Companion animals and tick-borne diseases

A systematic review

Systematic Review

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Public Health Ontario

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Introduction

Purpose and objectives

To provide the latest, evidence-based guidance on the surveillance of tick-borne diseases to our stakeholders, Public Health Ontario (PHO) undertook a systematic review to assess the scientific literature on companion animals as sources of spatial prevalence data for human tick-borne diseases, and the tick-borne disease risks companion animals pose to their owners. This work complements PHO's recent systematic reviews on blacklegged tick and human Lyme disease surveillance.

The American Society for the Prevention of Cruelty to Animals (ASPCA) defines companion animals as any "domesticated or domestic-bred animals whose physical, emotional, behavioral and social needs can be readily met as companions in the home, or in close daily relationship with humans." For this systematic review, we restrict companion animals to those that traditionally spend some time outdoors in a rural, suburban or urban peridomestic setting, such as cats, dogs and horses.

The objectives of this systematic review are to:

1. Assess the scientific literature on the seroprevelance of tick-borne infections in companion animals as possible spatial predictors of human risk.
2. Assess the scientific literature on the risks of tick-borne disease in companion animal owners.

Ticks and tick-borne diseases in Ontario

Based on surveillance data as of 2017, approximately 25 of the world's 900 tick species have been identified in Ontario, including native and adventive species; however, *Ixodes scapularis* (blacklegged tick), *Dermacentor variabilis* (American dog tick) and *Ixodes cookei* (groundhog tick) are the most common species the public submits for identification.[1-5] *Borrelia burgdorferi* sensu stricto, the agent of Lyme disease transmitted by blacklegged ticks, is the principal tick-borne pathogen of public health concern in Ontario.[4,6] *Anaplasma phagocytophilum*, *Babesia microti*, *Borrelia miyamotoi*, *Coxiella burnetii*, *Francisella tularensis*, Powassan virus (POWV) and *Rickettsia rickettsii* are additional tick-borne pathogens of concern given their contemporary or historical occurrence in Ontario (Table 1).[7,8] Other tick-borne human pathogens not yet identified in Ontario but found in adjacent jurisdictions include *Borrelia mayonii*, deer tick virus (DTV) and the *Ehrlichia muris*-like agent.[6] Healthcare professionals are realizing the notion of "exotic disease" is somewhat antiquated, with pathogens routinely appearing outside historical distributions.[9] As tick-borne pathogens continue to emerge throughout North America and threaten Ontario, public health officials must be vigilant for additional human pathogens and their vectors.

Tick-borne disease surveillance is challenging, as the distribution of tick vectors is constantly changing due to landscape modifications, human population growth, migration of ticks and pathogens via their hosts, increased global travel and climate change.[5,10] In addition, researchers continue to detect novel pathogens, owing in part to advances in molecular detection methods in ticks, humans and non-human animals. In Ontario, tick-borne disease surveillance and assessment of human risk is primarily undertaken through passive techniques such as human case reporting via Ontario's integrated Public Health Information System (iPHIS), or through tick submissions by the public or healthcare professionals

for identification and pathogen testing.[11-13] Furthermore, public health officials use active tick surveillance (such as tick dragging, small mammal trapping) where indicated to estimate Lyme disease risk areas.[14] Ontario's surveillance system helps public health officials identify the spatial dynamics of Lyme disease and allows for public health professionals to conduct risk assessments at the local, regional and provincial level.

Table 1. Selected human, tick-borne pathogens of concern identified in humans, non-human animals or ticks in Ontario

Pathogen	Associated disease	Primary vector(s)	Identified in humans in ON?[4,6-8‡‡]	Identified in non-human animals in ON?[4,6-8]	Identified in ticks in ON?[4,6-8]
Anaplasma phagocytophilum*	Anaplasmosis	I. scapularis	No	Yes (deer, dogs, rodents)	Yes (I. scapularis)
Babesia microti	Babesiosis	I. scapularis	Yes†	Yes (rodents)	Yes (I. scapularis)
Borrelia burgdorferi	Lyme disease	I. scapularis	Yes	Yes (dogs, deer, rodents)	Yes (I. scapularis)
Borrelia miyamotoi	B. miyamotoi disease	I. scapularis	No	No	Yes (I. scapularis)
Coxiella burnetii**‡	Q fever	Dermacentor spp.	Yes	Yes (goats, rodents, sheep)	No
Francisella tularensis**‡	Tularemia	Dermacentor spp., Amblyomma americanum	Yes	Yes (dogs, multiple wildlife species)	Yes (D. variabilis, Haemaphysalis leporispalustris)
Powassan virus	POWV infection	I. cookei, Ixodes marxi	Yes	Yes (dogs, multiple wildlife species)	Yes (I. cookei)
Rickettsia rickettsii‡	Rocky Mountain spotted fever	D. variabilis, A. americanum	No	Yes (dogs)	Yes (D. variabilis)

*Includes *A. phagocytophilum* strains that are specific to deer (*Ap*-variant-1 strain) and humans (*Ap*-ha strain).

**Not exclusively a tick-borne infection, i.e., transmission via contact with infectious animals or aerosolization. The role of ticks in the transmission of C. burnetii is questionable.[15]

†Transmission via platelet transfusion.[16]

‡A recent study failed to detect *C. burnetii*, *F. tularensis* and *R. rickettsii* in Ontario's American dog ticks; therefore, the risk of tick-borne transmission of these pathogens is low in Ontario.[17]

‡‡While including pathogens detected in Ontarians, it does not imply tick-transmission in the province.

PHO continually assesses Ontario's surveillance programs and makes modifications based on the scientific evidence. While Ontario currently focuses its tick-borne disease surveillance on *B. burgdorferi* and blacklegged ticks – along with monitoring the potential emergence of anaplasmosis, babesiosis, deer tick virus and Powassan virus – the surveillance system is capable of detecting population changes in other tick species and the prevalence of additional pathogens.

One Health and tick-borne diseases

The One Health approach to infectious disease surveillance and management uses human and non-human animal disease data, coupled with ecological data, to identify disease risk in both time and space.[18] One Health is integral to vector-borne disease surveillance and management, as most vector-borne diseases have non-human animals as reservoirs or dead-end hosts. In New York, in 1999, perceptive veterinarians and epidemiologists linked the sudden die-off of crows and captive birds to an increase in human encephalitis cases of unknown etiology; research would identify the agent as West Nile virus (WNV), a mosquito-borne arbovirus that would spread rapidly across North America.[19-21] Since 1999, public and veterinary health officials monitor avian and equine WNV infections to help forecast WNV outbreaks and epizootics. In contrast to WNV, public health has not widely taken advantage of data collected from non-human animals as sources of surveillance data for human tick-borne diseases.

Tick-borne diseases in companion animals, livestock or wildlife provide important spatial information on human disease risk due to common exposures to tick vectors and pathogens. Given the ubiquitous nature of human and companion animal interactions, using companion animals as sources of surveillance data for human tick-borne diseases offers an opportunity for improving public and veterinary health surveillance. Employing animal health surveillance for assessing public health risks is considered widely as a "global public good."[22] The importance of animal health to public health is evident as public health organizations now monitor and report on animal disease data; for example, the Los Angeles County Department of Public Health produces the *Animal Disease Surveillance Report*.[23] Dogs have been closely associated with humans for over 30,000 years, leading to shared pathogens and vectors.[24] In 2015, the Canadian Animal Health Institute estimated there were 7 million cats and 6.4 million dogs in Canada, with approximately 35% of Canadians owning a cat and 32% owning a dog. Dogs, more so than cats or horses, have been widely utilized as surveillance tools for assessing the risks of human pathogen or toxin exposure. Given this close association between dogs and humans, dogs have provided important information on the human risks associated with cyanobacteria/algae toxins (United States of America [USA]), environmental contaminants/lymphoma (Italy), lead poisoning (Illinois), *Leishmania infantum* (China), *R. rickettsii* (Arizona), *Trypanosoma cruzi* (Texas) and zoonotic parasites (Canada).[25-33] In the last 20 years, increased veterinary care for companion animals has led to improved pathogen detection, disease diagnostics and treatment.[34] Increased attention to companion animal health has also resulted in the realization that humans and companion animals share a suite of pathogens as they cohabit within common exposure environments.

The focus of this systematic review (using companion animals as sources of pathogen prevalence data and the risks associated with companion animal ownership) will be North American studies, making results more generalizable to the Ontario situation.

Methodology

Search strategy

We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for reporting in a systematic review.[35] We conducted, with PHO Library Services, a scientific literature search of English-language articles using five electronic databases:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present (Ovid Interface: January 1, 1970–July 8, 2016);
- Embase (Ovid Platform: January 1, 1974–Week 32, 2016);
- BIOSIS Previews (2002–Week 32, 2016);
- Environment Complete (EBSCOhost Research Databases: January 1, 1970–July 8, 2016); and
- Scopus (January 1, 1970–July 8, 2016).

Our search used subject headings and keywords included "pets", "dogs", "cats", "Borrelia", "Anaplasma", "Babesia", "canine", "feline", "surveillance", "risk", "exposure", "home" and "sentinel." The primary search strategy was developed in MEDLINE and subsequently adapted for other databases to account for database-specific vocabulary and functionality differences. All searches are current as of July 8, 2016 (full search strategy for Ovid MEDLINE, Appendix 1).

Study selection

Two reviewers (MPN, CBR) independently screened titles and abstracts against inclusion and exclusion criteria and differences were resolved by consensus (Figure 1).

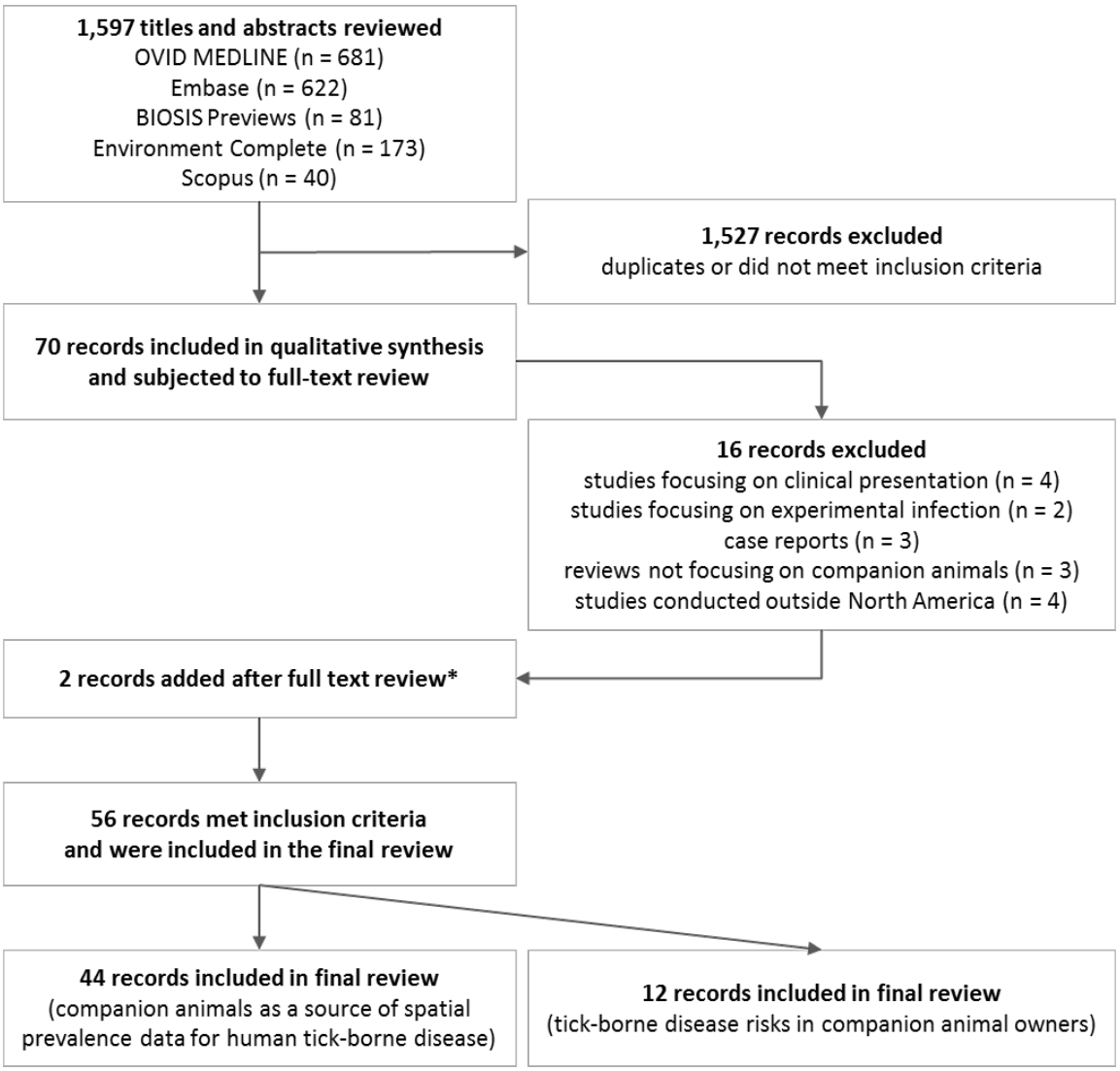
Inclusion criteria

Articles included in the review met the following inclusion criteria:

- studies describing the seroprevelance of tick-borne diseases as a measure of companion animal exposure (for objective 1 only);
- studies analyzing companion animal ownership as a putative risk factor of human tick-borne disease (for objective 2 only); and
- studies published in English from 1985 through 2016, and conducted in North America (the ecology of tick-borne diseases varies according to geography; studies from North America are more relevant to compare to the Ontario context).

Reviews were included in the initial qualitative synthesis to help identify further studies for inclusion, by reviewing references. While our focus is on blacklegged tick-associated pathogens, studies of pathogens associated with other tick vectors were included, as different ticks and pathogens are expanding their range in North America and will possibly spread into Ontario in the future.

Figure 1. Literature search and study selection for companion animals and tick-borne diseases



*Two studies added after full text review; two studies were referenced in two different articles.[36,37]

Exclusion criteria

Articles excluded from the review met one or more of the following criteria:

- studies focusing on clinical presentation in companion animals;
- studies on experimental infection of companion animals (not natural exposure);
- case reports; and
- studies conducted outside North America.

Data extraction and quality assessment

A data extraction table was populated with study metrics (first author, year of publication, study location, target pathogens); tick study details (collection and testing methods, sample size, results); companion animal study details (species, testing methods, sample size, results); correlation between animals and human/tick data; and risk factors for human disease.

To evaluate the quality of eligible primary studies and to reduce the risk of bias, two independent reviewers (MPN, CBR) completed critical appraisals for each paper with differences resolved by consensus (Appendix 2). We performed quality assessments of studies using the PHO MetaQAT[38] based upon four major MetaQAT categories: 1) assessment of relevancy (two questions); 2) assessment of reliability (three questions); 3) assessment of validity (six questions); and 4) assessment of applicability (one question). We did not calculate an overall quality score for each of the critically-appraised studies, as recommended in the literature.[35]

Meta-analysis

For inclusion in the meta-analysis of companion animal ownership as a risk factor associated with Lyme disease, studies were required to report individual-level data or adjusted odds ratios (aORs) with accompanying 95% confidence intervals (CIs) for each risk factor. We generated pooled odds ratios (ORs) of risk factors (by companion animal sub-group: cats, dogs, other pets) associated with Lyme disease in companion animal owners by using Episheet, an Excel add-in.[39,40]

Objective 1: Companion animals as a source for spatial prevalence data for human tick-borne disease

Forty-four studies were included in the final synthesis (Table 2, Appendix 2).[41-84] Thirty-five studies involved samples solely from the USA, followed by seven studies from Canada, one study from Mexico and one study with samples from Canada and USA. Of Canadian studies included in the final synthesis, five included samples from Ontario and four from British Columbia. Of USA studies included in final synthesis, 11 included samples from Maine and New York, 10 from Connecticut and nine each from Maryland, Massachusetts and Rhode Island.

Ninety-five percent (42/44) of studies included samples from dogs and three studies each included samples from horses and cats (Table 2). Seventy-five percent (33/44) of studies focused on *B. burgdorferi*, 23% (10/44) of studies included other pathogens in conjunction with *B. burgdorferi* and one study investigated *Ehrlichia* pathogens.

Six studies were published from 1985 to 1992, eight from 1993 to 2000, 11 from 2001 to 2008 and 19 during the period from 2009 to 2016. Eighty-nine percent (39/44) of studies met at least 10 of the 12 quality criteria from MetaQAT (Appendix 2).

Table 2. Studies examining companion animal surveillance data and spatial relationships to human tick-borne disease in North America

Year published **Location (reference)**	**Companion animal studied**	**Pathogen detection method (confirmatory, complementary)***	**Pathogens: no. samples seropositive (n)****	**Source of sera (basis for selection if applicable)** **How sera selected**	**Spatial relationship of companion animal seroprevelance to human disease**
1985 Connecticut [41]	Dog	IFA	*Bb*: 60 (307)	Veterinarian practices (stratified spatially based on LD activity) Unknown	Dog seroprevalence and number human cases congruent spatially†
1986 Wisconsin[42]	Dog	IFA (culture)	*Bb*: 206 (380)	Licensed pet vendors All sera from available dogs	Spatial relationship between dog seroprevalence and human cases

Year published Location (reference)	Companion animal studied	Pathogen detection method (confirmatory, complementary)*	Pathogens: no. samples seropositive (n)**	Source of sera (basis for selection if applicable) How sera selected	Spatial relationship of companion animal seroprevelance to human disease
				prior to sale	unclear (did not assess)
1987 California, Connecticut, New York, Rhode Island[43]	Dog	ELISA (IFA)	*Bb*: 192 (271)	Single centralized diagnostic center Any sera from symptomatic dogs (joint or limb disorders, fever, anorexia or fatigue)	Spatial relationship between dog seroprevalence and human cases unclear (did not assess); study focused only on areas with blacklegged ticks
1989 Oklahoma[44]	Dog	IFA	*Bb*: 45 (256) *Rr*: 99 (256)	Single centralized diagnostic center Any sera from dogs submitted for *Bb*/*Rr* testing (based on clinical signs)	Spatial relationship between dog seroprevalence and human cases unclear for both pathogens (did not assess); confirms low seroprevalence in low-risk area
1991 Massachusetts[45]	Dog	ELISA	*Bb*: 611 (3,011)	Veterinary practices (stratified spatially based on LD activity) Any sera from dogs visiting veterinary practice	Dog seroprevalence positively correlated spatially with human case incidence rates (logistic regression, R^2 = 0.80, $p < 0.0001$)
1991 Maine[46]	Dog	ELISA	*Bb*: 36 (828)	Veterinary practices (stratified	Dog seroprevalence increased with

Year published Location (reference)	Companion animal studied	Pathogen detection method (confirmatory, complementary)*	Pathogens: no. samples seropositive (n)**	Source of sera (basis for selection if applicable) How sera selected	Spatial relationship of companion animal seroprevelance to human disease
				spatially based on LD activity and/or presence of blacklegged ticks) Any sera from dogs undergoing routine health checks	decreasing distance from the coast (odds ratios for three distances ≥ 3.89, $p < 0.03$); dog seroprevalence and number human cases congruent spatially
1993 Ontario[47]	Dog	ELISA (IFA, WB)	*Bb*: 8 (1,095)	Multiple centralized diagnostic centers Random sample of all dog sera submitted for diagnostic testing	Spatial relationship between dog seroprevalence and human cases unclear (did not assess); confirms low seroprevalence in low-risk area (at time of study)
1993 Massachusetts, Maryland, New Hampshire, Pennsylvania[48]	Dog	ELISA	*Bb*: 136 (884)	Veterinary practices Random sample of all dog sera undergoing routine health checks	Dog seroprevalence positively correlated spatially with blacklegged tick prevalence on white-tailed deer (logistic regression, $R^2 = 0.63$, $p < 0.002$), human case incidence rates ($R^2 = 0.48$, $p < 0.05$) and human case numbers (R^2

Year published Location (reference)	Companion animal studied	Pathogen detection method (confirmatory, complementary)*	Pathogens: no. samples seropositive (n)**	Source of sera (basis for selection if applicable) How sera selected	Spatial relationship of companion animal seroprevelance to human disease
					= 0.61, $p <$ 0.0001)
1993 Connecticut, Massachusetts, New York[49]	Dog Horse	ELISA (IFA)	*Bb*: 28 (40) *Bb*: 21 (31)	Veterinary practices (where LD present) All sera available from horses and dogs	Spatial relationship between dog seroprevalence and human cases unclear (did not assess); study conducted only in areas with blacklegged ticks
1993 New York[50]	Dog	ELISA (WB)	*Bb*: 711 (1,446)	Veterinary practices Any sera from dogs undergoing routine health checks	Dog seroprevalence varied by region within a county (south, north, central) [ANOVA (by region), F = 9.8, $p < 0.01$]; increased seroprevalence in a south to north gradient
1993 Maine[51]	Cat Dog	IFA ELISA	*Bb*: 12 (53)	Single centralized diagnostic center Any sera from a cat or dog available for testing on island	Cat/dog seroprevalence, tick positivity and other animal seroprevalence congruent spatially, but not congruent with human seroprevalence
1996 British	Dog	IFA (WB)	*Bb*: 5 (287)	Veterinary practices,	Spatial relationship

Year published Location (reference)	Companion animal studied	Pathogen detection method (confirmatory, complementary)*	Pathogens: no. samples seropositive (n)**	Source of sera (basis for selection if applicable) How sera selected	Spatial relationship of companion animal seroprevelance to human disease
Columbia[52]				centralized diagnostic centers (stratified spatially based on *Bb* infection in blacklegged ticks and rodents) Any sera from dogs undergoing routine health checks	between dog seroprevalence and human cases unclear (did not assess); confirms low seroprevalence in low-risk area
1996 Maine[53]	Dog	ELISA	*Bb*: 14 (71)	Veterinary practices Any sera from dogs undergoing routine health checks (dogs with history of LD vaccination excluded)	Dog seroprevalence not congruent spatially with human seroprevalence, but congruent with deer sightings
2000 California[54]	Dog	ELISA (IFA, WB)	*Bb*: 21 (917)	Veterinary practices, trappers, animal shelters, humane societies Unknown	Spatial relationship between dog seroprevalence and human cases unclear; confirms low dog seroprevalence in low risk area
2001 Illinois,	Dog	ELISA (WB)	*Bb*: 105 (1,077)	Veterinary practices (stratified	Dog seroprevalence was positively

Year published Location (reference)	Companion animal studied	Pathogen detection method (confirmatory, complementary)*	Pathogens: no. samples seropositive (n)**	Source of sera (basis for selection if applicable) How sera selected	Spatial relationship of companion animal seroprevelance to human disease
Wisconsin[55]				spatially based on LD activity and/or presence of blacklegged ticks) Any sera from dogs undergoing routine health checks	correlated spatially with human disease incidence rates (Pearson correlation, r = 0.59, $p < 0.05$) and blacklegged tick abundance (r = 0.54, $p < 0.05$)
2001 Rhode Island[56]	Dog	IFA ELISA IFA	*Ap*: 4 (277) *Bb*: 84 (277) *Rr*: 20 (277)	Veterinary practices and animal shelters (stratified spatially based on abundance of blacklegged ticks) Any sera from dogs undergoing routine health checks (dogs with history of LD vaccination excluded)	Dog seroprevalence positively correlated spatially with blacklegged tick abundance for *Bb* (regression, R^2 = 0.47, $p < 0.001$) and *Ap* (R^2 = 0.53, $p < 0.001$), but not *Rr* (R^2 = 0.03, p = 0.44)
2004 Maryland, North Carolina, Pennsylvania, Virginia[57]	Dog	SNAP 3Dx IFA	*Bb*: 78 (1,666) *Rr*: 344 (1,174)	Single centralized diagnostic center Any sera from dogs undergoing testing for tick-	Dog seroprevalence and number of human cases congruent spatially for *Bb* and *Rr*

Year published Location (reference)	Companion animal studied	Pathogen detection method (confirmatory, complementary)*	Pathogens: no. samples seropositive (n)**	Source of sera (basis for selection if applicable) How sera selected	Spatial relationship of companion animal seroprevelance to human disease
				borne diseases	
2004 Rhode Island[58]	Dog	ELISA	*Bb*: 143 (277)	Veterinary practices, animal shelters (stratified spatially based on abundance of blacklegged ticks) Any sera from dogs undergoing routine health checks (dogs with history of LD vaccination excluded)	Dog seroprevalence was positively correlated spatially with blacklegged tick abundance (Pearson correlations, $r > 0.95$, $p < 0.05$), blacklegged tick positivity ($r > 0.97$, $r < 0.01$) and human case numbers ($r > 0.96$, $p < 0.05$)
2005 Connecticut, Maryland, New York, New Hampshire[59]	Cat	IFA ELISA (WB)	*Ap*: 28 (93) *Bb*: 9 (93)	Single centralized diagnostic center All sera from cats as part of *Bb* passive surveillance system	Spatial relationship between dog seroprevalence and human cases unclear (did not assess); study conducted only in areas with blacklegged ticks
2005 Maine[60]	Dog	SNAP 3Dx	*Bb*: 761 (9,511)	Veterinary practices Any sera from dogs undergoing routine health checks (dogs with history of	Dog seroprevalence was positively correlated spatially (at county level) with blacklegged tick abundance (Pearson

Year published Location (reference)	Companion animal studied	Pathogen detection method (confirmatory, complementary)*	Pathogens: no. samples seropositive (n)**	Source of sera (basis for selection if applicable) How sera selected	Spatial relationship of companion animal seroprevelance to human disease
				LD vaccination excluded)	correlation, r = 0.41, $p < 0.001$) and human case numbers (r = 0.15, $p < 0.05$)
2006 Ontario[61]	Cat/dog	IFA (WB)	*Bb*: 24 (24)	Veterinary practices Unknown. Cats and dogs omitted if they received LD vaccine, antibiotics or exposed in LD endemic area	Spatial relationship between dog seroprevalence and human cases unclear (did not assess); sampling locations for cats and dogs unknown
2006 Ontario, Quebec[62]	Dog	IFA (PCR) SNAP 3Dx IFA (PCR)	*Ap*: 0 (53) *Bb*: 2 (108) *Rr*: 3 (68)	Single centralized diagnostic center Any sera from dogs submitted for any diagnostic testing	Spatial relationship between dog seroprevalence and human cases unclear(did not assess); low numbers of seropositive dogs
2007 California[63]	Dog	IFA (PCR) WB (PCR)	*Ap*: 17 (97) *Bb*: 4 (97)	Veterinary practice (rural areas only) Any sera from dogs undergoing routine health checks	Spatial relationship between dog seroprevalence and human cases unclear for both pathogens (did not assess); confirms low seroprevalence in low-risk area

Year published Location (reference)	Companion animal studied	Pathogen detection method (confirmatory, complementary)*	Pathogens: no. samples seropositive (n)**	Source of sera (basis for selection if applicable) How sera selected	Spatial relationship of companion animal seroprevelance to human disease
2008 Minnesota[64]	Dog	SNAP 4Dx SNAP 4Dx PCR PCR	*Ap*: 217 (731 *Bb*: 80 (731) *Ap*: 26 (273) (PCR) *Ee*: 1 (273) (PCR)	Single veterinary practice Any sera from dogs undergoing routine health checks	Spatial relationship between dog seroprevalence and human cases unclear (did not assess); study from a single practice
2008 Mexico[65]	Dog	*Bb* IgG Antibody ELISA Kit	*Bb*: 24 (384)	Veterinary practices Random sample of sera from dogs examined at practices	Spatial relationship between dog seroprevalence and human cases unclear (did not assess); confirms low seroprevalence in low-risk area (no vectors present)
2009 USA[66]	Dog	SNAP 3DX/4DX	*Bb*: 49,817 (982,336)	Veterinary practices Any sera from dogs undergoing SNAP testing	Dog seroprevalence and number of human cases congruent spatially
2009 Michigan[67]	Dog	SNAP 3Dx (IFA, WB)	*Bb*: 2 (353)	Randomly selected veterinary practices (stratified spatially based on LD activity) Any sera from dogs undergoing	Dog seroprevalence and human cases not congruent spatially

Year published Location (reference)	Companion animal studied	Pathogen detection method (confirmatory, complementary)*	Pathogens: no. samples seropositive (n)**	Source of sera (basis for selection if applicable) How sera selected	Spatial relationship of companion animal seroprevelance to human disease
				routine health checks	
2010 Florida[68]	Dog	SNAP 3Dx	*Bb*: 5 (1,500)	Veterinary practices, veterinary college, racetracks, shelters Unknown	Spatial relationship between dog seroprevalence and human cases unclear (did not assess); sampling locations for dogs unknown
2011 British Columbia[69]	Dog	SNAP 4Dx	*Bb*: 0 (88)	One-time veterinary clinics in remote areas Any sera from dogs undergoing routine health checks	Spatial relationship between dog seroprevalence and human cases unclear (did not assess); confirms low seroprevalence in low-risk area
2011 USA[70]	Dog	SNAP 3Dx/4Dx	*Bb*: See Bowman et al. 2009[66]	Veterinary practices Any sera from dogs undergoing SNAP testing	Dog seroprevalence positively correlated spatially with human case incidence rates across all states (linear regression, R^2 = 0.75, $p < 0.001$); low-incidence rate states (R^2 = 0.0, $p > 0.4$); high-incidence rate states (R^2 =

Year published Location (reference)	Companion animal studied	Pathogen detection method (confirmatory, complementary)*	Pathogens: no. samples seropositive (n)**	Source of sera (basis for selection if applicable) How sera selected	Spatial relationship of companion animal seroprevelance to human disease
					0.33, $p = 0.03$)
2011 Maine[71]	Dog	SNAP 4Dx	*Bb*: 138 (1,087)	Veterinary practices (stratified spatially based on practice size and location) Any sera from dogs undergoing routine health checks	Dog seroprevalence positively correlated spatially with human case numbers (Pearson correlation, $r = 0.84$, $p < 0.0001$) and tick submissions ($r = 0.63$, $p = 0.009$)
2011 Canada[72]	Dog	SNAP 4Dx	*Bb*: 624 (86,251)	Veterinary practices Any sera from dogs undergoing SNAP testing	Dog seroprevalence and number of human cases congruent spatially
2012 USA[73]	Dog	ELISA (IFA) ELISA	*Ec*: 240 (8,662) *Ee*: 439 (8,662)	Veterinary practices, colleges, commercial laboratories Any sera from dogs undergoing routine health checks	Dog seroprevalence positively correlated spatially with human incidence rates: *Ec* (linear regression, $R^2 = 0.73$, $p < 0.0001$), *Ee* ($R^2 = 0.72$, $p < 0.0001$)
2012 Minnesota[74]	Dog	IFA	*Bb*: 1,081 (1,229)	Single centralized diagnostic center	Spatial relationship between dog seroprevalence and exposure in

Year published Location (reference)	Companion animal studied	Pathogen detection method (confirmatory, complementary)*	Pathogens: no. samples seropositive (n)**	Source of sera (basis for selection if applicable) How sera selected	Spatial relationship of companion animal seroprevelance to human disease
				Any sera from dogs submitted for *Bb* testing	human cases unclear (did not assess); sampling locations for dogs unknown
2012 New York[75]	Dog Horse	Canine and Equine Lyme Multiplex Assay	*Bb*: 104 (451) *Bb*: 168 (2,100)	Veterinary practices Any sera from dogs or horses undergoing routine health checks or with suspicion of *Bb* infection	Spatial relationship between dog/horses seroprevalence and human cases unclear (did not assess)
2013 Colorado[76]	Dog	SNAP 3Dx/4Dx, Lyme Quant C6	*Bb*: 12 (sample size unknown)	Veterinary practices Any *Bb*-positive sera from dogs	Spatial relationship between dog seroprevalence and human cases unclear; confirms low dog seroprevalence in low-risk area
2014 New Jersey[77]	Dog	SNAP 4Dx	*Bb*: 10 (202)	Single veterinary practice Any sera from dogs undergoing routine health checks	Spatial relationship between dog seroprevalence and human cases unclear (did not assess); study from a single center
2014 Illinois[78]	Dog	Microscopy, IFA, WB, PCR, SNAP 3DX/4DX	*Bb*: 937 (1,000,000) *Rr*: 452	Randomly selected veterinary	Dog seroprevalence rates and human case rates

Year published Location (reference)	Companion animal studied	Pathogen detection method (confirmatory, complementary)*	Pathogens: no. samples seropositive (n)**	Source of sera (basis for selection if applicable) How sera selected	Spatial relationship of companion animal seroprevelance to human disease
			(1,000,000)	practices Questionnaire of veterinarians	congruent spatially
2014 USA[79]	Dog	SNAP 4Dx/ 4Dx Plus	*Bb*: 509,195 (6,996,197)	Veterinary practices and IDEXX data Any sera from dogs undergoing SNAP testing	Dog seroprevalence was positively correlated spatially with human incidence rates for *Bb* (linear regression, R^2 = 0.701, $p < 0.001$)
2014 Canada, USA[80]	Dog	SNAP Multi-Analyte Assay	*Ap*: 227 (6,582) *Bb*: 545 (6,582) *Ec*: 202 (6,582) *Ee*: 251 (6,582)	Single centralized diagnostic center Any sera from dogs with suspected tick-borne disease	Dog seroprevalence and number of human cases congruent for all pathogens, in USA only
2014 Saskatchewan[81]	Dog	SNAP 4DX	*Bb*: 2 (77)	Single remote veterinary practice Any sera from dogs undergoing routine health checks	Spatial relationship between dog seroprevalence and human cases unclear for both pathogens (did not assess); low number of seropositive dogs; low seroprevalence in dogs confirms a

Year published Location (reference)	Companion animal studied	Pathogen detection method (confirmatory, complementary)*	Pathogens: no. samples seropositive (n)**	Source of sera (basis for selection if applicable) How sera selected	Spatial relationship of companion animal seroprevelance to human disease
					low-risk area
2014 Ohio[82]	Dog	ELISA (WB, ViraStripe immunoassay)	*Bb*: 41 (355)	Single centralized diagnostic center Any sera from dogs undergoing routine health checks	Dog seroprevalence and number of human cases were congruent spatially
2014 USA[83]	Dog	SNAP 4DX IFA	*Bb*: 754 (14,496) *Rr*: 1,508 (14,496)	Single centralized diagnostic center Any sera from dogs with suspected vector-borne disease	Dog seroprevalence and human cases congruent spatially for both pathogens
2016 Virginia[84]	Horse	Equine Lyme Multiplex Assay	*Bb*: 83 (250)	Single centralized diagnostic center Any sera from horses undergoing routine examination	Spatial relationship between horse seroprevalence and human cases unclear (did not assess); sampling locations for horses unknown

*ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; LD, Lyme disease; WB, western blot.

**Pathogens associated with human disease only: *Ap*, *Anaplasma phagocytophilum*; *Bb*, *Borrelia burgdorferi*; *Ec*, *Ehrlichia chaffeensis*; *Ee*, *Ehrlichia ewingii*; *Rr*, *Rickettsia rickettsii*; co-exposures not included in table; results where test did not distinguish between human and non-human pathogens were excluded.

†Congruent: companion animal seroprevalence visually fit the known distribution of human cases; statistical tests not performed in these studies.

Spatial prevalence relationships

Twenty-seven percent (12/44) of studies looked at the statistical significance of the spatial relationship between companion animal serology results and human cases. In some multi-state studies, state- or county-specific dog *B*. *burgdorferi* seroprevalence was spatially correlated with human disease incidence rates,[70,79] and blacklegged tick prevalence on white-tailed deer (Table 2).[48] However, in one of these multi-state studies, state-specific canine *B*. *burgdorferi* seroprevalence was not spatially correlated with human disease in low-risk states (as defined in this USA study: median incidence = 0.3 cases/100,000 population), compared to the spatial correlation in higher-risk states (as defined in this USA study: median incidence = 24.1 cases/100,000 population); county-specific human incidence rates increased with increasing canine *B. burgdorferi* seroprevalence ($p < 0.001$).[70] State-specific canine seroprevalence rates for *E*. *chaffeensis* and *E*. *ewingii* were spatially correlated with human disease incidence rates in a multi-state study.[73]

For within-state studies, region or county-specific dog *B*. *burgdorferi* seroprevalence was spatially correlated with human disease incidence rates in Illinois, Massachusetts and Wisconsin [45,55] and with blacklegged tick abundance in Illinois and Wisconsin.[55] In addition, county-specific canine *B*. *burgdorferi* seroprevalence correlated spatially with human case numbers and blacklegged tick abundance in Maine and Rhode Island [58,60,71] and with *B*. *burgdorferi* prevalence in blacklegged ticks in Rhode Island.[56,58] One study tested the variation in canine *B*. *burgdorferi* seroprevalence as a function of distance from the Maine coast, finding a decreasing seroprevalence with increasing distance from the coast.[46] Another study examined the variation in canine *B*. *burgdorferi* seroprevalence across regions within Westchester County, NY, finding higher seroprevalence as you go north within the county.[50]

Companion animal seroprevalence was congruent in some studies (visual assessment of association in absence of statistical testing of association) with the known distribution of human disease. In four studies, increasing seroprevalence of several pathogens (e.g., *A*. *phagocytophilum*, *B*. *burgdorferi*) in dogs was spatially congruent with increasing human case numbers in multi-state or multi-provincial studies.[66,72,80,83] An additional four within-state studies conducted in Connecticut, Illinois, Maine and Ohio found spatial congruence between dog *B. burgdorferi* or *R. rickettsii* seroprevalence and human cases.[41,53,78,82] However, two studies undertaken in Maine and Michigan found that dog *B*. *burgdorferi* seroprevalence was not congruent with human case distribution, possibly indicating new foci of *B. burgdorferi* transmission or highlighting the low positive predictive value of testing in low-risk areas.[51,85]

Several studies used sera from a single veterinary practice or only provided data at the state or provincial level (i.e., Florida, Minnesota, New Jersey, Ontario, Virginia),[64,77] with no information provided on locality of exposure or where the companion animal resided. The data from these studies can be useful for adding further information on already identified high- or low-risk areas noted in studies previously mentioned. Due to a low number of seropositive animal samples, several studies could not elucidate a spatial relationship with human cases; rather these studies confirmed that the study area was low risk for tick-borne diseases (British Columbia, California, Mexico, Oklahoma, Ontario, Saskatchewan).[44,47,52,54,62,63,65,69,81] The Ontario study was conducted prior to recent increases in Lyme disease activity within the province.

Discussion

The systematic review provides evidence that dogs are a source of useful data for assessing Lyme disease risk in humans, especially through the generation of spatial prevalence data. Even though cats and horses provide *B*. *burgdorferi* seroprevalence data, there is simply not enough data available to assess their utility in understanding the spatial risks of Lyme disease in humans. Dogs are likely more sensitive indicators of *B*. *burgdorferi* transmission risks since they have higher exposure rates to infectious blacklegged ticks than humans.[60,86] While limitations existed in the reviewed studies (see next section), in 12 studies the spatial relationships between companion animal serology and human disease were corroborated statistically.

To assess how tick-borne disease data generated from companion animals contributes to our understanding of human tick-borne disease risks, we must first consider how companion animals respond to *B*. *burgdorferi* exposure in terms of serological findings and clinical presentation. However, the majority of studies investigated asymptomatic companion animals undergoing routine testing. Veterinarians diagnose *B*. *burgdorferi* infection in companion animals based on interpretation of serological test results, knowledge of pathogen and vector distribution, travel history and presence of clinical findings.

Clinical disease and presentation in dogs

Fewer than 5% of canines exposed to *B*. *burgdorferi*-infectious blacklegged ticks will develop clinical disease, similar to humans where approximately 3% of people exposed will develop Lyme disease.[87,88]

Dogs with putative Lyme disease initially present with non-specific symptoms or signs such as:

- anorexia,
- arthritis,
- depression,
- fever,
- lameness,
- lethargy,
- malaise,
- myalgia, and
- swollen lymph nodes.[89-91]

While these symptoms and signs are commonly reported in seropositive dogs, only transient anorexia, arthritis and fever have been attributed to natural *B*. *burgdorferi* infection (satisfying Koch's postulates), developing 2–5 months post-blacklegged tick exposure.[92] *Borrelia burgdorferi* antibodies are detected 3–5 weeks after exposure to infectious tick bites, with positive serology lasting for months to over a year.[87,93,94] As with humans, ELISA-based tests in dogs are insensitive during early infection.[95] Unlike the pathognomonic nature of erythema migrans in human Lyme disease, erythema migrans does not occur in dogs. Research on the clinical spectrum of disease in naturally-infected dogs is lacking, consequently there is no significant difference in the clinical picture of seropositive and seronegative dogs. Given that canine serology (in most studies reviewed here) did not distinguish between active or past infection, serological results did not provide accurate seasonal predictions of risk and exposure in humans;

however, this is not a major limitation as the temporal risks for Lyme disease in humans is well-defined.[92,94]

Clinical disease and presentation in cats

There have been no reports of clinical Lyme disease in naturally-infected cats. Experimental infections in cats lead to short-lived bacteremia with arthritis, lameness and meningitis.[96] However, there is no evidence that naturally-acquired *B*. *burgdorferi* produces clinical disease in cats, even in areas where *B*. *burgdorferi* seropositivity in cats is high.[97] Reasons for a lack of documented infection in cats include: 1) their ability to prevent spirochete dissemination after a blacklegged tick bite and/or 2) the feline immune system neutralizes spirochetes rapidly before any symptoms appear.[90] Similar to dogs, there is no significant difference in the signs and symptoms between seropositive and seronegative cats. While cats do not develop disease, they will mount an effective antibody response; similar to dogs, seropositivity in cats indicates the presence of *B*. *burgdorferi* in a given area.

Clinical disease and presentation in horses

Borrelia burgdorferi-seropositive horses are found in endemic regions; however, not all horses exposed to the pathogen develop disease. Approximately 10% of seropositive horses will develop signs of infection.[98,99]

Infected horses can display:

- hyperesthesia,
- laminitis,
- lethargy,
- low-grade fever,
- myalgia,
- skin lesions,
- swollen joints,
- sporadic or shifting lameness,
- uveitis, and
- weight loss.[100-102]

Horses with chronic infections display neurological signs such as ataxia, behavioral changes, depression, dysphagia, encephalitis, facial paralysis and head tilt.[103-105] In one study, experimental infection of seven ponies produced a serological response without any clinical signs of infection.[106] As with cats and dogs, it is difficult to distinguish distinctive patterns of signs and symptoms between seropositive and seronegative horses.

Limitations of systematic review

We must note several limitations in the reviewed studies. Since we did not perform a search of grey literature, we may have missed relevant literature and findings. Literature from public health and government agencies possibly have further information related to tick-borne diseases and companion animals. While our search strategy was comprehensive, it is still possible that we omitted or missed

studies; we found two studies, not included in the search results, after full review of 70 articles. In addition, our results are potentially biased towards positive results due to publication bias, especially important in the observational-type studies examined in this review. Due to the heterogeneity of study settings (spatially and temporally) and serological methodologies, it is difficult to compare methods and results across studies.

Limitations of studies reviewed

Pathogen detection, sensitivity and specificity

Pathogen detection methods, or combinations thereof, used in the reviewed studies varied. Thirty-seven of 44 studies used enzyme-linked immunosorbent assay (ELISA)-based methods for detecting tick-borne pathogens in companion animals, including commercial assays (e.g., IDEXX Laboratories, Inc. point-of-care tests: SNAP 4Dx Plus) and in-house assays targeting various antibodies. ELISA-based methods were the sole means of detecting pathogen exposure in 28 studies; therefore, we would expect a relatively lower positive predictive value for an ELISA in the absence of a complementary or confirmatory test. Immunofluorescence assays (IFA), Western Blots (WB) or PCR complemented ELISA-based tests were used in 12 studies. IFAs were used alone in seven studies, or as a complementary test to PCR, WB or cultures in another seven studies (in absence of ELISA-based methods). Four studies used PCR as a complement to other tests, usually to identify pathogen species. Criteria for deeming sera positive or negative varied among the studies. From 1985 through 2005, 95.0% (19/20) of studies included ELISA or IFA, while 10.0% (2/20) of studies included commercial assays (e.g., SNAP tests). From 2006 through 2016, 41.6% (10/24) of studies included ELISA, IFA or WB, while 83.3% (20/24) of studies included commercial assays.

Olson et al. reported a positive predictive value of 32% and a negative predictive value of 100%, using ELISA as initial screening test, followed by IFA and WB as confirmatory tests in California.[54] While not directly reported in most studies, the positive predictive value of serological tests is considerably lower in areas where there is a low pathogen seroprevalence in either companion animals or humans or where blacklegged ticks are rare. Performing studies in areas where the pathogen is rare or uncommon will lead to an increase in false positives.[47,54,70,72,76] A low positive predictive value is relatively common when testing a healthy or asymptomatic population.

Sensitivity and specificity measures were reported or available for commercial tests (*B. burgdorferi* only), including:

- SNAP 3Dx: sensitivity (gold standard: IFA/WB) = 92% (95% CI, 88–96%), specificity = 100% (97–100%).[107]
- SNAP 4Dx: sensitivity (gold standard: IFA/WB) = 99% (95–100%), specificity = 100% (98–100%).[108]
- SNAP 4Dx Plus: sensitivity (gold standard: IFA) = 94% (88–98%), specificity = 96% (93–98%)[109] (note: for 4Dx Plus, IDEXX does not provide a rationale for excluding WB as gold standard).

Non-random sampling

Most studies did not include random samples of companion animals; therefore, the sera tested do not come from a representative sample of the companion animal population. In several studies, researchers examined only symptomatic dogs or used samples of convenience (e.g., those visiting veterinary practices for annual health checks).[44,47,56,64,66,75,76,83,84] Three studies randomly selected dog sera for

testing; however, the dog sera was initially drawn from a dog population that had visited a veterinary practice (for routine health checks or other diagnostic procedures) and not truly a random sample of the population, in that dogs that did not visit a veterinary practice were omitted.[47,48,65] Examining only symptomatic animals regardless of symptomology can result in an overestimation of pathogen seroprevalence, as was acknowledged by several of the study authors.[43,44,57,74,75,80,83] In addition, use and availability of veterinary practices varied among regions studied, with samples biased towards urban centers.[70,78,79,82] In future studies, researchers should draw subjects from the wider companion animal populations, including subjects that do not visit veterinary offices and are asymptomatic.

Non-random sampling may lead to either an over-estimation or under-estimation of the seroprevalence in companion animals, leading to potential erroneous (absence or presence) conclusions of the spatial relationships between companion animal seroprevalence and human disease data.

Missing veterinary history and animal exposure/travel history

A recurring limitation in the reviewed studies was the absence of companion animal travel history, making it difficult to determine the likely area of exposure and spatial relationships with human disease.[45,66,79,83] Spatial inferences between companion animal seroprevalence and human disease was made difficult if studies used sera collected from centralized diagnostic centers (location of where samples originated from is unknown).[61,68,74,84] Further, in several studies factors such as the status of animal vaccination history, antibiotic use, age and activity level (indoor versus outdoor; active versus sedentary) were not described, even if they potentially influence exposure to infectious ticks and/or serological testing results.[48,52,54,64,67,71] Future studies should collect and report on a more fulsome picture of companion animal history, including medical, behavioural and travel history.

Objective 2: Companion animal ownership as a risk factor for Lyme disease

Twelve studies that assessed the risk of Lyme disease in companion animal owners were included in the final synthesis;[36,37,110-119] Researchers conducted three studies in New Jersey, followed by two studies each in California, Connecticut, Maryland and Pennsylvania. Reviewed studies examined the association of Lyme disease with cat ownership (n = 6 studies), other pet ownership (composition unknown) (n = 5), dog ownership (n = 4) and riding horses (n = 2) (Table 3).

Three studies were published from 1985 to 1992, four from 1993 to 2000, three from 2001 to 2008 and two during the period from 2009 to 2016. Ninety-two percent (11/12) of studies met at least 11 of the 12 quality criteria from MetaQAT (Appendix 2).

Table 3. Studies examining companion animal ownership as a risk factor for human Lyme disease

Year published **Location**	**Odds ratios (OR)** **Control for confounding?** **n_{case}, $n_{control}$**	**Data collection** **Case and control recruitment***	**Companion animal variable analyzed**	**Risk factors for increased or decreased risk for Lyme disease ($p < 0.05$)**
1988 Massachusetts[110]	Unmatched Mantel-Haenszel weighted ORs 18, 46	Questionnaire used to identify behavioural and environmental risk factors, along with medical history Human cases identified through positive serological testing (unknown methods); controls identified by negative serology	Dog ownership	Increased risk: none identified Protective: none identified
1989 Connecticut[119]	Not applicable	Anecdotal account only	Cat ownership	Increased risk: cat owners
1992 California[37]	Matched Logistic regression 31, 52	Questionnaire used to identify behavioural and environmental risk factors Cases identified through physician-diagnosed clinical manifestations consistent with LD and positive serological testing using IFA or anticomplement indirect	Ride horses; pet ownership	Increased risk: outdoor activity (woodcutting) Protective: none identified

Year published Location	Odds ratios (OR) Control for confounding? n_{case}, $n_{control}$	Data collection Case and control recruitment*	Companion animal variable analyzed	Risk factors for increased or decreased risk for Lyme disease ($p < 0.05$)
		immunofluorescence and WB; controls matched by age, sex and location of residence with negative serology		
1994 New Jersey[118]	Unmatched Logistic regression 57, 57	Questionnaire used to identify behavioural and environmental risk factors, along with medical history Cases identified through positive serological testing using IFA or ELISA; controls identified by negative serology	Pet ownership	Increased risk: pet ownership (rural residence only); years at residence; rural residence; history of medical problems Protective: none identified
1995 California[111]	Matched, unmatched Mantel-Haenszel weighted ORs for unmatched 101, 107	Questionnaire used to identify behavioural and environmental risk factors Cases identified through public health reporting and based on presence of physician-diagnosed erythema migrans; controls matched on age, sex and geographic location of residence with no report of LD	Cat contact in last month; dog contact in last month	Increased risk: deer and lizards observed near home; use of recreational trails Protective: none identified
1996 Delaware, Maryland, New Jersey, Pennsylvania[36]	Matched None used 44, 44	Questionnaire used to identify behavioural and environmental risk factors Cases identified through physician-diagnosed clinical manifestations consistent with LD and positive serological testing using ELISA and WB; controls matched by age, sex and	Pet ownership	Increased risk: blacklegged ticks on property; ground cover with moist humus; leaf litter in yard Protective: none identified

Year published Location	Odds ratios (OR) Control for confounding? n_{case}, $n_{control}$	Data collection Case and control recruitment*	Companion animal variable analyzed	Risk factors for increased or decreased risk for Lyme disease ($p < 0.05$)
		geography with negative serology		
1998 New Jersey[112]	Matched Multivariate conditional logistic regression 51, 51	Questionnaire used to identify behavioural and environmental risk factors, along with medical history (clinical manifestations for cases) Cases identified through positive serological testing using enzyme immunoassay and WB; controls matched on age and location of residence with negative serology	Cat ownership	Increased risk: presence of rock walls, woods, bird feeder and deer on property; clearing brush on property; living in rural area Protective: none identified
2001 Maryland[113]	Matched Multivariate logistic regression 37 (self-reported LD), 130 (self-reported no LD)	Questionnaire used to identify behavioural and environmental risk factors, along with medical history (clinical manifestations for cases) Cases identified by self-reported (clinician-diagnosed LD); controls matched by location of residence and no report of LD	Cat ownership; dog ownership	Increased risk: number of summers spent on island; gardening Protective: avoiding brush
2001 Pennsylvania[114]	Matched Mantel-Haenszel weighted ORs 294, 449	Questionnaire used to identify behavioural and environmental risk factors, along with medical history (clinical manifestations for cases) Cases identified through public health reporting based on physician-diagnosed clinical manifestations	Ride horses	Increased risk: age (10–19; ≥ 50); living in rural home; homes with yards, near woods or rock/wood piles; property with tick hosts; gardening Protective:

Year published Location	Odds ratios (OR) Control for confounding? n_{case}, $n_{control}$	Data collection Case and control recruitment*	Companion animal variable analyzed	Risk factors for increased or decreased risk for Lyme disease ($p < 0.05$)
		consistent with Lyme disease; controls matched on age and location of residence with no report of LD		checking for ticks after outside activity; use of repellents before going outside
2008 Connecticut[115]	Matched Conditional logistic regression 709; 1,128	Questionnaire used to identify behavioural and environmental risk factors, along with medical history Cases identified through active public health reporting of cases; controls matched on age and location of residence with no report of LD	Pet ownership	Increased risk: female Protective: use of protective clothing; use of tick repellents on skin or clothing
2009 Connecticut [116]	Matched Conditional logistic regression 364, 349	Questionnaire used to identify behavioural and environmental risk factors Cases identified through public health reporting based on physician-diagnosed erythema migrans; controls matched on age and neighbourhood of residence with no report of LD	Cat ownership	Increased risk: none identified Protective: checking for ticks within 36h of being outside; bathing within 2h after being outside; fencing in yard
2014 Rhode Island[117]	Unmatched Multivariate logistic regression 86, 400	Questionnaire used to identify behavioural and environmental risk factors Cases identified through positive serological testing using ELISA and WB; controls identified by negative serology	Cat ownership; dog ownership; owning other pets	Increased risk: increasing age; shrub edge density; increasing hours spent in vegetation; previous diagnosis of LD Protective: wearing protective

Year published Location	Odds ratios (OR) Control for confounding? n_{case}, $n_{control}$	Data collection Case and control recruitment*	Companion animal variable analyzed	Risk factors for increased or decreased risk for Lyme disease ($p < 0.05$)
				clothing

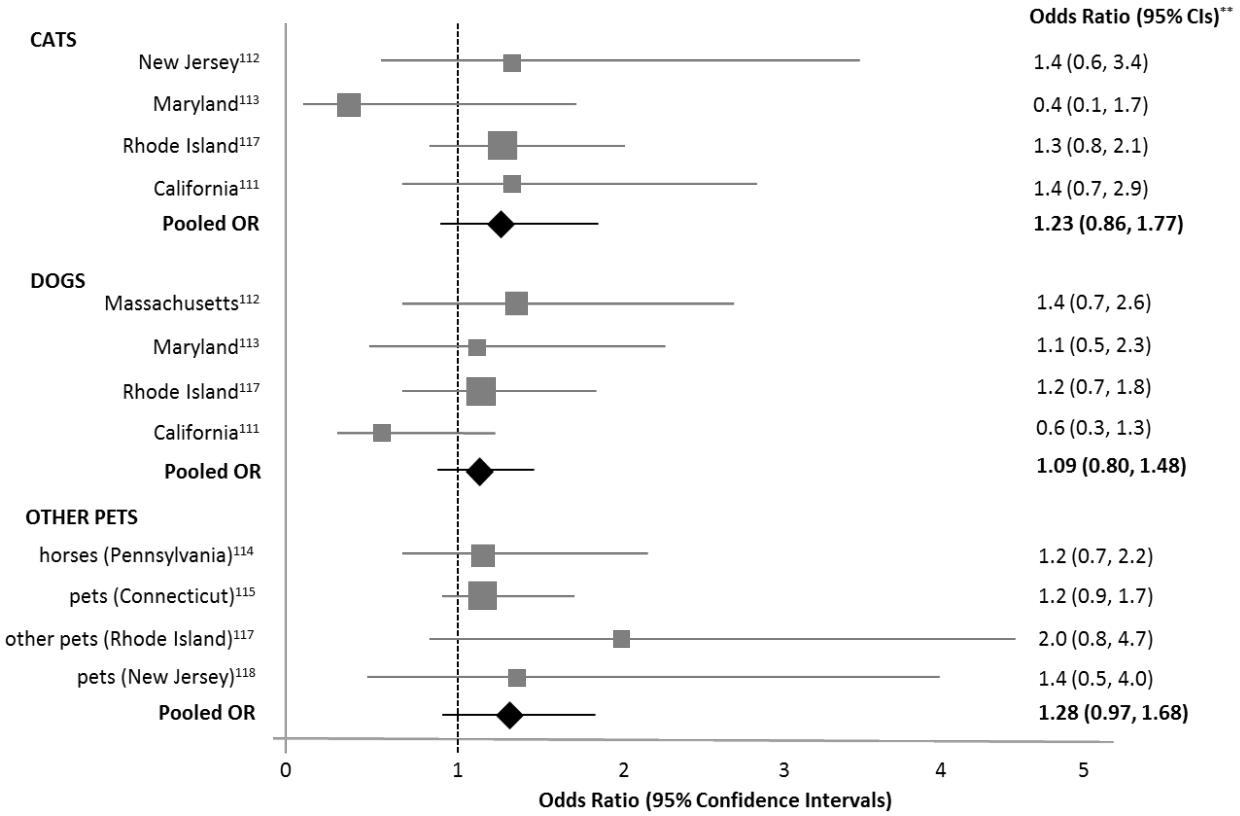
*ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; LD, Lyme disease; WB, western blot.

Companion animal ownership as a risk factor for Lyme disease

There is no evidence in the reviewed literature to suggest that companion animals increase an owner's risk of Lyme disease.[118] Two studies identified an increased risk of Lyme disease in companion animal owners; one study showed increased risk only under specific conditions and other did not provide statistical support for the increased risk. In New Jersey, researchers identified an increased risk of Lyme disease associated with pet ownership in rural areas only (aOR = 2.5; lower and upper 95% confidence intervals, 1.1, 5.4).[118] In the same study, without regard to rural versus urban residence, there was no increased risk associated with pet ownership (aOR = 1.4; 0.5, 4.0). The significant increased risk of Lyme disease to pet owners in rural New Jersey was part of a study investigating "high-risk outdoor workers," compared to all other studies reviewed where cases and controls were drawn from a population with a wider range of risk profiles. Curran and Fish, in a 1989 Connecticut case study, claimed that cat ownership increased Lyme disease risk; however, there was no statistical support for this conclusion.[119]

Eight studies assessed in this systematic review provided data that permitted calculations of pooled ORs.[110-115,117,118] We estimated pooled ORs to determine if there was increased risk of Lyme disease in owners by companion animal sub-groups (Figure 2). None of the results showed significant associations; however, there was a positive trend in ORs. For cats, the pooled OR was 1.23 (0.86, 1.77); dogs (pooled OR = 1.09; 0.80, 1.48); and other pets (pooled OR = 1.28; 0.97, 1.68). Studies investigating unidentified pet ownership as a risk factor were likely comprised of a mixture of pets made up largely of felines and canines; however, we cannot confirm the composition of pets in this sub-group. Tests of homogeneity for all sub-groups indicated little variation among study outcomes within sub-groups ($p > 0.05$).

Figure 2. Study-level and pooled odds ratios (OR) for companion animal sub-groups assessing risk of Lyme disease in respective animal owners*



*Different sized squares represent relative weights (larger square = higher weight), based on the random effects model within each companion animal sub-group. Diamonds represent pooled ORs (by companion animal group); all pooled ORs tested for homogeneity (cats: p = 0.47; dogs: p = 0.42; other pets: p = 0.77).

**Individual-level results are reported as adjusted ORs.

The reviewed studies identified other variables associated with increased or decreased risk for Lyme disease, independent of companion animal ownership. Increased risk of Lyme disease in subjects was associated with those living in an older home, living in a suburban or rural area, gardening on their property, spending more time outdoors, residing close to a wooded area, reporting animals on property (deer, lizards, mice) and those with woodpiles present on their property (Table 3).[112-117] Decreased relative risk or protective factors for Lyme disease included subjects that perform tick checks, wear protective clothing, use tick repellents, have fencing on their property and avoid the brush.

Discussion

Consistent with our findings that companion animal ownership does not appear to pose additional Lyme disease risk to owners, the Lyme disease risks associated with companion animal ownership varied in studies performed outside North America. In Italy, one study indicated there was no increased risk of Lyme disease for cat and dog owners (relative risk (RR) = 0.8; $X^2 = 3.8$, $p > 0.05$).[120] In the Netherlands, owning a dog was not a factor for increased risk of Lyme disease (OR not reported).[86] In suburban Beijing, China, there was no increased risk of Lyme disease for pet owners (OR not reported).[121] In rural Beijing, again there was no increased risk of Lyme disease in those that owned "any pet" (aOR) = 1.5;

0.8, 3.0).[122] In Germany, there was increased risk noted for cat owners, but not for dog owners; increased risk was noted in those 1–17 years old in weighted bivariate logistic regression (aOR = 1.6; 1.3, 1.9) and using weighed multivariable logistic regression (aOR = 1.5; 1.2, 1.9).[123] The ecology of *B. burgdorferi* in Germany is different (e.g., different species of *Borrelia* in Europe can cause Lyme disease) from that of North America; therefore, it is difficult to extrapolate German results to North American circumstances.

There is no evidence to suggest that companion animals act as a conduit for blacklegged ticks to humans, moving blacklegged ticks from a natural environment into a peridomestic environment.[119] The movement of ticks into the home by dogs is more important with the brown dog tick *Rhipicephalus sanguineus* (a vector of *R. rickettsii* in southwestern USA), a species that can survive solely on canines, feed on humans and thrives indoors. In addition, dogs are not considered a reservoir of *B. burgdorferi*. A 1994 study proposed that canines would maintain a *B. burgdorferi* bacteremia under laboratory conditions sufficient to infect other ticks and their owners;[124] however, canines are not considered an important reservoir of *B. burgdorferi*.[70,125,126]

There are several factors that contribute to the low reservoir competence of dogs, including:

1. dogs are not the preferred hosts for larval and nymphal blacklegged ticks;
2. *B. burgdorferi* is maintained in nature due to a high density of efficient reservoir hosts (i.e., white-footed mouse); and
3. dogs have an innate immune response that clears *B. burgdorferi* quickly after infection.[125-128]

Recent research conducted in Connecticut, Maryland and New York indicates that cat and/or dog owners have 1.8 times the risk of finding a tick crawling on them and 1.5 times the risk of finding ticks attached to them compared to those with no cat or dog.[129] While pets may increase owner exposure to ticks (likely via shared exposure while walking), the evidence to date does not show a similar increase in risk for tick-borne disease in owners. The tick species in this study were not reported and, while pets may increase tick exposure, the ticks encountered likely include non-*B. burgdorferi* vectors, such as the American dog tick *Dermacentor variabilis*.

Limitations of studies reviewed

Limited age range for cases and controls

The studies reviewed focused primarily on the adult population, limiting generalizability of risks to other age groups. For example, in Rhode Island, the average age of all participants was approximately 62 years,[117] followed by 49 years (Connecticut),[116] 47 years (Connecticut),[115] 43 years (New Jersey),[112] 39 years (Pennsylvania),[114] 38 years (California)[111] and 10 years (several states).[36] Future studies should include cases and controls from all age groups, stratifying results by age group where appropriate.

Confounding and misclassification

Although studies examining the association between companion animals and risk of Lyme disease in owners controlled for confounding, unmeasured confounders could still play a role and impact estimates.

Misclassification of cases and controls can occur in case-control studies and can lead to a lack of association between Lyme disease in companion animal owners and companion animals. In one study,

an exclusion criterion for controls was a previous Lyme disease diagnosis; however, these subjects could have been previously infected (case) but misclassified due to the clearance of antibodies over time.[111,118] Antibiotic use by patients is a limitation that could lead to negative serological testing, especially in an endemic region where patients may seek medical attention soon after potential exposures/onset of symptoms compared to patients in non-endemic regions.[113] Furthermore, serological tests might miss cases if they are tested too early after tick exposure (too little time for immune system to mount antibodies); for controls, it is possible exposure could have occurred after a negative serology result.

Recall bias

Recall bias is possible in the reviewed studies due to long periods between potential exposures and interviews, as noted in two studies.[114,115] In addition, cases often have better recall due to presence of disease and, in some cases, parents have better recall of their children's disease. While recall bias may be important for other tested risk factors, recall of pet ownership is expected to be fairly accurate.

Summary

Our systematic review indicates:

1. Dogs provide suitable spatial seroprevalence data for assessing the risks of tick-borne disease in humans.
2. Companion animal ownership does not appear to pose additional Lyme disease risk to owners.

Data collected from the testing of companion animals within the veterinary health system can help establish the distribution of *B*. *burgdorferi* while identifying new areas and the direction of pathogen movement. In addition, data collected from companion animals are valuable in estimating the prevalence of a pathogen over time and can help test hypotheses of pathogen ecology and epidemiology or test the efficacy of prevention efforts.

The best way to understand the shared risks of tick-borne pathogens to humans and companion animals is to ensure ongoing information sharing between veterinary, medical and public health professionals. Continual information sharing increases overall awareness, which leads to collaborative research of tick-borne pathogens in humans and companion animals. Included within these shared efforts is assessing the distribution of pathogens in humans and animals and tick vectors, leading to improved risk assessments and prevention of disease in Ontarians and their companion animals. PHO will continue to work with partners on ways to improve tick-borne disease surveillance.

Visit PHO's Lyme disease webpage for new Lyme disease information and resources.

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Appendix 1. Ovid MEDLINE search strategy for companion animals and tick-borne diseases

#	Searches
1	Lyme disease/ or Lyme neuroborreliosis/ or Borrelia burgdorferi group/ or Borrelia burgdorferi/ or Borrelia Infections/ or Anaplasma phagocytophilum/ or Babesia microti/ or Ixodes/ or Babesiosis/ or ((ticks/ or ixodidae/ or tick infestations/) and (lyme or burgdorferi or borreliosis or LD or LB or babesisosis or babesia or anaplasma or piroplasmosis or piroplasma infection).kf,kw,ti,ab.)
2	(lyme or ixodes or ixodida or ixodoidea or borrelia or Anaplasma phagocytophilum or Babesia micr oti or a phagocytophilum or b microti or babesia or borreliosis or neuroborreliosis or burgdorferi or scapularis or (Borrelia adj (burgdorferi or Anaplasma or babesia)) or ((arthritis or borreliosis or disease*) adj3 lyme)).ti,ab,kw,kf. and ("in data review" or "in process" or "pubmed not medline").st.
3	((lyme or ixodes or i scapularis or black legged tick? or blacklegged tick? or ixod$ tick? or ixode? or deer tick? or bear tick?) and (infect* or co-infect* or exposure* or introduce* or contact* or bite or bit or bitten or bites or biting or Anaplasma or a phagocytophilum or Babesia or b microti or Borrelia burgdorferi or b burgdorferi)).ti,kw,kf. or ((Tick or ticks) and (infect* or co-infect* or exposure* or introduce* or contact* or bite or bit or bitten or bites or biting) and (lyme or Anaplasma or a phagocytophilum or Babesia or b microti or Borrelia burgdorferi or b burgdorferi)).ab.
4	Pets/ or Dog Diseases/ or Dogs/ or cat diseases/ or Cats/ or ((canine* or dog* or feline or cat or cats or pet or pets or peridomestic*).ti,ab,kw,kf. and ("in data review" or "in process" or "pubmed not medline").st.)
5	Seroepidemiologic Studies/ or Serologic Tests/ or (serosurvey* or Serolog* or Seroprevalence).ti,ab,kw,kf.
6	Population Surveillance/ or Public Health Surveillance/ or Public Health Informatics/ or Sentinel Surveillance/ or Disease Notification/ or Communicable Diseases, Emerging/ or Disease Outbreaks/ or Incidence/ or ep.fs. or (surveil* or test* or detect* or vet or veterinar* or lab or laborator* or labs or ((disease$ or illness$ or infect*) adj3 (risk* or pattern* or identif* or notif* or trend* or predict*)) or monitor* or detect* or track* or signal* or alert* or predict*).ti,ab,kw,kf.
7	Risk/ or Risk factors/ or Disease Transmission, Infectious/ or Zoonoses/ or ((zoonoses or zoonot* or risk* or transmi*).ti,ab,kw,kf. and ("in data review" or "in process" or "pubmed not medline").st.)
8	((introduc* or contact* or exposure* or bite or bit or bitten or bites or biting or transfer* or transmi*) and (human or person or pet owner* or house or home or bed or yard or lawn)).ti,ab,kw,kf.

#	Searches
9	(1 or 2 or 3) and 4 and 5
10	(1 or 2 or 3) and 4 and (6 or 7 or 8)
11	9 or 10
12	(exp Africa/ or exp Caribbean Region/ or exp Central America/ or exp Latin America/ or exp South America/ or exp Asia/ or Developing Countries/ or Mexico/ or exp Australia/ or New Zealand/ or exp Europe/ or exp Developed Countries/) not (north america/ or exp Canada/ or exp United States/)
13	11 not 12
14	limit 13 to english
15	limit 14 to yr="1970 -Current"

Appendix 2. Summary quality assessment of studies reviewed

Year, first author	Assessment of relevancy	Assessment of reliability		Assessment of validity				Assessment of applicability
	1. Study applies to our research questions? 2. Study population similar to ON?	1. Study rationale clearly stated, addressing a clear issue?	2. Methods and results clearly described? 3. Study reproducible?	1. Research question congruent with study design?	2. Sources of bias? 3. Can chance findings be ruled out?	4. Conclusions clearly derived from results? 5. Limitations described?	6. Any major flaws in methods?	1. Can study results be interpreted & analyzed within context of public health?
1985, Magnarelli	• Yes • Yes	Yes	• No • No	Yes	• No • Yes	• Yes • Yes	Yes	Yes
1986, Burgess	• Yes • Yes	Yes	• Yes • Yes	Yes	• Yes • Yes	• Yes • Yes	No	Yes
1987, Magnarelli	• Yes • Yes	Yes	• Yes • Yes	Yes	• Yes • Yes	• Yes • Yes	No	Yes
1988, Eng	• Yes • Yes	Yes	• Yes • Yes	Yes	• Yes • Yes	• Yes • No	No	Yes
1989, Curran	• Yes • Yes	Yes	• No • No	Yes	• Yes • No	• No • No	No	Yes
1989, Rodgers	• Yes • No	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
1991, Lindenmayer	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
1991, Rand	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • No	No	Yes
1992, Lane	• Yes • No	Yes	• Yes • Yes	Yes	• Yes • Yes	• Yes • Yes	No	Yes
1993, Artsob	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
1993, Daniels	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
1993, Falco	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • No	No	Yes
1993, Fikrig	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
1993, Smith	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • No	No	Yes
1994,	• Yes	Yes	• Yes	Yes	• Yes	• Yes	No	Yes

Year, first author	Assessment of relevancy	Assessment of reliability		Assessment of validity				Assessment of applicability
	1. Study applies to our research questions? 2. Study population similar to ON?	1. Study rationale clearly stated, addressing a clear issue?	2. Methods and results clearly described? 3. Study reproducible?	1. Research question congruent with study design?	2. Sources of bias? 3. Can chance findings be ruled out?	4. Conclusions clearly derived from results? 5. Limitations described?	6. Any major flaws in methods?	1. Can study results be interpreted & analyzed within context of public health?
Schwartz	• Yes		• Yes		• Yes	• Yes		
1995, Ley	• Yes • No	Yes	• Yes • Yes	Yes	• Yes • Yes	• Yes • Yes	No	Yes
1996, Banerjee	• Yes • No	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
1996, Klein	• Yes • Yes	Yes	• Yes • Yes	Yes	• Yes • Yes	• Yes • Yes	No	Yes
1996, Rand	• Yes • Yes	Yes	• Yes • Yes	Yes	• Yes • Yes	• Yes • Yes	No	Yes
1998, Orloski	• Yes • Yes	Yes	• Yes • Yes	Yes	• Yes • Yes	• Yes • Yes	No	Yes
2000, Olson	• Yes • No	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2001, Armstrong	• Yes • Yes	Yes	• Yes • Yes	Yes	• Yes • Yes	• Yes • Yes	No	Yes
2001, Guerra	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2001, Hinrichsen	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2001, Smith	• Yes • Yes	Yes	• Yes • Yes	Yes	• Yes • Yes	• Yes • Yes	No	Yes
2004, Duncan	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2004, Johnson	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2005, Magnarelli	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2005, Stone	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2006, Gary	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2006, Morshed	• Yes • Yes	Yes	• No • No	Yes	• No • Yes	• Yes • Yes	Yes	Yes
2007, Foley	• Yes • No	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes

Year, first author	Assessment of relevancy	Assessment of reliability		Assessment of validity				Assessment of applicability
	1. Study applies to our research questions? 2. Study population similar to ON?	1. Study rationale clearly stated, addressing a clear issue?	2. Methods and results clearly described? 3. Study reproducible?	1. Research question congruent with study design?	2. Sources of bias? 3. Can chance findings be ruled out?	4. Conclusions clearly derived from results? 5. Limitations described?	6. Any major flaws in methods?	1. Can study results be interpreted & analyzed within context of public health?
2008, Beall	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2008, Tinoco-Garcia	• Yes • No	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2008, Vasquez	• Yes • Yes	Yes	• Yes • Yes	Yes	• Yes • Yes	• Yes • Yes	No	Yes
2009, Bowman	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2009, Connally	• Yes • Yes	Yes	• Yes • Yes	Yes	• Yes • Yes	• Yes • Yes	No	Yes
2009, Hamer	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2010, Tzipory	• Yes • No	Yes	• No • No	Yes	• No • Yes	• Yes • Yes	Yes	Yes
2011, Bryan	• Yes • No	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • No	No	Yes
2011, Mead	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2011, Rand	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2011, Villeneuve	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2012, Beall	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2012, Durrani	• Yes • Yes	Yes	• No • No	Yes	• No • Yes	• No • No	No	Yes
2012, Wagner	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2013, Millen	• Yes • No	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2014, Finch	• Yes • Yes	Yes	• Yes • Yes	Yes	• Yes • Yes	• Yes • Yes	No	Yes
2014, Gaito	• Yes • Yes	Yes	• Yes • Yes	Yes	• No • Yes	• Yes • No	No	Yes
2014, Herrmann	• Yes	Yes	• Yes	Yes	• Yes	• Yes	No	Yes

Year, first author	Assessment of relevancy		Assessment of reliability		Assessment of validity				Assessment of applicability
	1. Study applies to our research questions? 2. Study population similar to ON?		1. Study rationale clearly stated, addressing a clear issue?	2. Methods and results clearly described? 3. Study reproducible?	1. Research question congruent with study design?	2. Sources of bias? 3. Can chance findings be ruled out?	4. Conclusions clearly derived from results? 5. Limitations described?	6. Any major flaws in methods?	1. Can study results be interpreted & analyzed within context of public health?
	• Yes			• Yes		• Yes	• Yes		
2014, Little	• Yes • Yes		Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2014, Qurollo	• Yes • Yes		Yes	• Yes • Yes	Yes	• Yes • Yes	• Yes • Yes	No	Yes
2014, Schurer	• Yes • No		Yes	• Yes • Yes	Yes	• No • Yes	• Yes • No	No	Yes
2014, Wang	• Yes • Yes		Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2014, Yancey	• Yes • Yes		Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes
2016, Funk	• Yes • Yes		Yes	• Yes • Yes	Yes	• No • Yes	• Yes • Yes	No	Yes

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