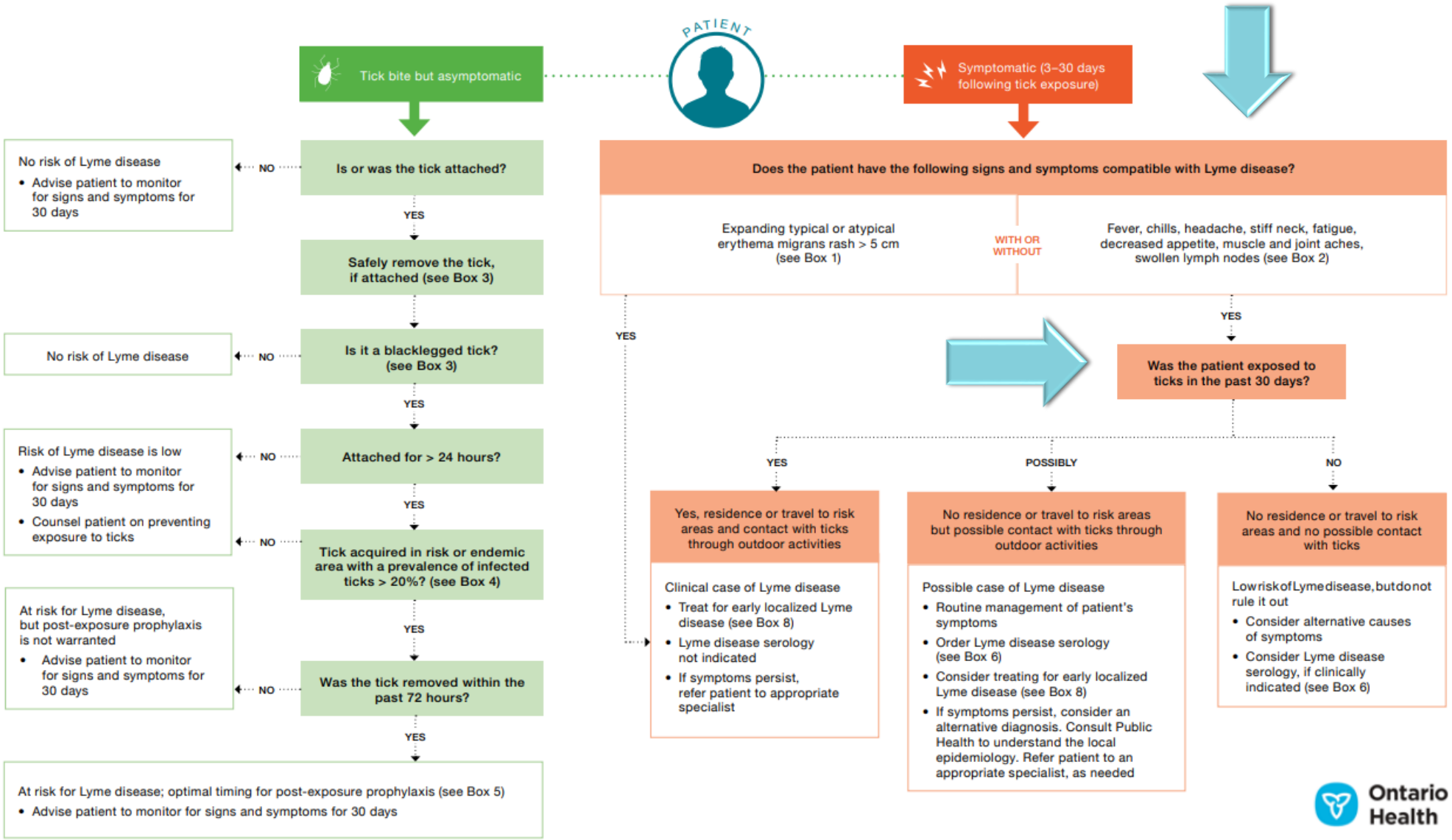

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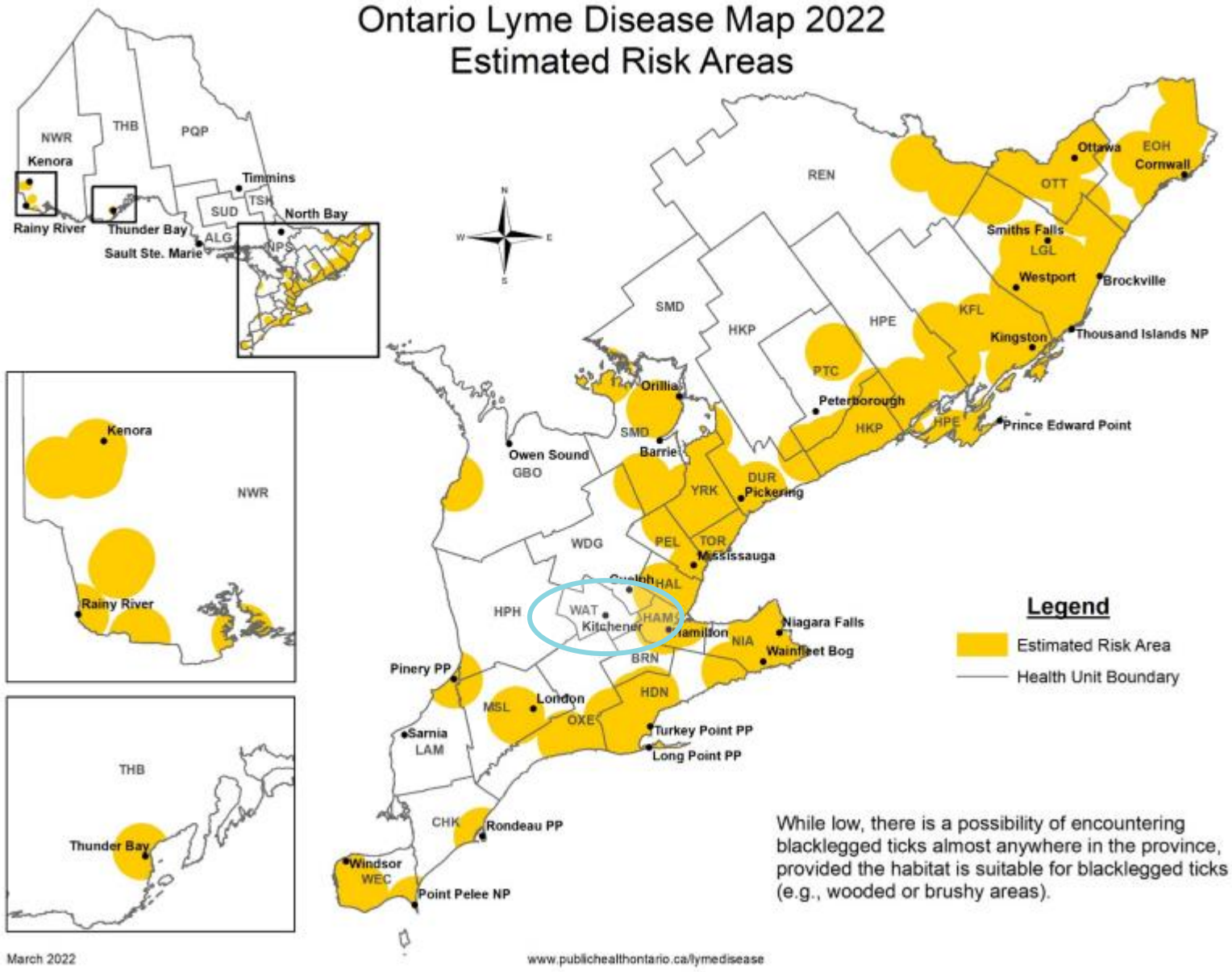

Source: Ontario Agency for Health Protection and Promotion (Public Health Ontario). Ontario Lyme disease map 2022 estimated risk areas [Internet]. Toronto, ON: Queen's Printer for Ontario; 2022 [cited 2023 Apr 6]. Available from:

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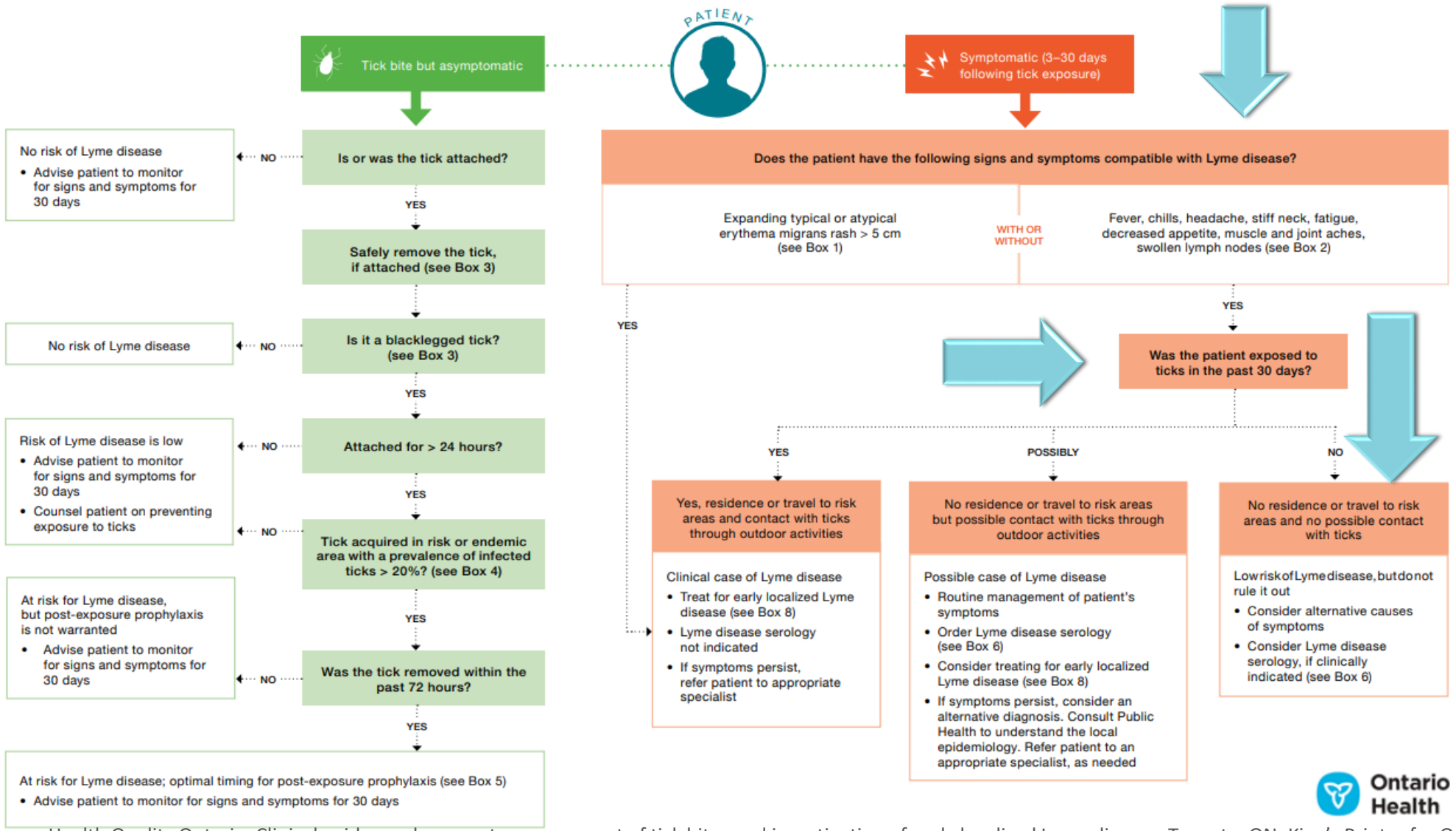

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Questions?

Acknowledgements

- Mark Nelder, Senior Program Specialist, Enteric, Zoonotic, Vector-Borne Diseases, Public Health Ontario
- Curtis Russell, Senior Program Specialist, Enteric, Zoonotic, Vector-Borne Diseases, Public Health Ontario

For More Information About This Presentation, Contact:

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Ontario

Links

- Ontario Agency for Health Protection and Promotion (Public Health Ontario). Lyme disease investigation tool [Internet]. Toronto, ON: King's Printer for Ontario; 2023 [updated 2023 Apr 3; cited 2023 Apr 13]. Available from:

- Ontario Agency for Health Protection and Promotion (Public Health Ontario). Test information index [Internet]. Toronto, ON: King's Printer for Ontario; 2023 [cited 2023 Apr 13]. Available from:
- Ontario Agency for Health Protection and Promotion (Public Health Ontario). Lyme disease [Internet]. Toronto, ON: King's Printer for Ontario; 2023 [cited 2023 Apr 13]. Available from:

- Health Quality Ontario. Guidance document: Lyme disease [Internet]. Toronto, ON: King's Printer for Ontario [cited 2023 Apr 13]. Available from:

- Ontario. Ministry of Health. Ontario public health standards. Infectious disease protocol. Appendix 1: case definitions and disease-specific information.Disease: Lyme disease. Effective: April 2023 [Internet]. Toronto, ON: Queen's Printer for Ontario; 2023 [cited 2023 Apr 13]. Available from: