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Sentinel surveillance for vector-borne disease: a case study of Lyme disease in Canada

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This thesis entitled

Sentinel surveillance for vector-borne disease: a case study of Lyme disease in Canada

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Abstract

Vector-borne diseases are emerging all over the globe. In Canada, Lyme disease (LD) has been identified as a priority emerging infectious disease. Public health surveillance, if effective, can track disease risk to inform public health authorities; however, due to finite resources, it must be optimized. Sentinel surveillance can cut costs, since a limited number of statistical units are measured repeatedly through time. Nonetheless, these sentinel units must be representative of the risk landscape to ensure an effective surveillance system. The first objective of this thesis was to evaluate the representativeness of sentinel tick surveillance for the risk of LD in Québec, Canada. Two types of tick-based active surveillance systems are already in place in Québec: 1) a sentinel system, where sentinel field sites are kept constant and visited every field season, and 2) a risk-based surveillance system where accessory sites are prioritized according to their risk profile. Acarological hazard measures, in the form of nymph density estimates, were derived from sentinel sites between 2015 and 2019 and compared with those obtained from accessory sites. Hazard measures derived from sentinel sites were also correlated with LD incidence at the municipal scale to see if they were representative of LD risk to human populations. It was shown that the sentinel tick-based surveillance system was able to follow spatiotemporal LD incidence trends in human populations across the study zone and provided a better indicator of LD incidence in comparison with the risk-based surveillance system. However, as sentinel sites were not chosen using a validated approach, it can be hypothesized that the spatial design for the system could be optimized through the development of a standardized, holistic approach for sentinel site selection. The second objective of this thesis was therefore to develop such an approach and apply it to a case example: sentinel surveillance of LD across Canada. A scoping review was used to inventory previous sentinel surveillance initiatives for vector-borne diseases, and catalogue criteria which had been used to select sentinel unit locations across the study zone. Relevant papers were subsequently analyzed using a realist-type review to create a decision tool to select relevant criteria for planning the spatial design of a sentinel surveillance system for vector-borne diseases. Finally, the tool was applied to guide the creation of a new sentinel tick-based surveillance network for LD risk in Canada; the retained criteria were incorporated into a spatial multi-criteria decision analysis to select sentinel regions for the active surveillance network. Overall, this thesis has explored sentinel surveillance for vector-borne disease and has developed and applied an approach to optimize and standardize spatial design planning

for vector-borne sentinel surveillance systems. In future work, this approach should be implemented, evaluated, and validated for other types of diseases and epidemiological contexts.

Key words: Lyme disease, *Borrelia burgdorferi*, *Ixodes* spp., Vector-borne diseases, Sentinel surveillance, Surveillance, Public health, Health sciences – epidemiology

Résumé

Les maladies vectorielles sont en processus d'émergence à travers le monde. Au Canada, la maladie de Lyme (ML) a été identifiée comme une maladie infectieuse émergente prioritaire. La surveillance, si elle est efficace, peut suivre le portrait d'une maladie en évolution afin d'informer les autorités de santé publique; toutefois, en raison de ressources limitées, elle doit être optimisée. La surveillance sentinelle permet de réduire les coûts, car un nombre limité d'unités statistiques sont mesurées de manière répétée dans le temps. Néanmoins, ces unités sentinelles doivent être représentatives du portrait épidémiologique de la maladie pour assurer l'efficacité du système de surveillance. Le premier objectif de cette thèse était d'évaluer la représentativité de la surveillance sentinelle pour décrire le risque de ML au Québec, Canada. Deux types de systèmes de surveillance active acarologique sont déjà en place au Québec : 1) un système sentinelle, où les sites de terrain sentinelles sont maintenus constants et visités à chaque saison de terrain, et 2) un système de surveillance basé sur le risque où les sites accessoires sont priorisés en fonction de leur profil de risque. Des mesures de danger acarologique, en termes d'estimations de la densité de nymphes, ont été dérivées des sites sentinelles entre 2015 et 2019 et comparées à celles obtenues dans les sites accessoires. Les mesures de danger acarologique dérivées des sites sentinelles ont également été corrélées avec le nombre de cas humains rapportés à l'échelle municipale pour déterminer si elles étaient représentatives du risque de ML pour la population humaine. Il a été démontré que le système de surveillance sentinelle était capable de suivre les tendances spatio-temporelles d'incidence de ML dans les populations humaines de la zone d'étude et fournissait un meilleur indicateur de l'incidence de ML par rapport au système de surveillance basé sur le risque. Cependant, bien que les modèles aient pu prédire le risque de maladie de Lyme, les sites sentinelles n'ayant pas été choisis selon une approche validée, on peut émettre l'hypothèse que l'utilisation d'une approche holistique standardisée pour la sélection de sites sentinelles pourrait optimiser le design spatial du système de surveillance. Le deuxième objectif de cette thèse était de développer une telle approche et de l'appliquer à une étude de cas : la surveillance acarologique sentinelle pour le risque de ML à travers le Canada. Une revue de la portée a été utilisée pour inventorier les initiatives précédentes de surveillance sentinelle pour les maladies vectorielles, et pour cataloguer les critères qui ont été utilisés pour sélectionner les emplacements des unités sentinelles dans la zone d'étude. Les articles pertinents ont ensuite été analysés à l'aide d'une revue du type réaliste afin de créer un outil décisionnel permettant de sélectionner des critères pertinents pour la

planification du design spatial d'un système de surveillance sentinelle pour les maladies vectorielles. Enfin, l'outil a été utilisé lors de la création d'un nouveau réseau de surveillance sentinelle pour le risque de ML au Canada; les critères retenus ont été incorporés dans une analyse multi-critères spatiale afin de sélectionner les régions sentinelles pour le réseau de surveillance acarologique active. Dans l'ensemble, cette thèse a exploré la surveillance sentinelle pour les maladies vectorielles, et a développé et testé une approche pour optimiser et standardiser la planification du design spatial des systèmes de surveillance sentinelle pour les maladies vectorielles. Dans de futurs travaux, cette approche devrait être mise en œuvre, évaluée et validée pour d'autres maladies et contextes épidémiologiques.

Mots clés : Maladie de Lyme, *Borrelia burgdorferi*, *Ixodes* spp., Maladies vectorielles, Surveillance sentinelle, Surveillance, Santé publique, Sciences de la santé - épidémiologie

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Acronyms

AB	Alberta
BC	British Columbia
CaLSeN	Canadian Lyme Sentinel Network
CDC	Centers for Disease Control
CIPARS	Canadian Integrated Program for Antimicrobial Resistance Surveillance
CLyDRN	Canadian Lyme Disease Research Network
CLSC	Centres locaux de services communautaires
CNDSS	Canadian Notifiable Disease Surveillance System
DEET	N,N-Diethyl-m-toluamide
DSP	Direction de santé publique
EIA	Enzyme immunoassay
EWS	Early Warning Systems
FAO	Food and Agriculture Organization of the United Nations
FNIHB	First Nations and Inuit Health Branch
GISRS	Global Influenza Surveillance and Response System
HIV	Human immunodeficiency virus
HPC	Health care provider
IB	Immunoblot

Ig	Immunoglobulins
INESSS	Institut national d'excellence en santé et services sociaux
LDES	Lyme Disease Enhanced Surveillance system
LD	Lyme disease
MB	Manitoba
MCDA	Multi-criteria decision analysis
MSSS	Ministère de la Santé et des Services sociaux
NB	New Brunswick
NL	Newfoundland and Labrador
NML	National Microbiology Laboratory
NS	Nova Scotia
OIE	World Organisation for Animal Health
ON	Ontario
Osps	Outer surface proteins
PEI	Prince Edward Island
PEP	Post-exposure prophylaxis
PHAC	Public Health Agency of Canada
PTLDS	Post-treatment Lyme Disease Syndrome
QC	Québec
RSS	Région socio-sanitaire

SK	Saskatchewan
TBD	Tick-borne disease
VBD	Vector-borne disease
WNV	West Nile Virus
WHO	World Health Organization

Introduction

The emergence of vector-borne diseases

Zoonotic diseases, those spread between animals and humans, are becoming an increasing public health burden (1, 2). An emerging zoonosis, as defined by the World Health Organization (WHO), the Food and Agriculture Organization (FAO) of the United Nations, and the World Organization for Animal Health (OIE) is one which is "newly recognized or newly evolved, or that has occurred previously but shows an increase in incidence or expansion in geographical, host or vector range" (3).

Vector-borne diseases (VBDs), a specific subset of zoonoses where pathogens are transmitted between species via an arthropod vector, are no exception to the trend (4). In the case of VBDs, climate change has been one of several factors that contribute to the changes seen in disease incidence (5). Increasing temperatures, changes in precipitation, and climate variability have led to changes in geographic ranges of vectors and their associated human disease-causing pathogens, thus modifying and in some cases expanding the geographic range of VBD case occurrence (6).

Over the past twenty years, VBDs have represented a growing proportion of emerging infectious diseases. According to the WHO, VBDs accounted for more than 17% of infectious disease burden in 2020 and caused more than 700 000 deaths per year worldwide (3). At the global scale, malaria and dengue pose the greatest public health burden amongst all VBDs – there are an estimated 400 million cases of dengue annually, and a recent WHO report has estimated over 241 million cases and 670 000 deaths arising from malaria (7, 8). Mechanisms which have led to the surge of these prominent mosquito-borne diseases include population growth and urbanization, the globalization of air transport, the spread of *Aedes* spp. mosquitoes globally, and the lack or scaling back of effective public health interventions (9, 10). Other VBDs with important global impacts include lymphatic filariasis, yellow fever, chikungunya, Rift Valley fever, West Nile fever, Zika virus disease, Japanese encephalitis, leishmaniasis and schistosomiasis (11). Although transmission of these pathogens by vectors represents the main threat to human populations, some of these VBDs can also be transmitted through different pathways which contribute to the burden of the diseases and add to the

complexity of their management. An example is Zika virus, which is transmitted most frequently through the bite of infected *Aedes* spp. mosquitoes, but can be transmitted vertically, from a mother to her child during pregnancy, sexually and via blood transfusions (12).*Yersinia pestis*, the pathogen which causes the plague, is classically spread by fleas but can be acquired through direct contact or droplet inhalation (13). *Francisella tularensi*, the bacterium responsible fors tularemia, is spread for a variety of tick species, but in some cases, can be acquired by inhaling dust or aerosols contaminated with the bacteria, or through ingesting contaminated water (14).

Although the continents most impacted by VBDs are Africa, Asia, and South America (15), North America has not been spared from the trend of increasing incidence of VBDs (6). Between 2004 and 2016, the numbers of reported VBDs cases have doubled in the United States' Notifiable Diseases Surveillance System (16). Concurrently in Canada, Lyme disease, along with West Nile Virus, are two of the main emerging vector-borne zoonotic diseases in the country (17, 18). Between 2010 and 2021, a total of 14,472 human cases of Lyme disease were reported throughout Canada (19) and during this same period, 1848 cases of West Nile were declared (20). Meanwhile, some VBDs which infrequently affect humans remain a concern for animal populations; although there have been no autochthonous human cases of eastern equine encephalitis virus in Canada, periodic outbreaks of the virus in horses and domestic bird populations (pheasants and emus) have occurred throughout the 2000s (17).

The emergence of Lyme disease in Canada

Lyme disease (LD) was originally discovered after the diagnosis of several children with inflammatory arthritis, in the town of Lyme, Connecticut, in 1975 (21-23). Further enquiries into the matter revealed that fifty-one residents (39 children and 12 adults) in Old Lyme, Lyme and East Haddam were diagnosed with a similar clinical picture (23). The cause of the disease was found to be a bacterium, the spirochete *Borrelia burgdorferi,* transmitted to its hosts by an arthropod vector, the blacklegged tick (*Ixodes scapularis*). In 1984, Lyme arthritis was reported to affect dogs, and this finding was confirmed in subsequent years (24-27). In the 1980s, indirect fluorescent antibody (IFA) tests were used to detect antibodies to *Borrelia* spp. in wild and domestic mammals living within LD foci, including the white-footed mouse and the white-tailed deer (28-30).

Through genomic analyses of *B. burgdorferi*, it was possible to determine that evolutionary changes were not the trigger of LD emergence; the spirochete had been present and geographically widespread across North America for over 60,000 years (31). Rather, a combination of multiple ecological changes was at the root of the LD epidemic: deforestation during the colonial period, about 500 years ago, created a fragmented landscape, and population explosion of white-tailed deer in the last century after intensive hunting practices diminished, supported by climate change, enabled dramatic range expansion of *Ixodes* spp. ticks (32-34).

Since the initial epidemic, *Ixodes scapularis* ticks have spread across New England and the Midwest USA, and subsequently LD has emerged throughout these regions. In Canada, the first *Ixodes scapularis* tick population to be documented was at Long Point, Ontario, in 1979, and remained the only known location of *Ixodes* spp. ticks in the early 1980s (35, 36). However, reports of establishment of blacklegged tick populations increased in eastern and central Canada in the 1980s, with tick populations expanding to more northernly latitudes in the 1990s and continuing to do so to this day (37-39).

In western North America, although *Borrelia burgdorferi* remains the pathogen responsible for LD, the tick vector found along the seaboard from Mexico to British Colombia is *Ixodes pacificus,* also known as the western blacklegged tick (40). In western Canada, the range of *Ixodes*

pacificus has also been expanding geographically, especially in southern British Columbia (35, 41).

As a consequence of increasing numbers of established tick populations across the country, public health authorities would soon begin to note a rise in LD incidence, especially at the turn of the 21st century (35). To track this concerning rise in risk, LD was added to the national notifiable disease list in Canada in 2009; during the first year, 144 cases were reported, increasing to 2,851 cases in 2021 (19, 42, 43).

Surveillance of vector-borne diseases

Surveillance is a public health activity used to follow disease trends and to better understand their spatial and temporal epidemiology (44). Surveillance data can be used to guide public health interventions, with the aim of controlling a disease or limiting its repercussions on human or animal populations (44). To control emerging disease, the key is early identification of the disease or of its growing impact and consequently, a rapid public health response (45, 46). Effective surveillance programmes have the capacity to generate early signals of increasing risk, informing relevant public health authorities in a timely manner and making it possible to put in place interventions that will reduce harm to populations (46).

Vector-borne zoonoses are complex systems, involving many interacting ecological factors, including a pathogen, animal host(s), and a vector, all within suitable environmental conditions (47). This can present a challenge for the development of an effective surveillance system; by the time the first human or animal case of a new VBD is diagnosed, the pathogen and the vector responsible for its transmission may be widespread in the environment (38, 48). Thus, surveillance for VBDs must be adapted to the specificities of these diseases and may involve sourcing multiple types of data, including, but not limited to, climate data, vector densities and ecological variables (49). In light of the complexity of monitoring VBDs, public health authorities must determine which VBDs should be prioritized within their territory and strive to understand their transmission cycle, in order to conduct effective and representative surveillance activities (50).

The approaches used for surveillance activities may take many forms and can be classified according to various characteritics (51). When considering how the operational structures are implemented, which permits the collection of data, they can be largely classified into active or passive surveillance (52) In active surveillance, public health authorities will plan and intiate surveillance activities to collect data e.g., fieldwork to sample vector densities. In passive surveillance, surveillance structures are put in place to allow data to be forwarded to public health authorities.

For VBD surveillance, it is possible to monitor each of the components of the transmission cycle, either using passive or active surveillance. For instance, we can look at the presence of vectors within the environment, the number of human or animal cases, pathogen prevalence

at the vector level, or even seroprevalence in animal or humans as a marker of exposure to pathogens (50). Sampling strategies may also vary according to resources, characteristics of the disease, and surveillance objectives (53). Surveillance systems can be exhaustive, which includes reporting data that occurs within the whole population of the geographical area covered by the surveillance system e.g., the Canadian Notifiable Disease Surveillance System (CNDSS) (53). Risk-based surveillance involves surveying statistical units according to their risk profile (54). Sentinel surveillance uses repeated sampling in a subset of a population to follow disease trends (53). Surveillance objectives will determine the type of data that will be collected by the surveillance system – for example, it is possible to conduct environmental, human disease, and/or veterinary disease surveillance (53).

Planning a surveillance system will involve complex decision making, as the surveillance strategy must be adapted to the disease(s) under investigation (55). Trade-offs between sensitivity and specificity of the surveillance system, and between exhaustivity of surveillance and resources available will impact final decisions. Furthermore, as the epidemiological portrait of the disease evolves, surveillance objectives must be revised (56). Thus, continuous evaluation of surveillance is required to ensure that the system remains relevant and can identify how it can be optimized.

Research focus

As Lyme disease emergence continues in southern Canada, surveillance initiatives have been put in place in many jurisdictions to monitor LD risk to human populations and track the geographic spread of *Ixodes* spp. tick populations. These initiatives should be continually evaluated, and the collected data analyzed, especially as the epidemiological portrait of the disease evolves.

Amongst surveillance initiatives for LD risk, active acarological surveillance using drag sampling has been employed in most provinces in Canada, although there is not a nationally coordinated active tick-based surveillance system. Active surveillance activities are thus initiated independent at the provincial and/or regional level. In Québec, active surveillance is carried out as part of the integrated surveillance for LD, conducted by the Insitut National de Santé Publique du Québec (INSPQ) in collaboration with the Université de Montréal (57). The aim of the surveillance system is to document the presence, abundance and geographic distribution of I. scapularis in Quebec and to know their *B. burgdorferi* infection status (57). Active surveillance has been carried out at sentinel sites in southern Québec since 2015. In parallel, active surveillance is conducted at accessory sites, which vary from one field season to another. A risk-based surveillance strategy is used; sites are prioritized according to LD risk at the municipal level[1], based on LD incidence and past tick-based surveillance indicators. Data generated from these two types of surveillance sites remains to be evaluated and compared, to provide insight into their representativeness in monitoring LD risk in human populations. The evaluation of sentinel surveillance could support its use as a cost-effective and representative surveillance strategy.

In Canada, standardized active surveillance efforts could provide a real-time portrait of the evolving risk of LD, and other tick-borne diseases (TBD), comparable across the country. A

[1] The INSPQ developed an algorithm to prioritize the municipalities where sampling should take place (unpublished). The algorithm integrates past surveillance data (LD incidence, number of tick submissions from passive surveillance and number of ticks collected during previous active surveillance) aggregated at the municipal level. Once municipalities are chosen, appropriate sampling sites are found within the retained municipalities. The algorithm has not been validated, and the surveillance strategy employed was modified as of 2022.

sentinel approach could allow for the feasibility of a pan-Canadian active surveillance system. However, to maximize the usefulness of such a system, careful planning is required.

This thesis will focus on active acarological surveillance at sentinel sites as a surveillance approach for LD.

Firstly, data from existing sentinel acarological surveillance in Québec will be analyzed and compared with risk-based acarological surveillance to evaluate its ability to follow spatiotemporal risk patterns. Although general criteria were developed to select sentinel sites, the lack of a systematic, rigorous site selection process was not utilized as it has not yet been described in the litterature. Therefore, in the second part of this thesisy, an approach to plan the spatial design of sentinel surveillance systems for VBDs, using available scientific knowledge, will be developed. It will be applied during the conception of a new tick-based sentinel network in Canada for the surveillance of LD risk.

Study location

1. Provincial scale: southern Québec

Québec is the largest province in Canada, located in the eastern side of the country. It is sandwiched between Ontario and New Brunswick and shares borders with the states of New York, Vermont, New Hampshire, and Maine in the south (**Figure 1**). Québec is separated administratively into 18 health regions (*régions socio-sanitaires*: RSS), which are themselves further subdivided into local centres for community services (*centres locaux de services communautaires*: CSLC) (58). These units are responsible for the administration of health and social services. The smallest scale is the municipal scale: between 1 (Sherbrooke and Rouyn-Noranda) and 28 municipalities will make up a CLSC (59). Notable exceptions are seen in urban centers such as Québec city, Montréal, Gatineau, Trois-Rivières, Longueil, Laval, Lévis, Mirabel, and Sept-îles, where the municipality is spread across multiple CLSCs.

Québec houses a total of 8.45 million residents, and the majority of the population is located in the south of the province. This also coincides with the area of emergence of LD. Since 2003, LD has been a notifiable disease in Québec and laboratories and physicians have the legal requirement to report new LD diagnoses under the Law of Public Health (Loi sur la Santé Publique, LSP). This allows public health authorities to monitor the evolving portrait of LD at the regional and provincial scales. The health regions where LD risk is currently emerging[2] include: Capitale-Nationale, Mauricie et Centre-du-Québec, Estrie, Outaouais, Montréal, Chaudière-Appalaches, Laval, Laurentides, Lanaudière, and Montérégie (**Figure 1**). This area is where active acarological surveillance activities are currently conducted through the joint collaboration of the INSPQ and the University of Montréal (see section 4.3.4. Active surveillance of ticks in Québec).

[2] In Québec, LD emergence is defined by the presence of human LD cases and/or the number of tick submissions from passive surveillance exceeding a threshold value (55)

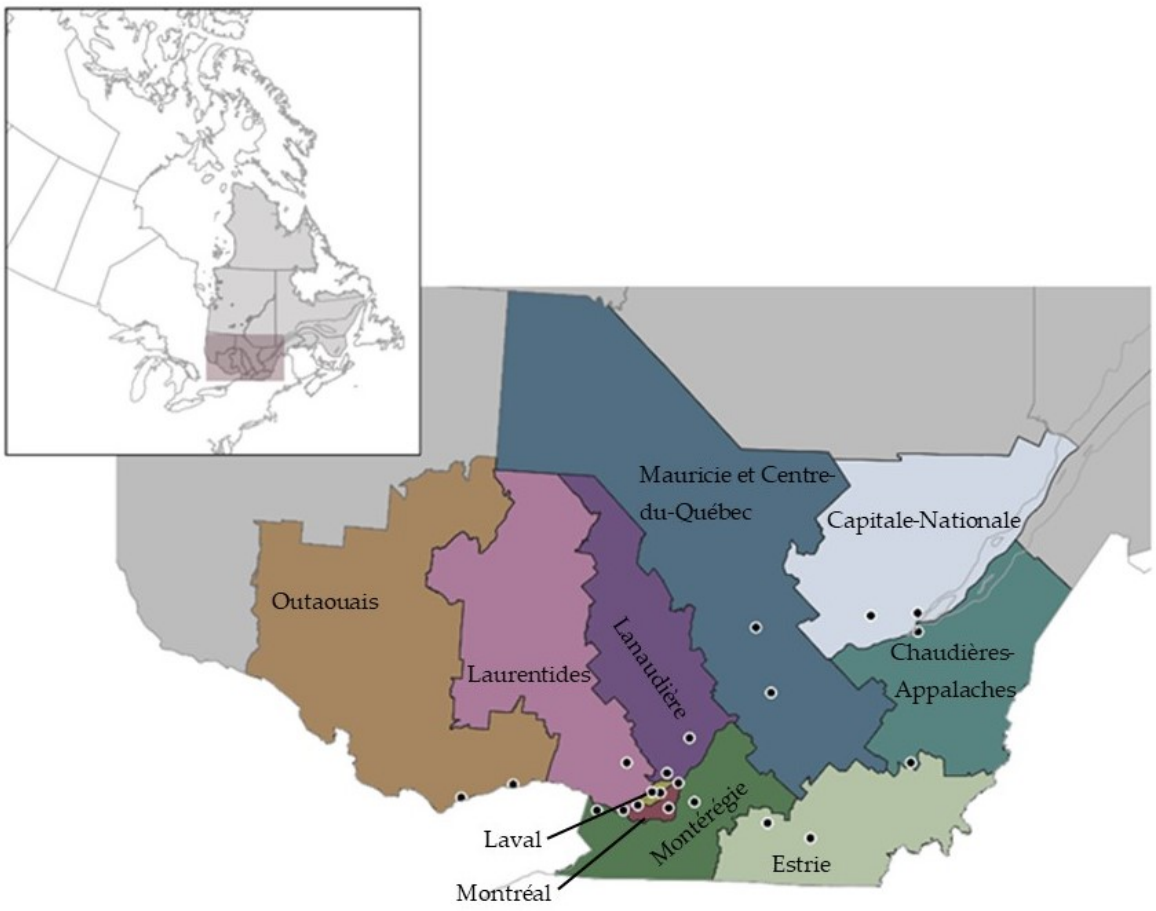

Figure 1. Location of the province of Québec in the east of Canada and the administrative regions (*Régions socio-sanitaires*: RSS) within Québec where Lyme disease is emerging. Black dots represent sentinel sites for active surveillance of LD risk selected in the province of Québec

2. National scale: southern Canada

In the second part of this thesis, the focus of the study location will broaden to the national scale. Canada is the second largest country in the world by area and has a total population of close to 37 million (60). Canada is made up of ten provinces that span the southern portion of the country: British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Québec, New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador (**Figure 2**). There are three territories in the north from about the 60th parallel: the Yukon, the Northwest Territories and Nunavut.

Figure 2. Map of Canada that is comprised of ten provinces and three territories. The study scale for the second half of this thesis is southern Canada spanning across all ten provinces (except Labrador).

Legend PEI: Prince Edward Island

Due to their southernly location, risk of LD is only considered to be emerging among the provinces, at the current time. Thus, within this thesis, the three northern territories and Labrador will not be included as part of the study zone. Furthermore, the study zone will further be restricted to the southern portion of each of the provinces, below the 53rd parallel, as LD risk is negligible in more northern regions.

A total of 2,851 LD human cases were reported in 2021 (19). The highest incidence of LD is found in eastern Canada, more specifically in Nova Scotia (85.6 cases/100 000), Ontario (8.0 cases/100 000), Québec (5.9 cases/100 000), Manitoba (4.8 cases/100 000), and New Brunswick (4.6 cases/100 000) (61). Although some cases are travel-related, only 6% of infections are likely to have been acquired outside of Canada (61).

Objectives

The main objective of this thesis is to contribute knowledge to optimize vector surveillance practices for vector-borne diseasesusing the case study of of LD emergence in Canada. More specifically, my thesis will focus on sentinel tick-based surveillance of LD risk and investigate how enzootic hazard measured at sentinel sites is associated with LD risk to human populations. The project will be split into five chapters to develop this concept; firstly, sentinel surveillance will be studied at the provincial level in Québec, and secondly, findings will be applied at the national level in Canada. Each chapter will have its respective sub-objectives (**Table 1Table 1**).

Table 1. Sub-objectives for each chapter within this thesis

Chapter I
o Compare sentinel surveillance with risk-based surveillance approaches for the purposes of monitoring spatiotemporal risk of LD
Chapter II
o Understand how enzootic hazard, in the form of nymph density, derived from sentinel site data is associated with LD risk in the human population in southern Québec o Determine the strengths and weaknesses of the provincial sentinel surveillance network established in Québec and formulate recommendations to optimize future sentinel surveillance networks for LD
Chapter III
o Identify elements of sentinel surveillance which are necessary to establish a representative and sensitive surveillance system for VBDs, through cataloguing criteria that have been used in past case studies to determine spatial distribution of sentinel units in a surveillance system

Chapter IV

- Develop a decision tool to support a systematic approach for selecting criteria used in the spatial design of sentinel surveillance systems, adaptable to different VBDs

Chapter V

- With the support of the decision tool, develop a spatial multi-criteria decision analysis (MCDA) approach to determine locations of sentinel units across Canada for the establishment of a pan-Canadian sentinel network for tick-based active surveillance of LD risk

Literature Review

This review aims to provide a global assessment of the impact of Lyme disease (LD) on North American human populations. Initially, general aspects of the disease will be introduced, including symptoms and long-term sequelae, diagnosis, management, and economic burden. The next section will present the developmental phases of the tick vector, the ecology of *Borrelia* reservoir hosts, and will summarize the dynamics of LD transmission. Subsequently, the current epidemiological situation of LD in Canada will be presented, beginning from the spatial dispersion of ticks and *Borrelia* to the rise in LD cases. Finally, the general concepts of surveillance will be explained and applied to monitoring of LD for public health purposes.

1. Lyme disease

LD is the most common vector-borne disease in the northern hemisphere (62). It is caused by spirochetes belonging to the *Borrelia burgdorferi* sensu lato (sl) complex (63). Not all *B. burgdorferi* sl species are pathogenicand in North America the principal genospecies associated with LD remains *B. burgdorferi* sensus stricto (hereafter referred to as *B. burgdorferi*) (64). In Eurasia, it is rather the genospecies *B. afzelli* and *B. garinii* which are most commonly responsible for Lyme borreliosis (65-67).

As with other VBDs, transmission from an infected host to another host requires an arthropod, in this case through the intermediary of ticks from the genus *Ixodes*. There are over 240 species in the *Ixodes* genus, representing the largest genus in the Ixodidae tick family (68, 69). However, only a few species within this genus are of known medical importance for the transmission of *Borrelia* pathogens. In southeastern Canada, the mid-eastern, and eastern United States, *Ixodes scapularis say* is the principal vector of Lyme (70, 71). In the mid-Atlantic region of the United States, *I. affinis* is known to be competent for *B. burgdorferi*, however the exact effets of this vector on LD risk and LD incidence in human population remains to be determined (72). In western North America, from Baja California to British Columbia, the main vector is *I. pacificus*, followed by possible (but debated) transmission by *I. angustus* (73-75). In Europe, the sheep tick *I. ricinus* is responsible for the spread of borreliosis (71, 76, 77)

whilst that lastly, in Asia, *I. granulatus* and *I. persulcatus* are the main sources of pathogenic *Borrelia* (78, 79).

As this study in set in North America, from here on, this literature review will focus on studies reporting on aspects of *B. burgdorferi* and *I. scapularis* and/or *I. pacificus*.

1.1. Pathogenesis

During the infection process of LD, it is the presence of outer surface proteins (Osps) which allow *Borrelia burgdorferi* transition between its tick-vector and animal hosts, subsequently leading to a clinical infection if the host is susceptible (80). Firstly, OspA allows *B. burgdorferi* to attach to the tick's midgut after the tick has taken a bloodmeal from an infected reservoir host (81, 82). Expression of the protein has been noted to increase as the spirochete moves into the tick's salivary glands during a subsequent bloodmeal, and thus, prior to injection into another host – at this time, production of OspC is activated, which is thought to permit the bacteria to adhere to human plasminogen, thus allowing penetration into the human host's skin and other tissues (81, 83).

In humans, dissemination of *B. burgdorferi* leads to the attachment of the bacteria to various host integrins causing an inflammatory response (84). The bacteria show tropism particularly for heart, nervous and articular tissues, which may be a consequence of the bacteria's production of matrix glycosaminoglycans and extracellular-matrix proteins (85, 86). This inflammatory process will lead to the symptoms of LD.

1.2. Signs and symptoms

LD presents a spectrum of clinical symptoms, both non-specific and pathognomonic (87). Furthermore, it is classified into three distinct stages, each one usually proceeding the other in a linear time fashion.

Stage 1, or early localised disease, begins 1-4 weeks after a tick bite, although typically less than 20% of pediatric or 50% of adult patients received a LD diagnosis recall having had an exposure to ticks (88, 89). The early stage is characterized by an expanding circular rash, known as a "bull's eye rash" or erythema migrans, in 70% of patients (90, 91). Otherwise, there is presence of constitutional symptoms, for example fever, swollen lymph nodes, myalgia, and fatigue (92, 93).

Stage 2 is known as the early disseminated infection, occurring from 1 to 4 months after the initial tick bite. At this stage, neurological manifestations occur in approximately 10% of patients and include lymphocytic meningitis, radiculoneuritis or cranial neuritis, affecting most commonly the facial nerve (90, 94-96). Cardiac involvement may also arise, such as atrioventricular conduction defects (97).

Stage 3 is identified as late persistent LD and is characterized by arthritis, which can develop months after the initial tick bite (80, 98). The arthritis primarily attacks large joints such as the knee and can persists for several years (64). Furthermore, chronic Lyme borreliosis can result in disabling symptoms such as fatigue, pain, and cognitive disturbances (95). This final stage of the disease, which results from late treatment of the early stages, is most feared by the public, physicians, and public health authorities due to these debilitating symptoms and the possibility that treatment may be refractory in treating the long-term sequelae (64).

Post-treatment Lyme Disease Syndrome (PTLDS), or chronic Lyme disease, is reported in a small percentage of cases. It involves fatigue and myalgia for a duration of over than 6 months after successful treatment of LD (99). It would be caused by an inflammatory response to the disease, as opposed to ongoing infection (100). Its entity remains a subject of debate, and details of the syndrome are beyond the scope of this literature review.

1.3. Diagnosis

The initial diagnosis is clinical, for instance made in light of presence of erythema migrans or flu-like symptoms with a history of potential exposition to ticks (101, 102). In Canada, laboratory confirmation of infection by *B. burgdorferi* is done by the two-tiered approach (**Figure 3**) (102, 103).

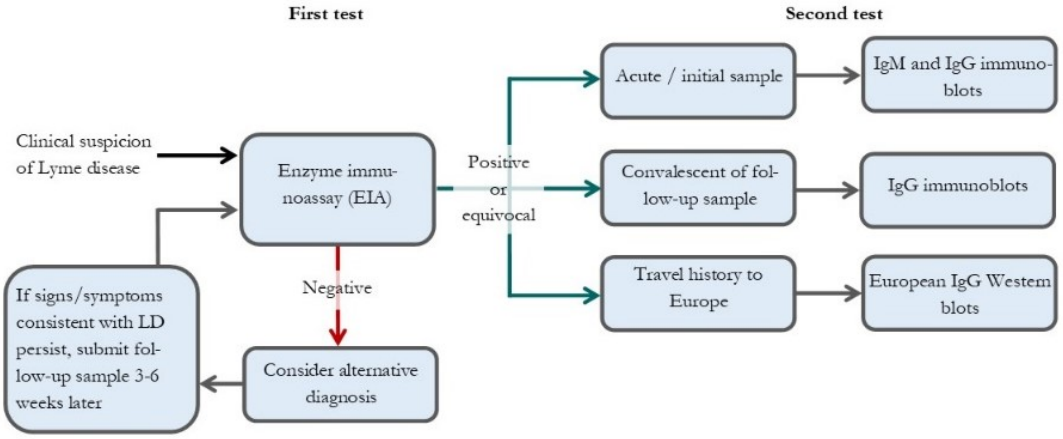

Figure 3. Diagram of two-tiered testing carried out in Canada for the diagnosis of Lyme disease (103-105)

This approach consists of using an enzyme immunoassay (EIA) screening test, and if the latter is positive, it is followed by a confirmatory immunoblot (IB) test, specifically a Western blot (104-106). Both tests permit the detection of immunoglobulins (Ig) in the patient's serum. In responding to LD infection, the immune system firstly produces IgM antibodies, within about two weeks of the tick bite (107)). Then at about a month after the tick bite, IgG antibodies will be found (102). These antibodies remain in the bloodstream for months to years, regardless of whether treatment with antimicrobials has been administered (108).The initial EIA test is highly sensitive for Lyme disease and allows detection of IgM and/or IgG antibiotics against *B. burgdorferi* (102). Its high sensitivity is attributed to the use of whole cell sonicate preparation of *B. burgdorferi* which results in the presence of multiple antigens in the EIA (106). However, these antigens can lead to cross-reactions with a variety of different antibodies from the animal host (e.g., originating from autoimmune disorders, Epstein-Barr virus infection, bacterial endocarditis, syphilis, *Helicobacter pylori* infection) which can lead to false positives and so, lack of specificity (104, 107). The second tier, in this case the western blot, is subsequently utilized to increase specificity (102, 106). The western blot is a serological method, which employs electrophoretically separated *B. burgdorferi* protein antigens to detect presence of serum antibodies (108). To confirm a diagnosis of LD, a positive Western blot is required, whilst that seroconversion from IgM to IgG observed by an IB gives definitive evidence of a recent infection (106).

Sensitivity of the two-tiered method depends on the stage of the disease: it low during the early infection whilst the immunological response begins (30-40%) and increases to 70-100% in disseminated LD (106). Meanwhile, specificity is over 95% throughout the evolution of the disease (106).

1.4. Treatment and preventive measures

The early localized stage of LD responds well to treatment with a 10 to 14-day course of oral antibiotics, such as doxycycline, amoxicillin, or cefuroxime (109-111). Antibiotics will shorten the duration of erythema migrans, if present, but most importantly, will prevent dissemination of the disease (109).

Later stages of LD require treatment with a longer course of antibiotics, usually lasting at least 28 days (112). The same antibiotics are used as in the early stage. In the case of ongoing arthritis, which occurs in a substantial proportion of patients, a second month-long course of antimicrobials may be required (112). Intravenous antibiotics such as ceftriaxone or penicillin may be prescribed in the presence of neurological or cardiac symptoms (112) .

To avoid acquisition of LD, several prevention methods are encouraged by public health authorities, aiming to diminish tick bites. These include wearing light-coloured long-sleeved shirt and pants, which reduce skin-tick contact and allow individuals to see ticks more readily (80). N,N-Diethyl-m-toluamide (DEET) spray can be used to repel ticks and other insects, whilst that permethrin impregnated clothing can effectively reduce tick bites for up to 60 washes (80, 112). Furthermore, individuals should walk on cleared paths whilst hiking, and put clothes in a tumble dryer with high heat for at least 10 minutes upon returning in order to kill any ticks which have adhered to the material (80). The best method of prevention remains to carry out a full body check after any outdoor activity and removing any attached ticks with tweezers (112). This will prevent the transmission of LD, as a period between 24 and 48 hours is required from the time of attachment of the tick for *B. burgdorferi* to move from the tick's midgut to its salivary glands, and then into the host's bloodstream (113, 114).

In the case that a tick bite has been discovered, post-exposure prophylaxis (PEP) with doxycycline may be provided according to guidelines provided by the jurisdiction. For instance, in the province of Québec, the Institut national d'excellence en santé et en services sociaux (INESSS) has explicit guidelines as to when PEP should be given (115). Doxycycline

will be prescribed (unless there is a medical contraindication) when the tick has been attached between 24 to 72 hours and the tick is likely to originate from a municipality where the risk of LD is high i.e., where tick populations have a *B. burgdorferi* infection rate of over 20% (83, 115).

Vaccination was developed for LD in the 1990s (116). Low efficacy of these vaccines was an important limitation to their usefulness: vaccine efficacy was calculated to be less than 80%, thus, 20% of vaccinated individuals would not be sufficiently protected from LD (116). Complicated vaccination schedules[3] were another barrier to their use, along with the potential need for yearly booster to prevent a decrease in immunity (117, 118). Finally, extensive media coverage of potential side effects, supported by anti-vaccines groups, in a time of low public tolerance for vaccine risk led to low demand for the vaccine and lawsuits, resulting in the manufacturer withdrawing its product from the market (116). Following these events, no LD vaccine are currently available to human populations.

1.5. Economic impact on human populations

Apart from debilitating long-term sequelae for individuals having suffered from disseminated disease (e.g., Lyme arthritis), LD results in a significant economic burden on populations that is important to consider as part of the management strategy and resource allocation. Inflated annual economic impact of LD in the United Stated totaled to nearly 300M USD, which represents similar costs as West Nile virus and Zika virus (119-121). Costs attributed to LD may be direct or indirect (122).

Direct costs include those attributed to treatment, medical hospitalization, outpatient management and diagnostic testing for LD itself or associated complications (radiology, follow-up blood tests, etc.). The direct costs also include the burden of over-usage or inappropriate diagnostic testing, which highlights the importance of public health authorities in educating physicians and surveying the presence or absence of LD risk within their administrative boundaries (122).

Indirect costs are relative to loss of productivity, for instance from absenteeism from work to attend outpatient consultations or during hospitalisation, which is estimated at 12.1 weeks on

[3] According to the CDC (116), optimal protection required 3 doses: the second dose is administered one month after the first dose, and the third dose is administered 12 months after the first dose. The second and third dose should be administered several weeks before the beginning of the tick season. Length of protective immunity was unknown , and it was suspected that yearly booster may have been required.

average (122). These also include out-of-pocket, informal care that patients seek out, such as household assistance or caregiving required due to the disabling nature of LD.

These significant costs attributed to the management of LD justify the need for further research and evaluation of LD risk to human population, through surveillance initiatives, to allow for targeted preventive interventions.

2. Lyme disease transmission

2.1. Description of *Ixode*s spp.

In Québec alone, there are 12 different species of ticks that can be found; however, only *Ixodes spp.* tick have been shown to transmit *B. burgdorferi* to humans (123). As described earlier, *Ixodes* spp. ticks are a genus of the family Ixodidae, colloquially known as hard ticks. *Ixodes scapularis* and *Ixodes pacificus* are the main acarids in North America transmitting *B. burgdorferi* to human (124). In addition to transmitting *Borrelia,* these two species can infect humans with *Babesia microti, Anaplasma phagocytophilum, B. miyamotoi*, *B. mayonii*, *E. muris eauclairensis* and Powassan virus (91, 125).

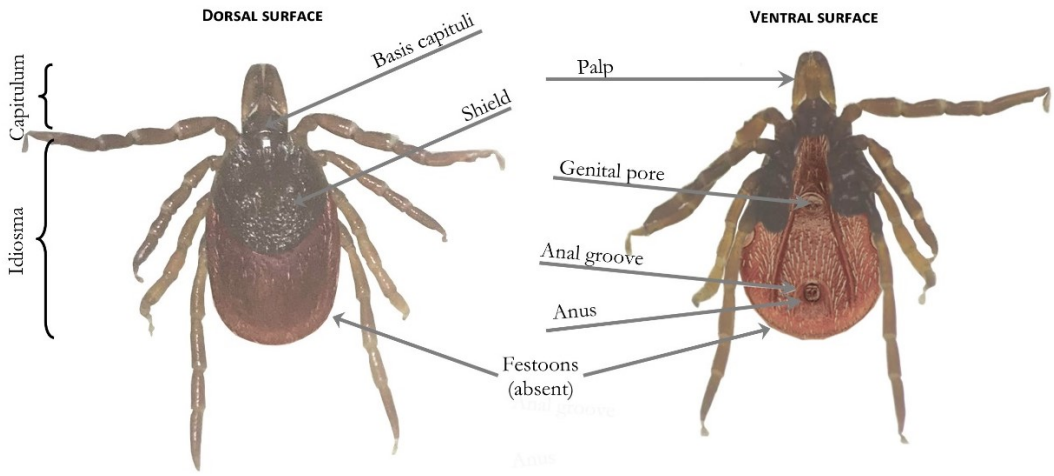

Figure 4. Blacklegged tick *(Ixodes scapularis)* morphological features, adapted from (126). A tick's body is composed of a capitulum (also called gnathosoma) and an idiosma (the body). The capitulum represents the mouth parts, including the palps and basis capitulum, which connects the capitulum to the iodiosma. The iodiosma holds the legs, the shield, and several orifices e.g., genital pore and anus

To determine the species of the tick, morphologic identification is carried out. The tick's body is composed of a capitulum, or gnathosoma, and the idiosma (**Figure 4**). The capitulum, often referred to as the head, projects anteroventrally and represents the mouthparts, such as the palps, along with a basal chitinous, or basis capitulum, which connects the capitulum to the iodiosma. The iodiosma is the body proper, oval-shaped and holds the legs – 3 pairs for larvae, and 4 pairs for nymphs and adults. The iodiosma bears a shield, several orifices (the genital pore and the anus) and characteristic markings (the anal groove and festoons) (127). The mouth parts of the capitulum and the body proper will show morphological differences based on species (**Table 2**) and between stages of the same species (**Figure 5**) (127, 128).

Table 2. Characteristics of different tick genera adapted from the INSPQ (128)

Genus	Dorsal shield	Festoon	Eyes	Anal groove in relation to anus	Length of palps in relation to basis capituli
Ixodes	Inornate	✗	✗	Above	Variable
Dermacentor	Ornate	✓	✓	Below	Similar
Amblyomma	Ornate	✓	✓	Below	Longer
Rhipicephalus	Inornate	✓	✓	Below	Similar
Haemaphysalis	Inornate	✓	✗	Below	Similar

Ixodes scapularis are recognized by their rectangular basis capitula, oval body shape, anterior anal groove, and the absence of festoons, in comparison with other tick species (69). Females are distinguishable due to their characteristic orange-red body that is readily seen due to their partial black and oval shields surrounding the black scutum (69). Meanwhile, males have a complete shield, uniform in colour and without light spots. The female, nymph and larva have distinctive long palps, which are longer than their basis capitulum.

Figure 5. Morphological differences between stages of *Ixodes scapularis* ticks (127). (1) Females are distinguishable due to their characteristic orange-red body, which is readily seen due to their partial black and oval shield; (2) males have a complete shield, uniform in color and without light spots; (3) females, nymphs and larvae have distinctive long palps, longer than the basis capitulum; (4) larvae have three pairs of legs

2.2. *Ixodes* spp. life cycle

Ixodes ticks are hard ticks (Ixodidae family); they are characterized by periodic feeding periods that are required to survive and to progress to a subsequent stage in their life cycle. The life cycle is composed of four distinct stages: egg, larva, nymph, and adult. Ticks will consume two bloodmeals to evolve from larva to adult (124). Females will take a last third bloodmeal prior to laying eggs.

Although life cycle phenology can depend on geographical habitat of the ticks (129), the general concepts remain similar. Below is a description of the life cycle seen in northeastern North American *Ixodes scapularis* ticks (124).

The female lays eggs in the springtime, which will hatch into larvae. These larvae will usually take their first blood meal on rodents, and this will allow the larva to molt into a nymph – the bloodmeal normally occurs mid-summer. Afterwards nymphs will go into diapause to survive the wintertime. Upon regaining activity in early spring, nymphs will resume questing behavior to find a host, at this stage usually a small mammal or bird. Nymphs evolve into adults at the end of summer or early autumn. A nymph that has not succeeded in finding a host during the

summer can go through a second overwinter diapause until the next springtime. Lastly, in autumn, male and female ticks will mate on-host typically, however it may take place off-host (124). The female will take a final blood meal, usually on larger mammals, such as white-tailed deer (*Odocoileus virginianus*). The female tick will lay eggs at the point where she drops off her last host.

2.3. Host animals

In the LD transmission cycle, host animals are primordial not only for the maintenance of *B. burgdorferi* in the environment (reservoir hosts) but are also required for tick survival. Host animals will also play a vital role is the dispersion of ticks (see section 3.1. Spatio-temporal spread of *Ixodes* spp. in Canada).

To ensure an interaction between the tick and its host, a minimal host density threshold needs to be reached, and furthermore, density of hosts will have a direct impact of tick abundance (34). Some literature suggests the necessity of white-tailed deer at a minimum of 7 deer/km^2 to allow for establishment of tick populations (130, 131).

Reservoir hosts are responsible for maintaining *B. burgdorferi* in the environment. As of yet, studies found no vertical transmission from the female tick to her eggs (132). Thus, larvae will hatch from their eggs uninfected and will subsequently become infected with *B. burgdorferi* during bloodmeals.

Hosts that have the capacity of retaining *B. burgdorferi* in their system are called reservoir hosts. Successful transmission of *B. burgdorferi* from reservoir hosts to the tick varies greatly upon host species (**Table 3**) (133). For LD transmission cycle in Canada, the main reservoir host is recognized as the white footed mouse (*Peromyscus leucopus*). Meanwhile, although white-tailed deer are important in the life cycle of *Ixodes* for males and females to meet for reproduction, they are incompetent hosts and cannot propagate *B. burgdorferi* within an ecosystem (133).

Table 3. Mean reservoir competence for *B. burgdorferi* and mean *I. scapularis* body burden reported with standard errors for vertebrate hosts, according to one study[1](133)

Species	Mean tick body burden (SE)	Mean reservoir competence (SE)[2]

White-footed mouse	27.8 (3.3)	92.1 (2.9)
Eastern chipmunk	36.0 (11)	55.0 (6.4)
White-tailed deer	239 (99)	4.6 (2.3)
Racoon	127 (30)	1.3 (0.6)
Virginia opossum	254 (115)	2.6 (1.1)
Stiped skunk	66.8 (12.7)	9.7 (8.4)
Short-tailed shrew	62.9 (17.3)	41.8 (6.7)
Sorex shrews	55.5 (32)	51.2 (15)
Red and grey squirrel	142 (58)	14.7 (5.1)

[1] Mean tick body burden and mean reservoir competence presented for a range of species as a guide, to illustre an additional factor of complexity of the LD transmission cycle; these figures could vary between studies according to methods used and are presented as a guide – a more in-depth analysis of mean reservoir competence reported across the literature is beyond the scope of this thesis.

[2] Fully engorged larvae attached to animal hosts, which molted into nymphs, were used to assess for mean reservoir competence. The number of larvae used to evaluate mean reservoir competence was between 4 and 33. Presence of *B. burgdorferi* was assessed using direct immunofluorescence antibody microscopy, which has limits in discerning between *B. burdorferi* and sympatric genospecies of *Borrelia* (134), detected at a rate of up to 2.5% in nymphs. There, reservoir competence may be inflated, but are provided as a guide for comparing between host species.

3. Epidemiology of Lyme disease

3.1. Spatio-temporal spread of *Ixodes* spp. in Canada

Independently, *Ixodes* ticks have the capacity to displace themselves negligible distances (135). For larger scale spatial spread, *I. scapularis* has been shown to be dispersed across southern Canada through two different mechanisms: firstly, across short distances by land-dwelling mammals and secondly, they can be dispersed across longer distances by migratory birds, overcoming physical barriers such as the Great Lakes, the sea and mountain ranges (136, 137).

The main land-dwelling vertebrate contributors to the short-distance spread of ticks are white-tailed deer – in fall, deer carry multiple ticks including already-mated females (2). After dropping off their hosts, the females may lay around 2000 eggs, contributing to the establishment of a tick population in a new location (2). Due to their small home range, the

role of white-footed mice in the range expansion of *Ixodes* has been debated, and multiple linear regression models suggests that *P. leucopus* indeed does not play a significant role (8).

For long-distance spread, the migration of birds represents the main mechanism of dispersal of *Ixodes* ticks (138). In the northern hemisphere, this spread is unidirectional, from south to north, due to the host-seeking period of immature ticks overlapping with spring migration. In a study, up to 70% of migrating passerines were found to be transporting *Ixodes* ticks north of their capture location, with up to 17% reaching the boreal region of eastern Canada (139). It is important to note that the most northernly locations remain climatically unsuitable to support the establishment of a new tick population (140).

This leads to the contribution of climate change as a catalyst for TBD in North America. Poleward spread of ticks and tick-borne pathogen is supported as temperate zones become warmer and more suitable for these species (6). Temperature, calculated as cumulative degree days, is the most important determinant of reproductive success in suitable habitats, and so impacts zn the probability of tick population establishment in new locations (6, 141, 142).

3.2. Incidence and epidemiology of Lyme disease in Canada

Since 2009, LD has been added to the Canadian Notifiable Disease Surveillance System (CNDSS) of the Public Health Agency of Canada (PHAC). In 2010, the Lyme Disease Enhanced Surveillance (LDES) system was implemented as a complementary resource for data collection and analysis. This allows public health authorities to follow disease trends across the country and capture any increase in incidence.

LD diagnoses are in great majority made between the months of May and November, with most cases reported in summer months (June to August) and peaking in July (21, 143). This period coincides with timing of nymphal *Ixodes spp.* feeding in Canada (144), the stage associated with the higher risk to humans due to its small size, making it easily missed on self-examination (145). Some years, diagnoses made in November and December could indicate that tick activity may have continued later in the season.

Eastern provinces have reported increasing numbers of Lyme disease cases in the last ten years, with Nova Scotia, Ontario and Québec having the highest incidence of LD (**Table 4**) (21). Meanwhile, in the western provinces the incidence has remained constant, and relatively

lower. No provincially acquired cases have yet been reported in Saskatchewan, Alberta or Newfoundland and Labrador, whilst no cases have been reported in any of the territories (Yukon, Northwest Territories or Nunavut). Between 2009 and 2015, the number of municipalities across Canada where LD was reported to have been acquired increased more than five-fold, from 21 to 109 (21).

Table 4. Number of Lyme disease cases and incidence within each province from 2015 to 2019 (61, 126, 146-153). N.B. Data were taken from the government of Canada and provincial government websites and do not distinguish between locally acquired or travel-related cases. Whilst the majority of cases diagnosed in British Columbia, Manitoba, Ontario, Québec, New Brunswick, and Nova Scotia are locally acquired, those diagnosed in Alberta, Saskatchewan, Prince-Edward Island and Newfoundland and Labrador are mostly travel related. Thus far, no cases have been reported from the Yukon, the Northwest Territories or Nunavut.

Province	**Number of cases reported (incidence per 100,000 population)**				
	2015	**2016**	**2017**	**2018**	**2019**
British Columbia	22 (0.5)	40 (0.8)	18 (0.4)	9 (0.2)	14 (0.3)
Alberta	14 (0.3)	10 (0.2)	13 (0.3)	15 (0.4)	14 (0.3)
Saskatchewan	0	1 (0.1)	1 (0.1)	2 (0.2)	1 (0.1)
Manitoba	26 (1.9)	41 (3.0)	42 (3.1)	54 (4.0)	65 (4.8)
Ontario	448 (3.2)	386 (2.8)	959 (6.7)	628 (4.4)	1168 (8.0)
Québec	160 (1.9)	177 (2.1)	329 (3.9)	304 (3.6)	500 (5.9)
New Brunswick	11 (1.4)	8 (1.0)	29 (3.8)	20 (2.6)	36 (4.6)
Nova Scotia	254 (26.5)	326 (34.0)	586 (61.1)	451 (47.0)	830 (85.6)
Prince Edward Island	0	0	0	1 (0.7)	6 (3.8)
Newfoundland and Labrador	0	0	0	2 (0.4)	0
Total	917 (2.0)	992 (2.0)	2025 (4.5)	1487 (3.3)	2634 (5.9)

Peak incidence according to age is bimodal, the first peak for children aged between 5 and 14 years and a second peak for adults aged between 55 and 74 years (21, 61, 151). There are more males than females who receive a diagnosis of Lyme borreliosis for all age groups, except for 10- to 14-year-olds (21, 61, 151).

The CNDSS also captures clinical manifestations of LD in over half of reported cases. Overall, the most common manifestations include single erythema migrans, present in 74.5% of cases, and arthritis in 35.7%. These were followed by Bell's palsy (paralysis of the seventh cranial nerve, the facial nerve), multiple erythema migrans and cardiac complications. Multiple clinical manifestations were present in around a third of cases (21). The clinical picture varies in children under the age of 15, where erythema migrans is more frequent whilst neurological and cardiac manifestations are less common.

Another important difference in the presentation of disease between children and adults is the stage during which the LD is diagnosed. Children aged up to 9 years old more frequently presented during the early stage of the disease compared to older age groups. For late disseminated disease, children under 15 were more likely to present with arthritis compared to older age groups (21).

4. Public health surveillance

The first recorded public health surveillance took place in 3180 B.C. within Egyptian civilization, where an epidemic was recognized and termed "the great pestilence" (154, 155). Meanwhile, the first public health act that can be attributed to surveillance occurred in 1348, when quarantine measures were imposed as an effort to control the bubonic plague near the Republic of Venice (154). Public health authorities boarded ships in the port to prevent passengers with plague-like symptoms from disembarking (154). Concepts of surveillance have greatly evolved but the essence of monitoring diseases to inform authorities and limit their spread has remained.

As defined by the WHO, public health surveillance is the "ongoing, systematic collection, analysis and interpretation of health-related data essential to the planning, implementation,

and evaluation of public health practice" (156, 157). Effective surveillance systems have the ability to monitor the evolution of a disease, disorder, or condition, to provide an understanding of the disease process and/or to act as an Early Warning System (EWS). Such information can guide public health interventions, by giving an epidemiological portrait of the situation to target appropriate populations and later, evaluate the success of interventions.

An effective surveillance system has several key functions, including detection and notification of health events, collection of data, confirmation of cases/outbreaks, analysis of data, feedback to data providers or feed-forward to more central levels and lastly, reporting data to the next administrative level and the general population as appropriate (52). The CDC has broken down the principal aspects of public health surveillance in four key functions along the spectrum of disease management: surveillance, risk factor identifications, intervention evaluation, and implementation (**Figure 6**) (158).

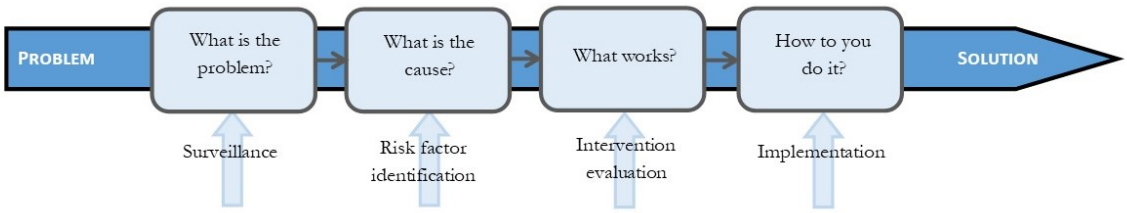

Figure 6. Public health approach to surveillance ; the CDC has broken down the principal aspects of public health surveillance is four key functions along the spectrum of disease management: surveillance, risk factor identifications, intervention evaluation, and implementation (159)

The use of public health surveillance includes contact tracing of infectious diseases, detecting epidemics, health problems or changes in health behaviour, estimating the scope or magnitude of health problems, measuring trends and characterizing disease, monitoring changes in infectious and environmental agents, assessing the effectiveness of intervention programs, and developing hypotheses to stimulate research (158, 159).

Each step along the surveillance continuum can be evaluated using a systematic process to ensure that it meets its surveillance objectives (53). Evaluation will support the development of standardized, sustainable, and integrated surveillance systems, adapted to current demands

(160). Furthermore, research has been identified as a cornerstone for the development and optimization of public health surveillance practices (161). Such research can identify limitations and strengths of different surveillance methods; thus, rigorous research-based evidence allows for better decision-making and resource allocation (161).

4.1. Classification of surveillance

Efficient public health surveillance is adapted to the disease(s) under investigation and its (their) situation within the study zone (52). Thus, to compare and analyze different modalities of surveillance networks, it becomes necessary to classify these networks. Many different methods of classifications exist, however the criteria established by Dufour and Audigé will be retained in this work (51). Although these guidelines were introduced for veterinary surveillance, they can also be applied more generally to any public health surveillance system. Seven criteria are used to classify the surveillance networks (**Table 5**). They will be specifically described in the context of TBD.

1) **Area of surveillance.** Firstly, the area or geographical scale of the surveillance network is described. The networks could be local, covering for instance municipalities or small-scale areas. It is said regional when the geographical area is smaller than a country, for example integrated WNV surveillance in Québec (162), or national when the surveillance gives enough information to represent a whole country, for instance the Equinella surveillance network for infectious disease surveillance in horses based in Switzerland (37). Lastly, international surveillance networks investigate several countries as seen in initiative from the WHO in the Global Influenza Surveillance and Response System (GISRS) (163).

2) **Surveillance type.** For this criterion, surveillance can be considered as focused, when a restricted number of diseases are investigated, as in the integrated surveillance network for LD or WNV in Québec (57, 162), or broad-based when several diseases, or again syndromes, are monitored within the same surveillance network, such as in the GeoSentinel Surveillance network investigating fever in travellers (164).

3) **Epidemiological situation.** Surveillance networks will be adapted to the current epidemiological situation of the disease(s) under investigation. These include new diseases as seen during the COVID-19 pandemic (165); exotic diseases, those which are not currently present within the study zone but are at risk of emerging, for instance malaria or Dengue virus in Europe (166); emerging diseases whereby presence of the disease in relatively new and number of cases are increasing, such as WNV in Québec (162); and lastly, endemic diseases which are well known to occur in the study zone, as seen with malaria on the African continent (167).

   The epidemiological situation is crucial to know as it will impact surveillance objectives, which subsequently dictate surveillance strategies (56). In TBD, the stage of disease emergence will contribute to orientate the surveillance system towards **environmental surveillance** (e.g., acarological surveillance) and/or **epidemiological surveillanc**e (i.e., disease surveillance).

4) **Population monitored.** The population monitored could include suspected cases, as is seen in syndromic surveillance. However, surveillance could employ susceptible individuals as in sentinel herd systems or the general public (44). For TBD, and VBD in general, environmental surveillance is often used, e.g., active acarological surveillance. In this case, the geographical area where sampling is undertaken can be considered the « population » under surveillance within the area of surveillance.

5) **Sampling strategy.** The surveillance network may be exhaustive, referring to monitoring the entirety of the population (or geographical area if we are conducting environmental surveillance). This is infrequently done due to high-volume resources needed to accomplish this. Such a strategy can be employed when to ensure that a country or study zone are disease-free, as in the case of bovine brucellosis in France (168). Normally, and usually more feasibility, a sub-group or sample of the total population will be investigated by the surveillance network.

6) **Data collection methods.** Surveillance can largely be split into two large groups: passive and active surveillance. Passive surveillance occurs when a structure sis put in

place which enables institutions or other actors to report disease data to public health authorities. Meanwhile, active surveillance requires an action from the public health authority or surveillance body to collect the required data. For instance, collecting ticks from domestic animals for LD surveillance could present either of the two types of surveillance (169). Firstly, if a treating veterinarian collects a tick from a dog during a consultation, they can send the tick to surveillance laboratories – this is passive surveillance. Meanwhile, public health authorities could decide to go out on the field, for example in a park, and collect ticks themselves from any dog passing by – this is active surveillance. Some surveillance systems can utilize both types of methods, active and passive, and are called mixed.

7) **Type of management.** Autonomous surveillance networks are established *de novo*; they have been developed independently from any other public health activities. Conversely, networks may arise due to need for evaluation or monitoring of a previously established public health intervention. These integrated surveillance networks are merged to these pre-existing activities. The Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) was established with the purpose of following resistance trends following implementation of judicious prescribing guidelines (170).

Table 5. Criteria established by Dufour & Audigé for the classification of surveillance systems (51)

Criteria No.	Criteria	Classification
1	Area of surveillance	Local; national; regional; international
2	Surveillance type	Focused/broad-based
3	Epidemiological situation	New / exotic / emerging / endemic disease
4	Population monitored	Suspect cases / susceptible individuals
5	Sampling strategy	Sample/exhaustive
6	Data collection methods	Passive/active/mixed
7	Type of management	Autonomous/integrated

4.2. A focus on sentinel surveillance

Sentinel surveillance is a specific subtype of surveillance. It refers to the use of a pre-selected sample(s) from the study population, chosen to be representative of particular groups of individuals, which are sampled repetitively through time (171).

Sentinels can be used to survey outcomes (i.e., disease cases) or risk factors (e.g., presence of vectors or detection of pathogens). Sentinels have been used in the context of infectious diseases, including sentinel animals for monitoring arboviruses. Sentinels can also include medical health clinics or physicians, reference laboratories, or sentinel sites where field activities, such as vector collection, are carried out. A well-designed and adapted sentinel network can successfully follow disease trends or act as an Early Warning System (EWS), permitting the early identification of outbreaks (171).

Advantages of sentinel surveillance includes limiting resources due to limited sampling costs as compared with broader surveillance strategies. A sentinel approach may be advantageous when dealing with sensitive issues such as human immunodeficiency virus (HIV), as the number of participants needed is reduced and there is the possibility of establishing a bond of trust through time (53, 172, 173).

Nonetheless, prior to implementing sentinel surveillance, its limitations must be taken into consideration. Firstly, sentinels are often selected by judgement or convenience sampling which introduces selection bias (53). Sentinel surveillance does not have the capacity to detect cases which occur outside the catchment areas of the sentinel units, and this reduces the chances of identifying presence of rare diseases (53). When data collection relies on a few select individuals (e.g., doctors, veterinarians, participants), presence of compliance or reporting bias should be evaluated (53, 174).

4.3. Surveying hazard and risk

Public health surveillance involves the ongoing, systematic collection, analysis, and interpretation of health-related data, allowing public health authorities to measure trends and characterize disease (175). In the case of infectious diseases, surveillance data can be used to monitor changes in risk of the disease within a population (175). The epidemiological term «

risk » is defined as the probability of an adverse event occurring (176). Thus, for a risk to exist, there must necessarily be presence of a **hazard** and an **exposure** to the former (formula 1). Here, **hazard** refers to the presence of a potential source of harm or danger, where danger is an element which could cause injury or an adverse effect (176).

Risk = hazard * exposure ***Formula 1.***

Depending upon the type of data collected within the surveillance system, the data can be an indicator of hazard or risk. For TBDs, active field surveillance of (infected) ticks would characterize hazard. Diuk-Wasser specifically refers to this measure as **enzootic hazard** (177). Although a potential source of harm is identified, the risk (probability of the adverse effect occurring i.e.., acquisition of LD) cannot be estimated as the exposure to the source of harm is unknown. Hence, the presence of a hazard does not automatically convey the presence of risk. For instance, if there is a high density of ticks in a particular woodlot, but no individuals visit the woodlot, although a hazard has been identified, there is limited risk to the human population.

For the risk to be estimated, the exposure (derived from the human-vector interface) must be known. Passive surveillance of ticks, when patients visit a medical or veterinary clinic after a tick bite and the tick is submitted for analysis, has been describe as a measure of risk of LD (178). A tick submission would entail a hazard (presence of infected ticks) and an exposure.

Other epidemiological definitions mention that risk is further modulated by an individual's **coping capacity** (sometimes referred to as vulnerability) (formula 2). This terms refers to an individual's response if they have been exposed to the hazard (179). An individual which has been bitten by a tick has been exposed to a hazard. The individual's intrinsic coping capacity will determine whether they will remove the tick prior to pathogen transmission and/or will seek prophylaxis or a medical treating if symptoms occur. Subsequently, passive reporting of LD cases englobes hazard, exposure, and coping capacity, and can be considered a measure of risk.

Risk = hazard * exposure * coping capacity ***Formula 2.***

4.4. Current surveillance strategies for Lyme disease in Canada

Due to the spread of *Ixodes* species and *B. burgdorferi* and the important health and economical impact that LD has on our populations, public health surveillance is a vital tool for monitoring the extent of the disease, to inform the public, and to put in place appropriate public health interventions. As mentioned in section 4.3. Surveying hazard and risk, surveillance data can be used as a measure of disease hazard and/or risk, and this concept can be applied for the surveillance of LD (**Figure 7**).

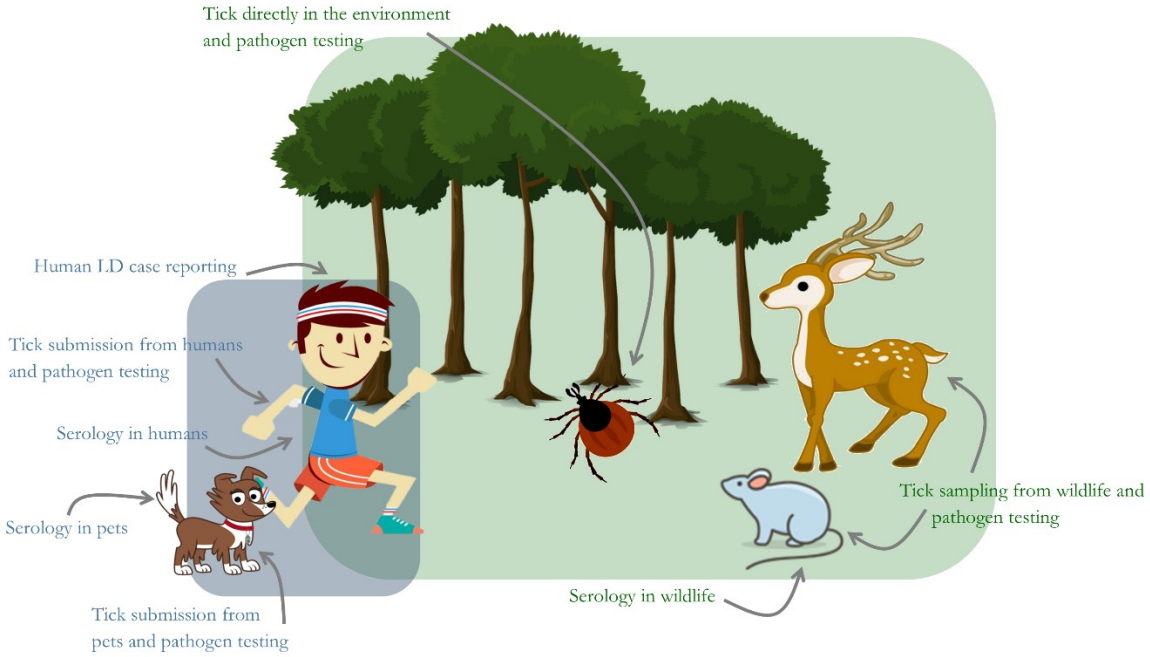

Figure 7. Approaches for surveillance of *I. scapularis, B. burgdorferi,* or Lyme disease cases; surveillance can be conducted in the environment to monitor hazard and presence of risk factors (green) or can be used to monitor disease incidence or risk of disease (blue)

Currently in Canada, there are three main ways in which surveillance data on LD or LD risk are gathered: through the reporting of human cases, analysis of ticks through the passive surveillance system, and analysis of ticks through active surveillance initiatives (57).

4.3.1. Human cases

As aforementioned, LD was added to the CNDSS list in 2009, and so, physicians have a legal obligation to report new diagnoses to their respective public health authorities. Physicians

should report both confirmed and probable cases (**Table 6**). The objective of this surveillance system is to keep track of the number of people infected with LD (180).

In Canada, the national case definition of a confirmed case of LD requires clinical evidence consistent with LD symptoms followed by a laboratory confirmation of exposure to *B. burgdorferi* (181). The lab confirmation is done through an isolation of *B. burgdorferi* from a clinical specimen or through detection of *B. burgdorferi* DNA by PCR on synovial fluid, cerebrospinal fluid, EM tissue or blood (104, 182). When the two-tiered test is used (ELISA followed by IB), the serological evidence is only confirmatory in patients with objective clinical signs of LD with a history of residence in, or a visit to, a LD risk area.

In the case of a positive serological test, with clinical evidence of illness but without a history of residence or visit to a LD risk area, the case is characterized as "probable". A probable case also corresponds to a patient with clinician-observed erythema migrans without laboratory evidence with a history of residence in or visit to a LD risk area (183, 184).

Table 6. Case definitions and classification (suspected, probable, confirmed) for Lyme disease in Canada (185)

Case classification	Case definition
Confirmed	Clinical evidence of illness with laboratory confirmation by one of the following methods: • isolation of *Borrelia burgdorferi* (*B. burgdorferi*) from a clinical specimen as specified by current guidelines • detection of *B. burgdorferi* DNA by PCR testing on synovial fluid, cerebrospinal fluid, EM tissue biopsies or blood and by methods specified by current guidelines OR Clinical evidence of illness with a history of residence in, or visit to, a Lyme disease risk area; and with laboratory evidence of infection in the form of a positive serologic test using the two-tiered approach
Probable	Clinical evidence of illness without a history of residence in, or visit to, a Lyme disease risk area; and with laboratory evidence of infection in the form of a positive serologic test as defined above under confirmed cases OR Clinician-observed erythema migrans without laboratory evidence but with history of residence in, or visit to, a Lyme disease risk area.

4.3.2. Passive surveillance of ticks

Passive tick surveillance was started in Canada in the 1990s, coordinated by federal public health laboratories with the support of provincial public health authorities (178). The objectives of passive surveillance are to identify areas where tick populations are emerging and where people are most at risk of getting LD (180). Passive tick surveillance involves submission of ticks found on humans or pets by medical and veterinary clinics (186). At the time of tick removal, information is gathered from the patient, including specification of the municipality where the tick was encountered.

During the analysis of ticks, the species is first identified at provincial Public Health Laboratories[4], including tick instar, stage of engorgement, host species. Any blacklegged ticks are later sent to the National Microbiology Laboratory (NML) for PCR studies to test for

[4] Some provinces will send tick specimens directly to the NML

infections with pathogens including *B. burgdorferi, B, miyamotoi, Babesia microti*, *Babesia odocoilei, Anaplasma phagocytophilum* and Powassan virus (187). The data from laboratory analyses and information form are kept in a centralized database at the NML.

Passive surveillance of ticks can provide a signal of tick presence in the environment. More specifically, those found of humans will give a direct measure of the tick-human interface, or exposure, in addition to providing an infection prevalence for pathogens (178, 186).

4.3.3. Active surveillance of ticks

For active surveillance of ticks, the most common methods include rodent capture and drag flannel sampling (103). Rodent capture involves setting traps to catch white-footed mice (*Peromyscus leucopus)* and other small mammals and removing the ticks attached to these animals. It is considered the gold standard for active surveillance for detecting established tick populations, however, requires important financial and time resources, in addition to trained staff (188). Thus, for larger scale surveillance activities, the drag flannel method is preferred.

Drag flannel sampling involves dragging horizontally a 1m x 1m ($1m^2$) sheet of flannel on the forest ground (**Figure 8**). Questing ticks in the environment will attach to the flannel. The flannel is checked at regular intervals, and any ticks present are removed with a pair of tweezers and placed in microtubes. The specimens can be analyzed, to identify tick species and to test for presence of pathogens.

Figure 8. Drag flannel sampling

In Canada, there are no coordinated active surveillance programmes for *Ixodes spp.* ticks. Rather, provincial public health authorities or academics have conducted independent surveillance studies when resources are available, in response to passive surveillance signals or pressure from citizens. The data are kept by the independent surveillance teams and are not centralized at the federal level; raw data is not always accessible to the public and often aggregated to create risk maps. Active surveillance effort will vary greatly between provinces:

- **British Columbia**

  Some active surveillance initiatives have been conducted by the BC Centre for Disease Control (BCCDC), the Centre of Coastal Health, and Vancouver Island Health Authority to investigate the presence of *B. burgdorferi* and other tick-borne pathogens (103). Active surveillance initiatives included both rodent capture and drag flannel sampling and were carried out between 2004 and 2015, mostly concentrated in Vancouver, the Okanagan, and Vancouver and Gulf Islands (189-191). Surveillance initiatives carried out by these organisations were mostly sporadic and not integrated into a specific surveillance programme. Results are available through published articles; both *I. pacififcus* and *I. agustus* during active surveillance e.g., during field activities in 2013, a total of 798 *I. pacificus* (14 adults, 235 nymphs, 549 larvae) and 36 *I. angustus* (4

adults, 12 nymphs, 20 larvae) were collected during rodent capture in the Vancouver area (191).

- **Alberta**

  The Government of Alberta have put in place the Enhanced Tick Surveillance Program, which carries out both active and passive surveillance (192). The program is a collaborative partnership between Alberta Health, Alberta Agriculture and Forestry, Alberta Health Services, Alberta Public Laboratories, and the First Nations and Inuit Health Branch (FNIHB). Active surveillance is centered around Edmonton, no *Ixodes* spp. ticks have been found as of 2021 (152, 193).

- **Saskatchewan**

  Active surveillance for blacklegged ticks has been conducted in Saskatchewan since 2009, with the number of surveys increasing in 2014, by the Government of Saskatchewan (146, 194). Despite several years of active sampling, no *Ixodes* spp. have been found within the province during these surveillance activities (194).

- **Manitoba**

  Active surveillance is conducted by Manitoba Health yearly, surveillance sites are chosen using passive surveillance data (147). Raw data from active surveillance is not available publicly, however Manitoba Health integrates data from active surveillance to create a risk map for LD (147).

- **Ontario**

  Public Health Ontario conduct active surveillance yearly, using passive surveillance data to identify priority areas for drag flannel sampling (195). Historically, small mammal trapping was also carried out, however discontinued to focus on timely identification of new risk areas and more effective monitoring of expanding risk areas. Raw data from active surveillance is not available publicly, however Public Health Ontario integrates data from active surveillance to create a risk map for LD (196).

- **Québec**

  The Institut National de Santé Publique du Québec (INSPQ), in collaboration with the Université de Montréal, conducts annual active surveillance for LD. This surveillance started in 2007, however has taken more amplitude since 2015 (150) (see section 4.3.4. Active surveillance in Québec). Raw data is aggregated at the provincial

level and published on the INSPQ's website, and data at the municipal scale is integrated into a risk map for LD (197).

- **New Brunswick**

  Active tick surveillance is New Brunswick is carried out during the summer months, by a collaboration between the Government of New Brunswick and the University of New Brunswick (198). Raw data from active surveillance is not available publicly, however the Government of New Brunswick integrates data from active surveillance to create a risk map for LD (199).

- **Nova Scotia**

  The PHAC has funded active surveillance in Nova Scotia historically from 2003 to 2012 when a total of 103 were surveyed, and again between 2016 and 2018 when a total of 22 sites were sampled. There are no ongoing active surveillance efforts that are carried out in the province. However, past active surveillance data have contributed fo the creation of LD risk maps for the province and *I. scapularis* populations are known to be widespread within the province (200).

- **Prince Edward Island (PEI)**

  There have not been previous active surveillance efforts carried out in PEI, either by academics or provincial public health authorities.

- **Newfoundland and Labrador (NL)**

  There have not been previous active surveillance efforts carried out in NL, either by academics or provincial public health authorities.

4.3.4. Active surveillance in Québec

As the first chapters of this thesis will explore active sentinel surveillance in Québec, a more detailed description of active surveillance initiatives already in place within the province is provided.

In Québec, active tick surveillance started in 2007 (150). The objectives of tick-based surveillance are to document the presence, abundance, and geographical distribution of *I. scapularis* in the territory of Quebec and to know their infection status with *B. burgdorferi* (57). Data is also incorporated in a risk map, produced yearly by the INSPQ to inform upon LD

within its territory and to indicate which municipalities are endemic. The following criteria are used to determine endemicity:

- three locally acquired human cases in the past 5 years, or
- ≥ 23 submissions of *I. scapularis* in passive tick surveillance from human patients, in the past 5 years, or
- three stages (larva, nymph, adult) or ≥ 6 specimens of the same stage of *I. scapularis*, collected in one year in active surveillance, of which ≥ 1 nymph or adult is *B. burgdorferi* positive.

Between 2007 and 2012, decentralized active surveillance efforts took place, initiated by different partners including the INSPQ and LSPQ, PHAC, the Ministère de la santé et des services sociaux (MSSS), the University of Montréal, and various public health directorates (Directions de santé publique: DSP). Initially, active surveillance was concentrated in the south of the province, in the region of Montérégie (**Figure 1**) and those adjacent (150).

From 2014, the INSPQ financed by the MSSS and in collaboration with the University of Montreal began a coordinated active acarological surveillance effort. Nine RSS were surveyed in 2014, increasing to 10 RSS from 2015 onwards (**Figure 1**). The objective of the surveillance system is to confirm presence of *I. scapularis* and to identify endemicity of LD at the municipal scale. By combining the data from active acarological surveillance and passive surveillance (acarological, human cases), an integrated surveillance system is produced (55). Risk maps for the south of the province are created using these multiple sources of data (181). The *Groupe d'experts sur les maladies transmises par les tiques* is a panel of experts in tick-borne diseases (TBDs) which was put in place by the INSPQ to advise on public health matters regarding TBD and is responsible for the elaboration of Québec's surveillance strategy.

Acarological surveillance is conducted yearly using drag flannel sampling. From 2015, a dual approach active surveillance plan was created as prescribed by the *Groupe d'experts sur les maladies transmises par les tiques*. The active surveillance plan consisted of:

1) **Sentinel tick surveillance**. Sentinel sites are sampling parcels that stay the same through time and are visited twice every year. They were chosen by the group of experts to be geographically representative of the RSS; two sites were chosen in each of the 10 RSS part of the surveillance system, except for Montreal where 3 sites were

chosen (P.A. Leighton, personal communication). Other criteria included ecological suitability for *I. scapularis* presence (i.e., deciduous or mixed forests) and using parks with a high volume of visitors. The aim of these sites is to give a longitudinal portrait of tick presence and they have been the same since 2015. Data generated from these sites remains to be evaluated to determine if the sentinel tick-based surveillance system is maintained as is or modified to better meet surveillance objectives.

2) **Risk-based tick surveillance.** The second type of sites visited during sampling season were chosen using a risk-based site selection algorithm developed by the INSPQ (unpublished). The aim of these sites is to determine whether a municipality meets the criteria for endemicity for LD[5] and to identify an established tick population in areas where their establishment was expected e.g., from passive tick surveillance data (169, 197). These sites are known as "secondary sites" (however, within the chapters of this thesis, will be called "accessory sites"). They are visited once during the summer and change year to year according to surveillance data and risk signal as determined by the algorithm.

   The criteria incorporated into the site selection algorithm include (57):

   - Indication of the presence of *I. scapularis* ticks by human or acarological surveillance data,
   - Regional priorities,
   - High number citizens visiting the park (for human exposure to ticks),
   - Peri-urban environment (which may reflect human use),
   - Park size (to meet collection protocol),
   - Habitat suitability for the establishment of *I. scapularis* ticks,
   - Accessibility and organizational constraints.

The site selection algorithm has been subject to change over time, and these changes are not documented in the literature. Although the algorithm is based on previous studies conducted in Canada (169), the site selection process has never been validated, to evaluate whether the

[5] The INSPQ has developped a series of criteria based on LD case reporting, passive tick surveillance, and active tick surveillance to identify municipalities as endemic for LD (167, 195)

retained sites meet surveillance objectives. As of yet, although data from both types of sites, sentinel and accessory, are used in surveillance reports, they have not been subject to formal statistical and epidemiological analyses. Thus, the ability of Québec's active surveillance system to track spatiotemporal LD risk remains to be assessed, and both types of site selection methods should be compared analytically to determine which method best represents LD occurrence.

4.3.5. Strength and weaknesses of current surveillance

To ensure an effective surveillance strategy for LD, the respective strengths and weaknesses of each type of surveillance activity should be evaluated.

1) LD case reporting

LD case reporting is done across Canada to keep track of the number of people infected with LD. As there is a nationwide case definition, case reporting is standardized across the country. It is worth acknowledging that case reporting can be subject to under-ascertainment, where cases do not seek health care and underreporting, where a case visits a healthcare professional, but the case is not reported (35, 53). Under-ascertainment can result from unequal geographical distribution of, and access to, healthcare, asymptomatic carrier states, unawareness of the disease amongst the general population, different attitude towards medical consultations due to experience, location, and socio-economical characteristics, or cases not consulting healthcare services e.g., they cannot take time off work, cannot afford medical services, or feel that their illness does not warrant medical attention. Meanwhile, underreporting can result if a patient is not visibly ill when consulting a doctor, if a patient has two or more reportable conditions, but only one of these is reported, or if the doctor forgets to report the case (53). Ogden *et al.* (201) have conducted a study which concludes that a high degree of underestimation (underreporting and under-ascertainment) of LD cases in Canada is unlikely, emphasizing another strength of this surveillance approach. Overall, human case reporting may be thought of as a specific signal for LD emergence.

Amongst the main limitations, human case reporting may be subject to lack of geographic and temporal precision. It may take weeks before symptoms begin and as only 50% of adult cases

remember that they had been bitten by a tick, it is not always possible to establish with certainty in which municipality LD was acquired (201). Case reporting occurs late in the process of disease emergence; by the time first cases of reported, *B. burgdoferi* may be widely established in the environment. A recent example illustrating this phenomenon is the anaplasmosis outbreak seen in the Estrie region in the province of Québec during the summer of 2021: field studies showed that *Anaplasma phagocytophilum* had increased significantly within its ecological niche at the time of this outbreak (202). Thus, using human case reporting has limited capacity to act as an effective EWS and in the context of this outbreak, animal cases were reported earlier than human cases.

2) Passive tick surveillance

Passive tick surveillance (described in section 4.3.2. Passive surveillance of ticks) is used to identify areas where tick populations are emerging and where people are most at risk of getting LD. It has been associated closely with risk of LD in human populations and has been shown to provide an early signal for emerging risk (169, 178). Hence, the number of tick submissions, standardized by the population size, provides a measure of enzootic hazard that correlates with LD risk.

An important limitation of passive tick surveillance is that it requires a human population large enough to find and submit ticks (178). Furthermore, it has low sensitivity in the context of emerging tick populations, as tick densities are very low and it will impact the ability of passive tick surveillance to detect the presence of an established population of ticks (178). Specificity, where passive surveillance is used to discriminate whether there is an established population of ticks within a geographical area, can be hindered by finding adventitious ticks, (178, 203). Passive tick surveillance is resource-intensive, due to the need for laboratory confirmation of the tick species and PCR analysis of the specimens. With the growing presence of tick populations in Canada, the program was reduced over the years. From 2009, cutbacks were seen in the analysis of ticks coming from veterinary patients e.g., specimens were no longer routinely analyzed through the passive surveillance system when originating from Montérégie (57). Thereafter, from 2014, all submissions from regions of high prevalence (**Table 7**) were no longer accepted. Very recently, in the summer of 2022, the acarological passive surveillance system was suspended, as the costs were considered to outweigh the benefits of maintaining

the system. Therefore, due to these changes, comparability of surveillance data across recent years is hindered.

Table 7. Health unit where passive acarological surveillance was discontinued in the province of Québec

Health unit	Province	Year discontinued
Haute-Yamaska	Québec	2014
La Pommeraie	Québec	2014
Le Suroît	Québec	2014
Haut St-Laurent	Québec	2014
Kingston, Frontenac, Lennox, Addington (KFL)	Ontario	2014
Eastern Ontario (EOH)	Ontario	2014
Leeds, Greenville, Lanark (LGL)	Ontario	2014
All health units	Ontario	2020

3) Active surveillance of ticks

Active surveillance can identify established tick population with high geographic specificity (178) and can provide an uninfluenced measure of tick densities across time when other surveillance measures may be impacted by human behaviour. For instance, during the summer of 2020, public health restrictions and avoidance of healthcare services may have had an impact on passive tick submissions and case reporting.

Active surveillance activities, such as drag flannel, are resource intensive (178). They require the presence of a team of trained field agents, who travel across a (often large) surveillance zone to complete the fieldwork. Specimens collected during active surveillance must be analyzed by laboratories to determine pathogen prevalence. If the surveillance area is very large, e.g., Québec or Canada, the sampling parcels must be carefully chosen to meet surveillance objectives. Furthermore, the sensitivity and accuracy[6] of active surveillance by drag flannel sampling is impacted by several factors, such as temperature (which dictates the questing behaviour of ticks), rainfall (the flannel can become wet if it rains or the ground is wet, preventing ticks from attaching themselves tto the fabric) and field agent experience (204).

[6] Sensitivity is impacted as sites may be considered « tick-free » by drag sampling, when ticks are present; accuracy may also be impacted as tick densities measured during sampling may vary according to sampling conditions

In Canada, there is no coordinated and standardized effort for active LD surveillance. In their framework, Clow *et al.* (56) have stressed that standardization is one of the four fundamental aspects which should be integrated in the planning of a surveillance programme for TBD, including inclusivity, comprehensibility, and sustainability (see section 4.5. Developing a sustainable Lyme disease surveillance network).

For several provinces, decentralized data storage means that it is not possible (or very difficult) to find the number of visits which were carried out across time or precise sampling locations. Thus, comparing enzootic hazard across the country is very tedious, especially due to several other factors that may have an impact on results. Firstly, sampling effort and protocols vary greatly between provinces. For instance, the number of sites sampled during the field season is not consistent across provinces: up to 120 sites are visited by the INSPQ in Québec, about 25 sites in Saskatchewan, and 0-5 sites are be visited in Alberta. Some provinces, such as Ontario, use time as the effort measure, whilst others, such as Québec, will use a distance measure (169, 195). The timing of active surveillance visits differs; whilst some provinces only go out in the summer, others will also target the autumn. Due to the seasonal phenology of ticks, this has a direct impact of tick density interpretation. Furthermore, the selection of sampling sites is done differently in each province; usually, provincial public health authorities will develop their own indicators (e.g., based on passive surveillance data) to decide on which areas to target. For all these reasons, comparability of tick densities measured through these independent sampling efforts is hindered. The use of standardized protocols could be of greater utility for data sharing and analysis.

4.5. Developing a sustainable Lyme disease surveillance network

As LD remains a VBD of major public health concern in Canada (17), it becomes crucial to develop a sustainable surveillance network. As aforementioned, case reporting provides a standardized, centralized, and comparable surveillance measure (56). However, it may not be the earliest signal of disease emergence. Meanwhile, passive surveillance has been shown to have the ability to provide an early warning signal but has become unsustainable in the long term due to the volume of tick submissions, surpassing laboratory capacities. It may become replaced by new technologies, such as eTick, an online app that allows tick species identification by photograph (205). Although such a technology could identify the

establishment of tick populations in new geographic areas, this remains to be validated. To test for *B. burgdorferi* prevalence and for the emergence of new and rarer pathogens e.g., Powassan virus, *A. phagocytophilum*, specimens must be forwarded to the laboratory, which could result in similar limitations to traditional passive acarological surveillance. Finally, active surveillance has high specificity for identifying tick population establishment and the enzootic hazard measure derived from field visits is not dependent on human behavior. Specimens collected through active surveillance can be tested for *B. burgdorferi* and other pathogens of public health importance. However, it remains very resource intensive and cannot be used to survey in depth large study areas.

The difficulty associated with active surveillance, including lack of a standardized protocol across Canada and significant efforts required to survey a large study zone, could be addressed by sentinel surveillance (see section 4.2. A focus on sentinel surveillance). Hence, a sentinel approach to active surveillance could meet the four fundamental aspects of a surveillance programme for TBD (56):

1) **Inclusivity**: A coordinated active tick surveillance effort will require actors from each province to ensure that fieldwork is carried out at the appropriate time; their input will ensure that the surveillance network is adapted to their epidemiological context
2) **Standardization**: A standardized sampling protocol can be developed with collaboration of stakeholders and a centralized database can provide easy access to the data
3) **Comprehensibility**: Tick specimens collected through active surveillance can be tested for other pathogens of public health significance, to provide a comprehensive surveillance programme. The standardized and comparable data collected through sentinel surveillance could be integrated to data coming from other types of surveillance, including passive surveillance.
4) **Sustainability**: By targeting areas of scientific interest, in the context of LD, surveillance efforts are focused and limited to a subset of geographically constrained sampling units, which can mean a sustainable active surveillance network across Canada. As the number of specimens collected through sentinel surveillance would be significantly lower than those submitted by passive surveillance, analysis of specimens remains feasible. If the number of ticks collected through active surveillance becomes

too high, a subset of the specimens can be analyzed to obtain an estimate of the infection prevalence at the sampling site.

Overview of the literature review

This literature review has provided the groundwork to understand the importance of LD to human population in North America and in Canada. The transmission cycle of LD, including the interactions between *B. burgdorferi*, *Ixodes* spp. ticks, animal hosts, and humans, has been explained to illustrate how the disease spreads geographically and which elements are necessary for its emergence. Once these elements have been explored, it is possible to assess the requirements for successful surveillance and balance the strengths and limitations of current surveillance strategies. To overcome limitations, sentinel surveillance, which is the focus of this thesis, has been proposed as a solution.

Chapter I: Quality over quantity in active tick surveillance: sentinel surveillance outperforms risk-based surveillance for tracking tick-borne disease emergence in southern Canada

Abstract

Lyme disease has been emerging in southern Quebec since the start of the century, with many municipalities now endemic. An active tick surveillance programme has been in place in the province of Quebec, which consists of a limited number of "sentinel" field sites resampled each year and a larger set of "accessory" field sites that change yearly according to Lyme disease case surveillance signals. We aimed to evaluate whether a sentinel approach to active surveillance was more representative of Lyme disease risk to human populations, compared to risk-based surveillance. We compared enzootic hazard measures (average nymph densities) from sentinel and accessory sites with Lyme disease risk (number of Lyme disease cases) across the study area between 2015 and 2019 using local bivariate Moran's I analysis. Hazard measures from sentinel sites were observed to capture spatial risks significantly better than data from accessory sites (χ^2=20.473, p <0.001). In addition, sentinel sites successfully tracked the interannual trend in Lyme diseases case numbers, whereas accessory sites showed no association despite the larger sample size. Where tick surveillance aims to document changes in tick-borne disease risk over time and space, we suggest that repeated sampling of carefully selected field sites may be most effective, while risk-based surveillance may be more usefully applied to confirm the presence of emerging disease risk in a specific region of interest or to identify suitable sites for long-term monitoring as Lyme disease and other tick-borne diseases continue to emerge.

Introduction

Lyme disease (LD) is a tick-borne disease that has been emerging in southern Canada over the past three decades. *Ixodes scapularis* is the vector of *Borrelia burgdorferi* sensu stricto, agent of LD, east of the Rocky Mountains (1, 2). Populations of *I. scapularis* ticks first established in the

north-eastern and mid-western United States have expanded their geographic distribution northward via migratory birds to invade southern Canada (3) with the first established populations appearing in Manitoba, Ontario, Quebec and Nova Scotia (4). In response to this emerging health threat, public health authorities require effective surveillance systems to monitor the emerging risk of LD.

Active acarological surveillance, where forested field sites are sampled to collect questing ticks in the environment, is commonly used to assess enzootic hazard for LD (5). Active surveillance usually consists of drag sampling, where a piece of white flannel cloth is dragged across the forest floor such that questing ticks cling to the passing fabric, allowing them to be collected and analyzed. From such field studies, enzootic hazard is calculated as the density of nymphal ticks (DON), or often density of infected nymphs (DIN) (6, 7). DON and DIN have both been associated with LD risk in different studies in North America (8-11). Although some studies have evaluated the association between enzootic hazard and LD risk in the south of Canada where LD is in emergence, it is worth re-evaluating this link as the epidemiological portrait continues to evolve (10, 12). In addition, as increasingly large regions of southern Canada need to be surveyed as *Ixodes* spp. continue to increase their geographic range, there is a growing need to adapt active surveillance approaches in order to ensure their sustainability and relevance within the evolving epidemiological context (13).

Due to complex ecological requirements, tick population tend to expand their geographical range heterogeneously in space (14, 15). To reflect this, active surveillance systems must be able to capture this spatially heterogenous LD risk pattern across a region. Some provincial public health authorities have developed risk-based criteria, based on indication of *I. scapularis* presence ticks by human or acarological surveillance data, to decide which rotating sites to target, whilst others visit the same fixed sites through time (16-18). Currently, it is not known which of these approaches best represents LD risk in space and over time.

Amongst the ten provinces in Canada, Quebec is the province with the third highest number of reported LD cases (19, 20). Quebec is the largest and second most populated province in Canada, with a total population of nearly 8.5 million (21). Most of the population resides in the south of the province, where the highest *I. scapularis* tick densities occur. In the past five years, the number of human LD cases has more than tripled, an increase that is consistent with expanding geographic distribution of *I. scapularis* in the south of Canada (22).

Active tick surveillance has been carried out in southern Quebec since 2007, with a coordinated provincial surveillance system established in 2014 led by the Institut national de santé publique du Québec (INSPQ) in collaboration with the Université de Montréal (18, 23). From 2015-2019, active surveillance was carried out at two types of field sites: "sentinel" sites which are kept constant through time and are visited every year, and "accessory" sites which change every field season and are selected through a risk-based algorithm (24). These two types of sites were intended to serve different objectives within the surveillance program, with sentinel sites designed to provide a geographically representative surveillance signal allowing risk to be compared among regions and over time, and accessory sites selected each year to confirm the risk status of areas where LD was thought to be emerging. Sentinel surveillance was initiated in 2015 based on the hypothesis that repeated sampling of a small number of carefully selected sites could provide a more representative portrait of evolving LD risk i.e., LD incidence at the provincial scale than annual risk-based surveillance. In addition, sentinel surveillance has a number of important logistical advantages, including reduced annual effort for site selection and lower overall sampling efforts. However, the spatial and temporal representativity of sentinel versus risk-based surveillance have yet to be formally compared.

In this study, we analyze LD active tick surveillance data (density of nymphs) collected over a 5-year period (2015-2019) to test the hypothesis that sentinel tick surveillance provides a more representative signal of LD risk (LD incidence) in space and time than a risk-based approach, in the epidemiological context of pre-emerging/emerging LD risk in southern Quebec. By comparing the associations with Pearson correlations and local bivariate Moran's I between LD risk (human LD cases) and hazard measures derived by each type of active tick surveillance (i.e. sentinel versus risk-based), we demonstrate that sentinel surveillance provides a more reliable and representative portrait of emerging LD risk in this context.

Methods

Study Site

The province of Quebec is in the east of Canada, located between the provinces of Ontario and New Brunswick. The ten most southern administrative regions of the province encompass the emergence zone for *Ixodes scapularis* are targeted annually by the INSPQ for active surveillance initiatives (**Figure 9**). This study will examine data collected from 2015 to 2019 by active surveillance of LD on this study zone.

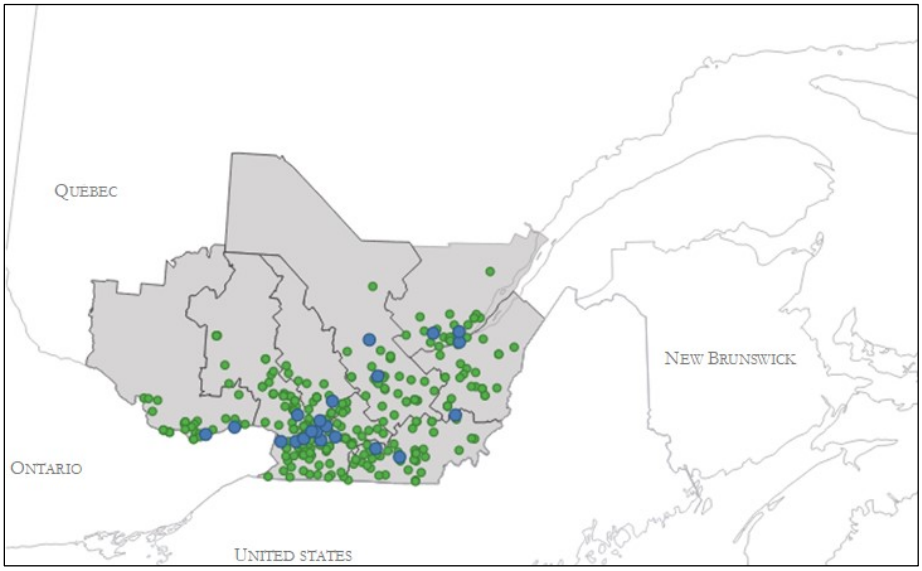

Figure 9. The ten most southern administrative regions in the province of Quebec, constituting the active tick surveillance zone targeted by the provincial Lyme disease surveillance program. Blue dots represent sentinel tick collection site locations, with two sites per region, except the Montreal region with three sites. The green dots represent accessory tick collection sites sampled during the study period from 2015 to 2019.

Active tick surveillance in Quebec

A network of 21 sentinel sites for the active tick surveillance was designed by the Quebec Tick-Borne Disease Expert Panel (*Groupe d'expert sur les maladies transmises par les tiques*), a panel formed by public health authorities, laboratory experts, scientific and medical advisors, and epidemiologists. Two sentinel sites were chosen per administrative region, except in Montreal where three sites were selected (**Figure 9**) (25). The sites were placed in provincial or regional parks that were readily accessible to the public, with suitable habitat for the establishment of

I. scapularis, and located in geographically distinct areas of the administrative region (18). These sentinel sites have remained the same through time and are usually visited twice during the field season (May-August); the first time in early June, followed by a second visit at least two weeks later. Sites where *B. burgdorferi* s.s. is documented to be enzootic (one site in Montérégie and another in Estrie) are only visited once. Occasionally, other sites were only visited once per season due to logistical constraints e.g., park closure.

In addition to the network of sentinel sites, 60-80 accessory sites are sampled once per field season. Accessory sites are selected according to the LD risk signal, generated from past passive and active acarological surveillance data and reported human cases.

Drag sampling methods for sentinel and accessory sites

A standardized drag sampling protocol is carried out during each site visit, in both sentinel and accessory sites. Two field technicians drag a $1m^2$ piece of white flannel cloth along two parallel transects: the first in the vegetation along the edge of a public footpath, and the second located in the forest 25m from the path. Each team member samples $1000m^2$ for total area sampled of $2000m^2$ per site. Presence of ticks on the cloth is checked every 25m, and collected ticks are stored in 70% ethanol tubes. Subsequently, ticks are classified by species at the Quebec Public Health Laboratory (Laboratoire de Santé Publique du Québec: LSPQ). The LSPQ will forward all *Ixodes spp.* specimens to the National Microbiology Laboratory for pathogen testing (*B. burgdorferi, B. miyamotoi, A. phagocytophilum, B. microti,* Powassan virus).

Statistical analyses

Enzootic hazard (DON) estimated from active surveillance

Enzootic hazard was calculated as density of nymphs (DON), in the form of *I. scap* nymphs / $100m^2$, as done in previous studies (24). Due to their small size, nymphs represent greater hazard to humans as they are likely to be missed during self-examination (26). As tick densities are relatively low in southern Quebec, we decided not to use Density of infected nymphs (DIN) which may not be representative due to small samples of collected ticks.

Using seasonality models of *I. scapularis* phenology in southern Quebec, we estimated nymph densities for a reference date of the 15th of June (27)[7]. Firstly, nymph densities were obtained by using the predict() function in R to calculate the predicted nymph density during 1) the reference date and 2) the actual sampling date according to seasonality models. The percentage change was determined between the two time points and used to adjust measured nymph densities, to correct for tick phenology. This allowed us to correct for temporal variability in nymph densities due to site visits occurring at different periods of the tick life cycle. We used these estimated nymph densities to compute the mean density per site across the study period. The data were georeferenced using the start location of the surveillance transect.

DON measured annually at sentinel sites and accessory sites were interpolated across the study zone to generate hazard maps based on each type of surveillance, respectively. Interpolation was done using a Kernel density estimation in QGIS version 3.18 Zurich. A distance of 80 kilometers was used as the radius of interpolation, as correlograms revealed spatial dependency of active surveillance data up to this distance (24, 28). The resulting hazard maps were used to assign an estimated value of DON based on sentinel surveillance and risk-based surveillance to each municipality across the study zone.

Temporal association between enzootic hazard (DON) and LD risk (number of Lyme disease cases)

To assess the association between enzootic hazard (average nymph density across the study zone derived from interpolated surfaces) and LD risk (number of human LD cases across the study zone reported through national LD surveillance) across the study period, Pearson correlations between these two variables were tested using R version 4.0.4 (29). The estimated DON mathematically adjusted for phenology was calculated at sentinel and accessory sites as described in the previous section. The resulting average nymph density derived from all sentinel or accessory sites in the same year was then correlated with total human cases reported that year.

Spatial association between enzootic hazard and LD risk across municipalities

[7] See (27) for full model details

Bivariate local Moran's I analyses were perfomred using GeoDa 1.18.0 to determine the spatial association between enzootic hazard and LD risk. Risk was represented by the number of LD cases standardized by the logarithm of human population across the 5-year study period at the municipal scale. Bivariate local Moran's I can capture the relationship between a value of one variable in space, and the average neighboring values for another variables (30). GeoDa creates cluster maps, that determine if the spatial association between the variables is significant or not across the municipalities. If significant, the maps indicates if 1) both variables represent "high" values, 2) both represent "low" values, or 3) one variable is a "high" value while the second is a "low" value. Furthermore, some municipalities may remain "undefined" if they do not have an attributed value of either one of the variables or may be "neighborless" if adjacent polygons are missing data.

The results from the Moran's I analyses were transcribed into a contingency table. From the contingency table, we were able to calculate if hazard measures are positively associated with risk (i.e., both risk and hazard are low or high), or if they diverged (i.e., risk is high whilst that hazard is low, or vice versa), for sentinel and accessory site hazard measures. Chi square tests were performed to evaluate significant statistical differences in hazard-risk associations between site types.

Results

Active surveillance

A total of 207 site visits across 21 sentinel sites were conducted between 2015 and 2019: 38 (2015), 45 (2016), 43 (2017), 39 (2018), and 42 (2019). A total of 346 visits were carried out over the same period across 264 accessory sites: 47 (2015); 104 (2016); 55 (2017), 65 (2018) and 75 (2019). Average nymph density across the study period was 0.13 (95% CI: 0.10-0.16) nymphs/100m^2 at sentinel sites and 0.08 (95% CI: 0.07-0.11) nymphs/100m^2 at accessory sites.

Sentinel sites identified the regions of Montérégie, Estrie and Outaouais as having the highest density of nymphs (**Table 8**), whereas accessory sites identified Outaouais followed by Montérégie. It is worth noting that for accessory sites in Mauricie-et-Centre-du-Québec, high

average nymph density in 2016 was due to a single site where 2.17 nymphs / 100m^2 were recorded.

Table 8. Average nymph densities with 95% confidence intervals across the study period, from 2015 to 2019, for sentinel and accessory sites across the ten administrative regions of the active surveillance system for Lyme disease in the province of Quebec, Canada

Admin region	Year 2015	2016	2017	2018	2019	Average
Sentinel sites						
CN	0	0	0	0	0	0
MC	**0.02** (0-0.05)	**0.01** (0-0.03)	0	0	0	**0.01** (0.-0.01)
ES	**0.74** (0-1.47)	**0.22** (0-0.43)	**0.27** (0-0.53)	**0.05** (0-0.1)	**0.05** (0-0.1)	**0.23** (0.11-0.35)
MT	**0.02** (0-0.05)	**0.05** (0-0.1)	**0.25** (0.09-0.41)	0	**0.1** (0.02-0.18)	**0.09** (0.05-0.14)
OU	**0.13** (0.09-0.17)	**0.06** (0.02-0.1)	**0.20** (0.15-0.25)	**0.03** (0.01-0.04)	**0.85** (0.3-1.4)	**0.20** (0.10-0.30)
CA	0	0	0	0	0	0
LV	**0.02** (0-0.05)	**0.01** (0-0.03)	**0.01** (0-0.03)	**0.03** (0-0.05)	**0.05** (0.01-0.09)	**0.02** (0.01-0.04)
LN	0	0	**0.02** (0-0.03)	0	0	**0.005** (0-0.01)
LA	**0.04** (0-0.08)	**0.04** (0.01-0.06)	**0.11** (0.05-0.18)	0	**0.02** (0-0.03)	**0.05** (0.03-0.06)
MR	**0.45** (0.02-0.88)	**0.38** (0.14-0.62)	**1.23** (0.55-1.90)	**0.47**(0-0.93)	**0.05** (0-0.1)	**0.57** (0.36-0.77)
Accessory sites						
CN	0	0	0	**0.05** (0-0.1)	**0.01** (0-0.02)	**0.01** (0-0.02)
MC	0	**0.54** (0-1.09)	0	**0.01** (02-0.01)	0	**0.06** (0-0.13)
ES	**0.01** (0-0.02)	0	**0.2** (0.05-0.35)	0	**0.02** (0.01-0.04)	**0.02** (0.01-0.04)
MT	0	0	**0.06** (0-0.13)	0	0	**0.02** (0-0.03)
OU	0	**0.35** (0.13-0.57)	**0.81** (0.28-1.36)	0	0	**0.31** (0.31-0.49)
CA	0	0	0	0	**0.01** (0-0.01)	**0.002** (0-0.004)
LV	**0.01** (0-0.02)	0	**0.06** (0-0.12)	0	0	**0.02** (0-0.04)

LN	0	0	**0.12** (0.01-0.23)	0	**0.12** (0.001-0.25)	**0.05** (0.02-0.09)
LA	0	**0.002** (0-0.003)	0	0	**0.03** (0.01-0.05)	**0.005** (0-00.008)
MR	**0.02** (0-0.04)	**0.37** (0.28-0.46)	**0.05** (0.01-0.08)	**0.01** (0-0.01)	**0.01** (0.01-0.02)	**0.19** (0.14-0.24)

Legend: CN: Capitale-Nationale; MC: Mauricie-et-Cemtre-du-Québec; ES : Estrie; MT : Montreal; OU : Outaouais; CA : Chaudières-Appalaches; LV : Laval; LN : Lanaudière; La : Laurentides; MR : Montérégie

Color code: No color: no nymphs found; light red: average nymph density between 0.01-0.20; dark red: average nymph density >0.20

These densities were subsequently adjusted using seasonality model to account for tick phenology prior to using the data for further analysis (**Figure 10**).

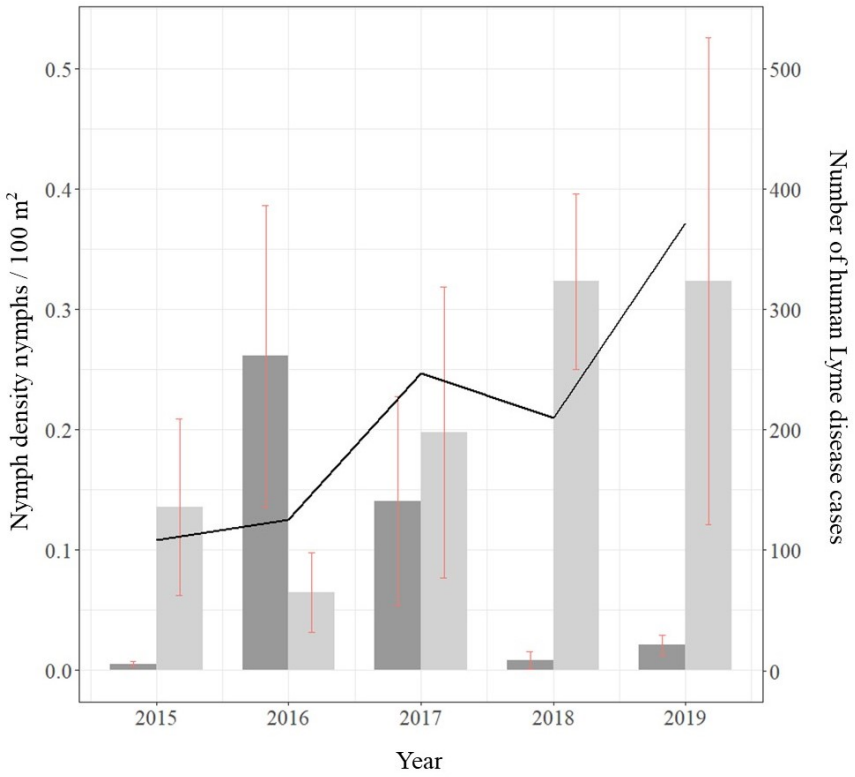

Figure 10. Average predicted nymph density (/100m²) with standard errors at the provincial level in Québec, Canada, from 2015 to 2019 . These were calculated using seasonality models for estimated densities on the 15th of June, derived from sentinel site data (light grey bar) and accessory site data (dark grey bar) and compared with the number of human Lyme disease cases in Québec (black line)

Statistical analyses

1. Temporal trends

Correlation between enzootic hazard (average nymph density) and LD risk (number of human cases) showed a positive association (r = 0.88; 95% CI: -0.02 – 0.99) for data obtained from sentinel sites. This association was found weakly significant by Pearson's correlation test (p=0.05). Meanwhile, for data collected from accessory sites, the correlation between enzootic hazard and LD risk was negative (r = -0.32; 95% CI: -0.937 – 0.784) and not significant (p=0.60).

2. Spatial trends

Interpolated data at the municipal level across Québec were used in local bivariate Moran's I to see if nymph densities collected during active surveillance methods were associated with the the degree of LD risk (number of human cases / logarithm of the population) (**Figure 11**). The cluster maps show whether there is significant spatial association between these two variables. Accessory site data had a greater proportion of non-significant classifications (n=490, 46.4%) compared to sentinel site data (n=348, 33.0%) (**Table 9**). Limited number of sampling sites during active surveillance meant that some of the study zone was undefined or neighborless in the analyses, as no data was collected in these areas to incorporate within the analysis.

Within significant associations, some showed positive associations (both variables either « high » or « low ») whilst others showed negative associations (one variable was « high » whilst the other was « low »). In the context of surveillance, positive associations between active surveillance and LD risk suggest reliability of active surveillance sites. In these analyses, sentinel sites showed positive association with LD risk for 388 (36.8%) municipalities, whereas accessory sites showed positive association with LD risk for 302 (28.6%). The proportion of positive vs. negative associations was significantly higher for sentinel vs. accessory sites (χ^2=20.473, p <0.001).

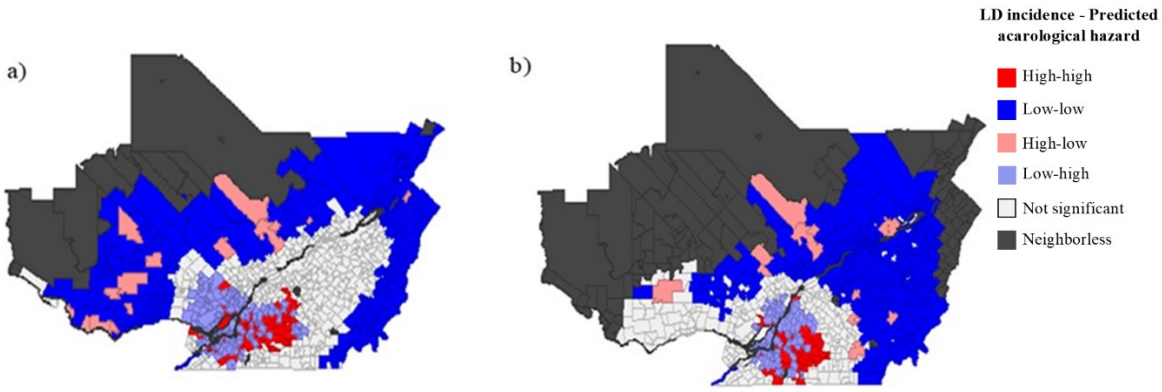

Figure 11. Cluster maps derived from local bivariate Moran's I comparing the relationship between human Lyme disease incidence with a) interpolated active tick surveillance data from sentinel sites and b) interpolated active tick surveillance data from accessory sites.

Table 9. Outcome of local bivariate Moran's I for human cases data compared with active surveillance data from sentinel and accessory sites

Local bivariate Moran's I outcome	Sentinel	Accessory
Not significant	348	490
High-High	44	53
Low-low	344	249
Low-High	124	181
High-Low	13	15
Neighborless	17	22
Undefined	165	45
Totals		
Positive association	388	302
Negative association	137	196

Discussion

This paper demonstrates how active tick surveillance at a limited number of high-quality sentinel sites can contribute to following spatiotemporal LD risk trends in a context of emerging disease over a 5-year period. In contrast, roughly twice the number of site visits carried out at accessory sites during this same period using a risk-based approach provided a less accurate geographic portrait of emerging risk and failed to capture the steep increase in human cases over time, even suggesting that risk had decreased rather than increased over the study period. Sentinel and risk-based surveillance provide complementary information and serve different purposes within a surveillance system; this study demonstrates that the analysis and interpretation of the resulting surveillance data should take these differences into account. Specifically, where surveillance aims to document changes in tick-borne disease risk over time and space, we suggest that repeated sampling of carefully selected field sites may be most effective, while risk-based surveillance may be more usefully applied to confirm the presence

of emerging disease risk in a specific region of interest or to identify suitable sites for long-term monitoring as LD and other tick-borne diseases continue to emerge.

In our analyses we used enzootic hazard measures, in the form of nymph density collected at sentinel and accessory sites, to track the temporal trend in LD risk between 2015 and 2019. A Pearson correlation test at the provincial level demonstrated that average nymph density calculated from sentinel sites was positivity correlated with LD risk (number of human LD cases), compared with average nymph density calculated from accessory sites where no significant correlation was found. As accessory sites change yearly, average nymph densities will not only account for interannual variation, but also the heterogeneous spatial distribution of tick populations that make the yearly variation more difficult to interpret. However, in previous research we noted that a positive association between nymph densities from sentinel sites and annual human cases was not always evident at the regional scale, e.g., in the Estrie region (24). It would be interesting to explore the reasons for regional variation in this relationship; for instance, it is possible that the sentinel sites chosen in Estrie were not adequate and representative sampling subunits. In the meantime, we suggest that average nymph density calculated from sentinel sites at a broader scale may be more robust and informative for evaluating interannual variation in LD risk.

The spatial relationship between enzootic hazard and LD risk was more reliably represented by sentinel sites compared to accessory sites, but both were weak predictors. Several factors, which have not been measured in our study, could contribution to this weak association. Firstly, human movement could contribute to the negative relationship between DON and LD risk if people are exposed to ticks outside of their municipality of residence (31). Although LD human reporting includes probably place of exposure, it can be challenging to ensure its accuracy. Another challenge in these analyses is the use of spatial scale. Pepin et al., showed that the type of landuse may affect the relationship between acarological hazard measures and LD incidence. For instance, analysis at the larger scale may be appropriate for municipalities with large forest cover, whilst that urban municipalities with dispersed forest cover may be better suited to finer scale analyses.

For both analyses, interpolation was used to permit representation of enzootic hazard across the full extent of the study zone. This could bring about an information bias, as the interpolating will not capture the fine-scale spatial heterogeneity of tick population

establishment. It is thus important to consider that sentinel surveillance provides a general risk indicator to follow spatiotemporal trends, whereas the targeted information derived from risk-based surveillance strategies may be more appropriate for confirming the establishment of endemic LD risk at the municipal scale (13). Areas where risk was not well captured by sentinel surveillance e.g., the North shore of Montreal (**Figure 11**) could subsequently be surveyed using an exploratory approach; risk-based surveillance (accessory sites) can be added to the surveillance strategy and the most informative sites retained as part of the sentinel system. While we show that two sentinel sites per administrative region were capable to capture broad-scale trends in LD risk, increasing the number of sentinel sites per region would be useful in allowing better geographic representativity and higher-resolution risk estimates.

Sentinel tick surveillance for in not a novel concept. Many studies, including in southern Canada, have sampled sites repeatedly to determine geographic or ecological risk of LD associated with presence of ticks (32-34), and a national sentinel surveillance system for tick-borne disease was launched in 2019 (35). New Brunswick uses a sentinel approach for their active acarological surveillance (unpublished data). However, this is not the case in all provinces, e.g., in Québec, where a dual approach is used as described in this article. The surveillance system put in place in Québec permitted the evaluation of both these surveillance approaches, as this had not been done before in the south of Canada, an area where LD is emerging. As the epidemiological portrait of LD is fast evolving, this relationship between enzootic hazard measured at sentinel sites and LD risk may have to be re-evaluated regularly to determine if this relationship holds. Clow *et al.* (13) propose a framework for surveillance of tick-borne diseases where surveillance is described as an adaptive process, with surveillance goals modified over time as the epidemiological context continues to evolve. Active surveillance at sentinel field sites is considered suitable for both the emergence and endemic phases of the disease process. Although we have shown the ability of sentinel sites to track spatiotemporal risk more reliably than accessory sites, this remains to be demonstrated for endemic regions. Furthermore, an important limitation of sentinel surveillance is its inefficiency in pre-emergence context; as sites are a limited subset of the entire population, they are not sensitive enough to capture early emergence signals. This highlights the complementary role of sentinel surveillance within larger surveillance network which integrates passive surveillance e.g., eTick (10, 36).

Our study has demonstrated the capacity of sentinel surveillance to track spatiotemporal risk of LD in a region where the risk is emerging. In Canada, where tick-borne diseases continue to emerge, this study can support planning of active surveillance strategies. Active surveillance at sentinel sites allows for comparable hazard measures through space and time, whilst limiting sampling effort to a restricted number of sites. A careful decision-making process must support site selection, to ensure that these are representative of the underlying epidemiological context and that the resulting data provide a robust portrait of emerging disease trends in space and time.

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Chapter II: Sentinel surveillance contributes to tracking Lyme disease spatiotemporal risk trends in southern Quebec, Canada

Abstract

Lyme disease (LD) is a tick-borne disease that has been emerging in temperate areas in North America, Europe, and Asia. In Quebec, Canada, the number of human LD cases is increasing rapidly and thus surveillance of LD risk is a public health priority. In this study, we aimed to evaluate the ability of active sentinel surveillance to track spatiotemporal trends in LD risk. Using drag flannel data from 2015–2019, we calculated density of nymphal ticks (DON), an index of enzootic hazard, across the study region (southern Quebec). A Poisson regression model was used to explore the association between the enzootic hazard and LD risk (annual number of human cases) at the municipal level. Predictions from models were able to track both spatial and interannual variation in risk. Furthermore, a risk map produced by using model predictions closely matched the official risk map published by provincial public health authorities, which requires the use of complex criteria-based risk assessment. Our study shows that active sentinel surveillance in Quebec provides a sustainable system to follow spatiotemporal trends in LD risk. Such a network can support public health authorities in informing the public about LD risk within their region or municipality and this method could be extended to support Lyme disease risk assessment at the national level in Canada.

Introduction

Lyme disease (LD) is a tick-borne disease that has been emerging in temperate areas in North America, Europe, and Asia (1-5). This emergence has been driven by the expansion of the geographical distribution of ixodid tick species (Acari: Ixodidae), which are vectors for LD pathogens (6, 7). In North America, ticks are dispersed over long distances by migratory birds from the United States into Canada, and their range expansion has been further facilitated by a range of anthropogenic factors including climate change, land use modification and range expansion of their animal hosts (6, 8).

As geographic range and abundance of ixodid ticks continue to increase, enzootic hazard of LD increases. In the context of LD, the enzootic hazard is defined as the potential source of harm for the disease derived by the enzootic cycling of *Borrelia burgdorferi* sensu stricto. In previous studies, the density of nymphs (DON) in the environment has been used as a measure of enzotic hazard (9), concording with findings that establishment of *I. scapularis* populations is typically followed by colonization of B. burgdorferi (10, 11). As a direct consequence of increasing hazard, LD risk rises in human populations; there is an increased likelihood of the adverse effect (acquisition of LD) occurring due to the increased abundance in a source of harm (12). Thus, effective surveillance of enzootic hazard has the potential to provide valuable information about geographic and temporal variation in LD risk.

Common acarological surveillance methods which could be used to track the enzootic hazard include passive and active surveillance. Passive surveillance involves the submission of ticks to reference laboratories by medical or veterinary clinics from their patients. Passive surveillance data, specifically detection of *Ixodes scapularis* or *Borrelia burgdoferi* s.s. in a new area, has been used as an early indicator of LD risk and has been shown to be closely correlated with the frequency of human LD cases (9, 13). However, analyzing high volumes of tick submissions can be very costly and resource intense, and may not remain feasible as tick populations continue to increase (14). While data from passive surveillance can provide information on tick presence or absence, it is often not possible to know precisely where the tick was found or to estimate tick population density.

Active surveillance involves direct collection of ticks from their environment by a field agent (15). For broader scale active surveillance initiatives, drag sampling is a method of choice (15). A sheet of white flannel cloth is dragged upon the forest floor, and questing ticks will cling to the fabric. The tick specimens can be collected and identified to species and life stage, and the tick species and life stage specific density can be calculated. For Ixodes ticks, the density of nymphal ticks (DON) can be used as a measure of enzootic hazard, especially in areas where LD risk is emerging and where nymph densities remain relatively low in active surveillance with very few ticks testing positive for *B. burgdorferi*. Nymphs are thought to represent the greatest risk of transmission of tick-borne disease due to their small size, high relative abundance compared to adult ticks, and activity period that spans the spring and summer months (16). While some associations between nymphal density and LD risk have been found

(17-19), these are not always strongly correlated (9). Furthermore, active surveillance requires intensive resources, both in the field and in the lab, and so surveying a large study zone can be a significant endeavor.

Sentinel surveillance, which involves repeated sampling of a select number of units from a population, has the potential to provide a feasible, sustainable surveillance system for LD by focusing active surveillance efforts on key locations and tracking this over time. Sentinel surveillance has been used historically, in many different infectious disease contexts, to maintain a surveillance system in various geographical regions at relatively low cost and with several logistical advantages in terms of data collection[8] (20, 21). As tick populations are dispersed heterogeneously across space, in part due to complex ecological requirements (22), sentinel surveillance has the added benefit that, once appropriate sites are found, efforts can be redirected into sampling activities. Lastly, expected inter-annual variation in tick density (21), and resulting LD risk, can be measured more reliably if sampling sites are kept constant over time.

Among the ten provinces in Canada, Quebec (**Figure 12**) has the third-highest number of reported human LD cases; furthermore, in the last five years, the number of cases has more than tripled (24, 25). Quebec is the largest and second most populated province in Canada, with a population of almost 8.5 million citizens (26). Most of the population resides in the south of the province, which coincides with the current LD emergence zone and highest *Ixodes scapularis* tick densities in the province. A sentinel surveillance network, composed of active surveillance sites sampled annually, was initiated by Quebec's institute of public health (Institut National de Santé Publique, INSPQ) in 2015 (14). The INSPQ's objectives for acarological surveillance are to document the presence, abundance and geographic distribution of *I. scapularis* in Quebec and to determine their *B. burgdorferi* infection status infection status (14). Furthermore, as the data from active tick surveillance is used to produce a risk map for LD for Québec, it is relevant to evaluate how well data collected through this surveillance system is tracking spatial and temporal variation in LD risk within the Quebec population. More broadly, sentinel surveillance has not been rigorously explored as a method for tracking spatial-

[8] E.g., limiting the effort needed for site selection, facilitating follow-up visits as teams are familiar with precise sampling locations, raising awareness in local partners.

temporal trends in tick-borne disease risk, and the Quebec surveillance program provides a unique context for assessing the strengths and limitations of this approach.

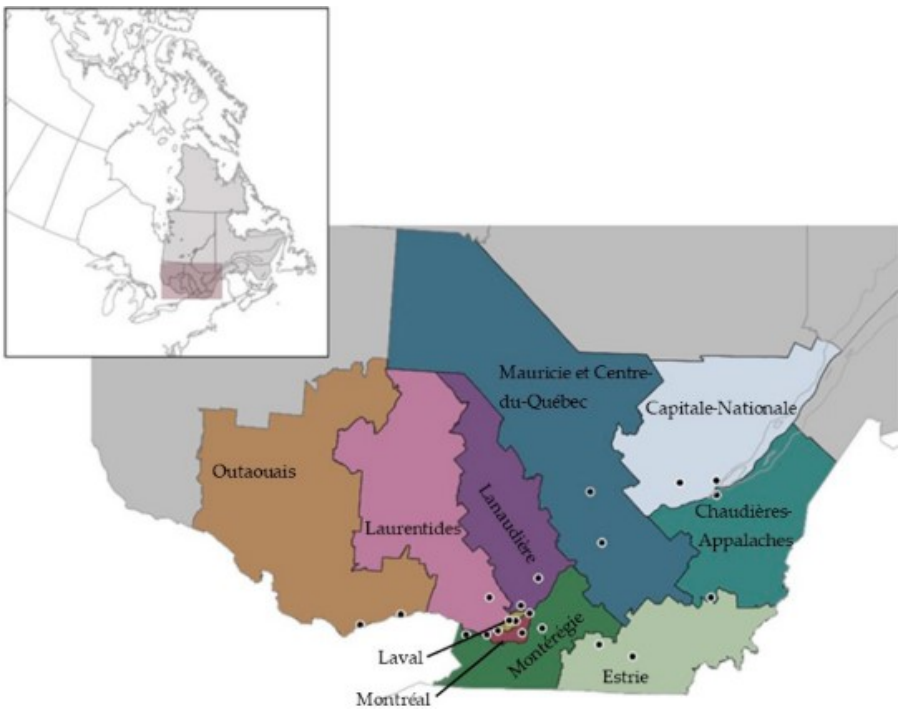

Figure 12. Health regions (*Régions socio-sanitaires*: RSS) part of Quebec's Lyme disease active surveillance system, with sentinel site distribution across the study zone ; two sites were chosen per region in the south of the province except for Montreal which had three sites.

In this study, we aimed to understand how the spatio-temporal index of enzootic hazard obtained through active tick surveillance across a network of sentinel sites relates to Lyme disease risk in the human population, as measured by the annual incidence of human LD cases. We hypothesize that data from sentinel sites can be used to interpolate LD enzootic hazard across our study zone and subsequently can inform public health authorities about LD risk to human populations. We demonstrate that, even with limited sampling effort, sentinel surveillance has the capacity to reliably capture regional trends in LD risk over a large geographical area, in this case the full extent of the LD emergence zone in southern Quebec.

Methods

Study Area

Quebec is located in the eastern part of Canada, sharing borders with the provinces of Ontario to the west and New Brunswick to the east. To the south, Quebec neighbors the states of New York, Vermont, New Hampshire, and Maine. Its area totals over 1,350,000 km^2, divided in 18 health regions (*Régions Socio-Sanitaires*: RSS), each with their own regional public health directorate (*Direction de Santé Publique*: DSP). Of the 18 RSS that make up the province, 10 are areas of key scientific interest for the emergence of Lyme disease, due to their more southernly geographical positions; this study will focus on these 10 RSS (**Figure 12**).

Sentinel Surveillance in Quebec

Since 2010, the INSPQ, the Public Health Agency of Canada (PHAC) and the University of Montreal have jointly coordinated active surveillance in southern Quebec (14). From 2015 onwards, a network of sentinel sites was designed by the group of experts on tick-borne diseases (*Groupe d'experts sur les maladies transmises par les tiques*), a panel formed by scientific and medical advisors, epidemiologists, public health officials, and laboratory experts specialized in vector-borne diseases. Two sites were chosen per region, except in the region of Montreal where three sites were selected due to high population density, for a total of 21 sentinel sites (**Figure 12**). The sites were placed in provincial or regional parks, characterized by suitable deciduous forest habitat for the establishment of tick populations, and located in geographically distinct areas of each RSS.

Sentinel sites were sampled twice during the summer activity period of nymphal *I. scapularis* ticks in southern Quebec (May–August): Once in late May to early June, followed by a second visit between July and mid-August. From 2018, two sites considered by public health authorities to have a well-established tick population due to the large number of ticks collected (one site in Montérégie and another in Estrie) were sampled only once per year, to allow for allocation of sampling resources to other sites where the risk was evolving. Exceptionally, some sites were only visited once per year due to logistical constraints, e.g., park closures. Finally, in 2016 and 2017 some sites were visited three times due to other research projects occurring concurrently.

A standardized drag sampling protocol was carried out at each site. Each site is sampled by two team field technicians, each dragging a 1 m^2 piece of flannel cloth horizontally on the ground along two transects: One along the vegetation at the edge of a public nature trail, and the second parallel transect in the forest 25m from the trail. Each team member sampled 1000m^2, for a total sample area of 2000m^2 per site. During sampling, the presence of ticks on the flannel was checked every 25m. Ticks were removed with tweezers, placed in tubes filled with 70% ethanol, and sent to the Quebec Public Health Laboratory (Laboratoire de Santé Publique du Québec: LSPQ) for species identification and pathogen testing.

Density of Questing Nymphs

To represent enzootic hazard, nymph densities (nymph/100 m^2 of surface area dragged) were calculated from sentinel site visits. Nymph density was used because nymphs have been shown to represent the greatest hazard to human health due to their small size, in comparison to the adult stage, their possibility of being infected, in comparison with the larval stage, and their activity peak during summer months (16).

Surveillance activities are carried out at different times during the summer, and tick phenology (seasonal activity) varies across this period (27), resulting in predictable variation in nymph densities observed during early and late visits to the same site. We therefore used seasonality models of *I. scapularis* phenology in the south of Quebec developed by Dumas *et al.* (28) to correct the raw nymph densities, using a reference date of June 15th, corresponding to the expected peak of nymph activity. Firstly, nymph densities were obtained by using the predict() function in R to calculate the predicted nymph density during 1) the reference date and 2) the actual sampling date according to seasonality models. The percentage change was determined between the two time points and used to adjust measured nymph densities, to correct for tick phenology. We used these corrected nymph densities to compute the mean density per site per year across the study period.

Notifiable Disease Surveillance System

Lyme disease has been a reportable disease in Quebec since 2003 (29). Any suspected or diagnosed cases of LD, based on a standardized case definition, must be reported to the notifiable diseases database, kept at the regional level. The case definition of LD in Canada is based on clinical manifestations, likely location of acquisition, and the use of diagnostic tests

as described by the federal public health guidelines (30). Once the cases are reported by physicians, each DSP is responsible for conducting a public health investigation of each case in their region. Thus, regional databases belong to each of the DSPs. For the purposes of this study, we requested access to the human case data at the municipal level for the 10 RSS covered by the Quebec active tick surveillance system (**Figure 12**), between 2015 and 2019.

Statistical Analyses

A Poisson mixed model was constructed to evaluate the relationship between average nymph density, the index enzootic hazard generated from sentinel surveillance, and human LD risk, measured as the annual number of human LD cases at the municipal level with human population as an offset (see below). We estimated annual hazard measures for each municipality by spatial interpolation of average nymph densities measured across the network of sentinel sites for each year of the study period. Interpolation was carried out using a Kernel density estimation in QGIS version 3.18 Zurich (31). A distance of 80 km was used as the radius of interpolation, as correlograms revealed spatial dependency of active surveillance data up to this distance (32).

Statistical models were fitted using the lme4 package in R version 3.6.2 (33). In addition to the risk (dependent variable) and the enzootic hazard (independent variable), the log of the human population was used as an offset. We used population data from Statistics Canada's Census of Population 2016 (26). The municipality code was added as a random effect to account for repeated measures taken across the five years of the study.

Conditional model predictions of the annual number of human cases in each municipality were compared graphically with observed number of cases reported through the Notifiable Disease Surveillance System.

Risk Mapping with Modelling Results

Lastly, we used our predictions to simulate the Quebec LD risk map using the risk criteria for human cases established by the INSPQ. Yearly, the INSPQ produces a LD risk map at the municipal scale (34). The risk map uses three levels of risk: Significant, present, and possible. As the INSPQ also uses passive surveillance data in addition to active surveillance data, we adapted the 2019 INSPQ criteria so these could be used for our data set, which also uses data derived from active surveillance (**Table 10**). Applying these criteria to our model predictions,

we constructed a risk map for 2019 and compared it to the risk map created by the INSPQ for the same year. The sensitivity and specificity of the classification, in comparison with the provincial risk map, are presented for the "significant" and "present" risk categories.

Table 10. Criteria used to classify risk level of Lyme disease at the municipal level in Quebec, adapted from the INSPQ (14)

Risk level	Criteria
Significant	• At least three reported cases of Lyme disease locally acquired in the last five years
Present	• A nymph density of at least 0.05 ticks / 100m2 • Two reported cases of LD locally acquired in the last five years
Possible	• Municipalities which do not meet 'significant' or 'present' criteria

Results

Human Cases

Between 2015 and 2019, there were a total of 1062 human LD cases acquired in Quebec and reported in the ten RSS included in the study: 108 (2015), 125 (2016), 247 (2017), 210 (2018), 372 (2019). Estrie was the region with the highest reported number of human cases of Lyme disease per 100,000 population, followed by Montérégie (**Figure 13**).

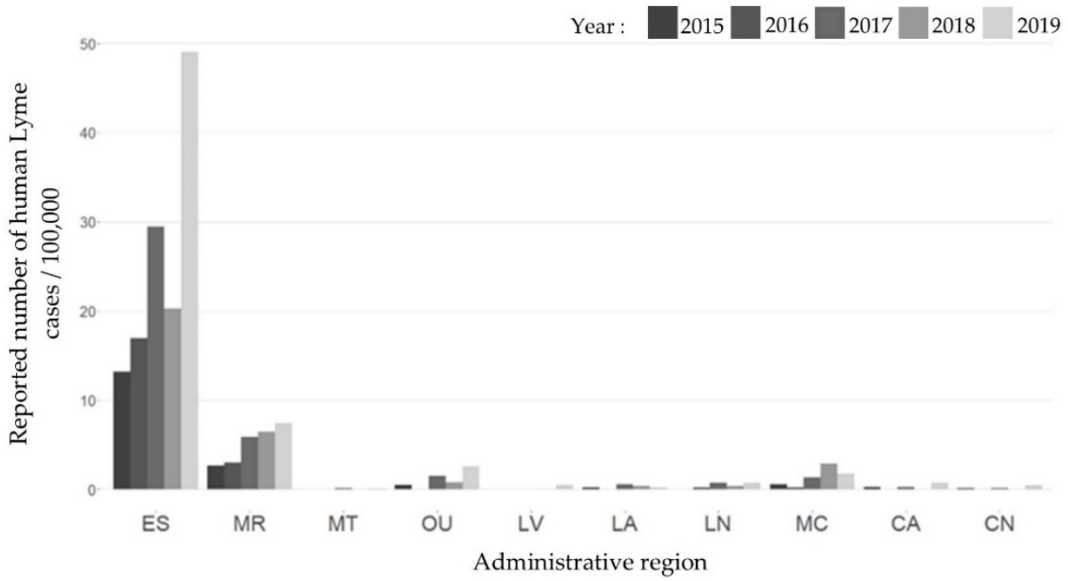

Figure 13. Reported number of human Lyme disease cases per 100,000 population for each region from 2015 to 2019

Legend: ES: Estrie; MR: Montérégie; MT: Montreal; OU: Outaouais; LV: Laval; LA: Laurentides; LN: Lanaudière; MC: Mauricie et Centre-du-Québec; CA: Chaudière-Appalaches; CN: Capitale-Nationale

Active Tick Surveillance

A total of 207 tick sampling visits were conducted across 21 sentinel sites between 2015 and 2019: 38 (2015), 45 (2016), 43 (2017), 39 (2018), and 42 (2019). Average predicted *I. scapularis* nymph densities per region were calculated from raw data for each year of the study as described in the "Materials and Methods" section (**Figure 14**). The highest densities of nymphs were found in Montérégie from 2017 to 2019 (1.48, 2.44, and 4.03 nymphs/100 m^2, respectively) and in Estrie in 2015 (1.27 nymphs/100 m^2). Trends in average nymph densities at the provincial level were compatible with trends seen in the number of reported LD cases from 2015 to 2019 (**Figure 15**).

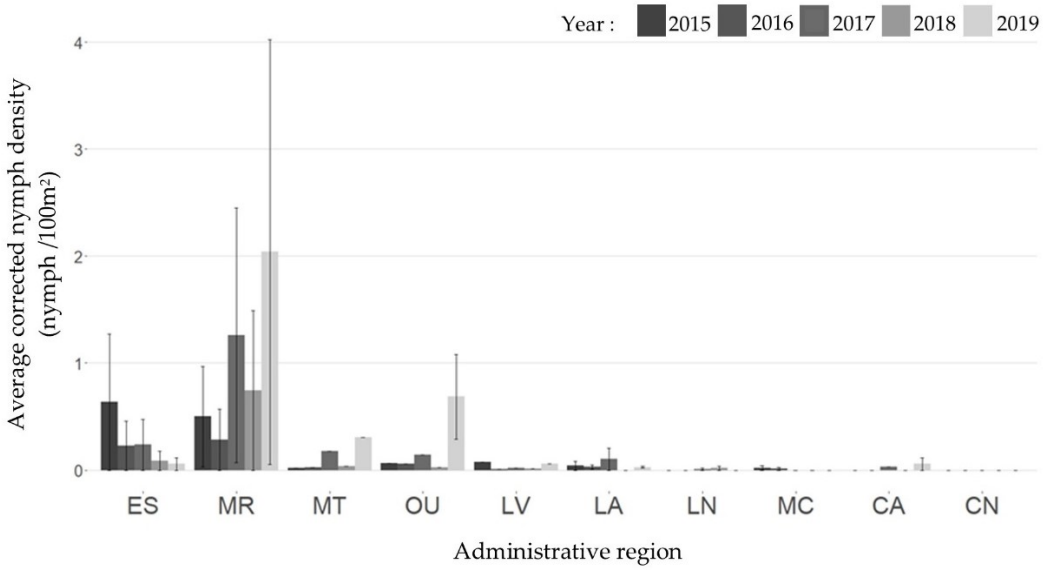

Figure 14. Average *I. scapularis* nymph densities per year in each *Région socio-sanitaire* (RSS) in Québec, Canada from 2015 to 2019 , corrected for the 15th of June using seasonality models (26)

Legend: ES: Estrie; MR: Montérégie; MT: Montreal; OU: Outaouais; LV: Laval; LA: Laurentides; LN: Lanaudière; MC: Mauricie-et-Centre-du-Québec; CA: Chaudière-Appalaches; CN: Capitale-Nationale

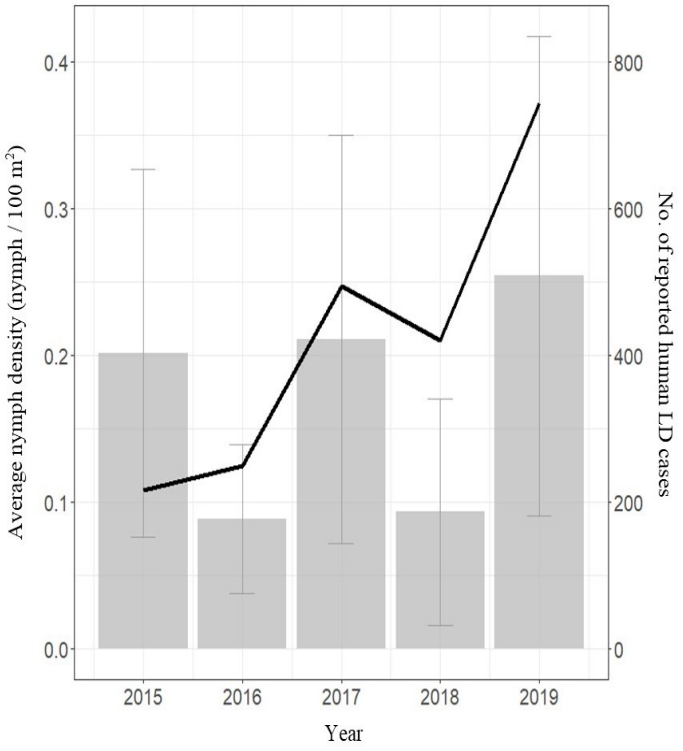

Figure 15. Diagram comparing average nymph densities at the provincial level from 2015 to 2019 (bars) with 95% confidence intervals, with observed number of human cases (line).

As administrative regions provide artificial boundaries, spatial interpolation of the data was carried out (**Figure 16**).

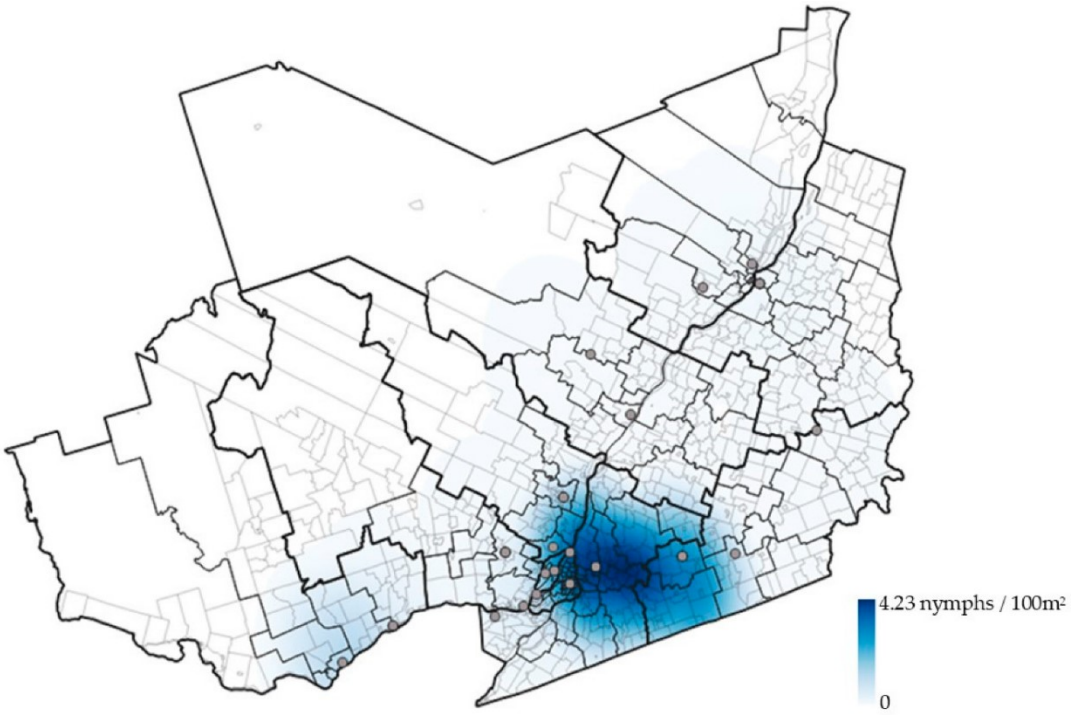

Figure 16. Interpolated enzootic risk for Lyme disease across the study zone (southern Quebec) for 2019; enzootic risk is derived from sentinel surveillance and interpolated using Kernel density estimation. Sentinel site locations are represented using grey points

Statistical Analyses

The Poisson regression model showed a significant relationship between predicted nymph density and number of cases of LD ($Z = 3.828$; $p < 0.001$), with municipality code as a random variable and the logarithm of the human population as an offset. The model estimated an increase of 1.38 cases for every unit increase in nymph density per 100 m^2 per logarithmic unit of the population. The marginal R^2 of the model was 0.021, and the conditional R^2 was 0.831. Thus, while nymph density explained some of the variation in the model, the random effect, municipality code, was crucial for following spatiotemporal trends.

Conditional predictions, which include the random effect, were calculated from the model and compared with the actual reported number of LD cases for each region of the study zone, across the study period (**Figure 16**). While predictions were generally able to capture inter-regional and inter-annual variations, predictions for Estrie between 2015 and 2019 did not show the increase in the number of human cases across this time period. However, when aggregated at the provincial level, predictions were able to follow trends (increase or decrease in risk) at this larger scale (**Figure 17**).

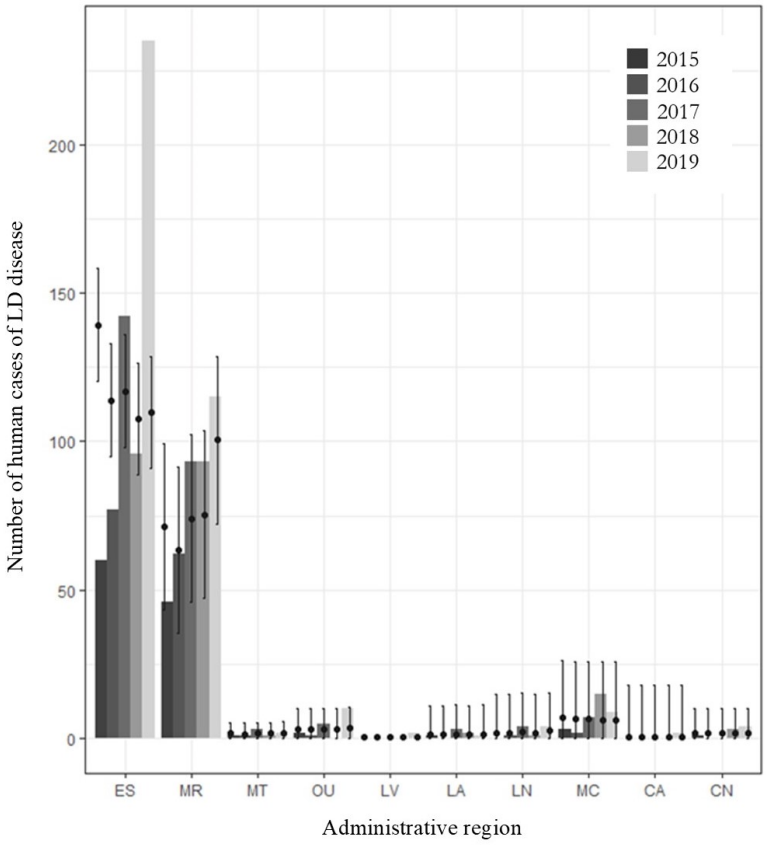

Figure 17. Comparison of model predictions of human Lyme disease cases (black dots) with confidence intervals, with observed number of human cases (bars) at the regional level across the study period from 2015 to 2019. Legend: ES: Estrie; MR: Montérégie; MT: Montréal; OU: Outaouais; LV: Laval; LA: Laurentides; LN: Lanaudière; MC: Mauricie-et-Centre-du-Québec; CA: Chaudière-Appalaches; CN: Capitale-Nationale.

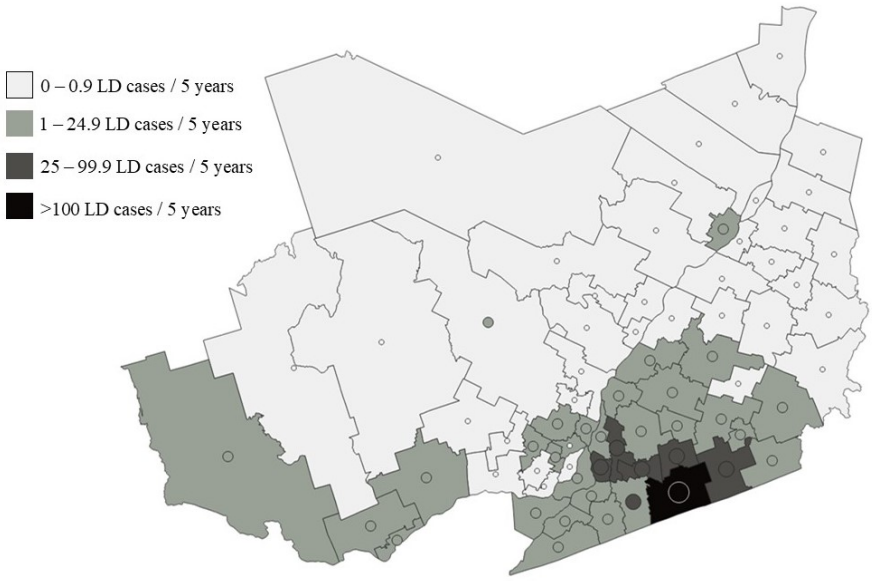

Figure 18. Map comparing predicted number human Lyme disease (LD) cases over the study period (2015–2019) with observed number of human LD cases, at the district level (called *réseaux locaux de services* (RLS) in Québec). The district scale was chosen for ease of visualisation. The district color represents the predicted number of LD cases whilst the superimposed circles represent the observed number of cases. The diameter of circles is scaled according to the logarithm of the number of human cases.

We compared the predicted number of human LD cases derived from our model and actual number of reported LD cases across the five-year study period at the district level (called *réseaux locaux de services* (RLS) in Québec) (**Figure 18**). The district scale was chosen for ease of visualisation. The model was able to estimate accurately the number of LD cases over a five-year period except for two RLS, one in Montérégie and the second in Lanaudière, where the number of LD cases was overestimated.

Risk Mapping with Modelling Results

Applying the criteria from Table 10 (see 'Methods' for more details) to the predictions from our fitted model allowed us to produce a classified LD risk map with the same risk categories as the Quebec provincial risk map produce by INSPQ for 2019 (**Figure 19**). Model predictions for municipalities in the highest risk category ("significant risk") closely matched the spatial distribution of this risk category in the provincial risk map. The municipalities within the risk-

level category "present" were predicted to be more widespread in the south of the province, and around Quebec City, than shown in the provincial risk map and PPV was relatively low at 22.3% for this risk level (**Table 11**). Predictions for the models were most sensitive and specific for identifying municipalities with a "significant" risk level at 78.2% and 99.3%, respectively.

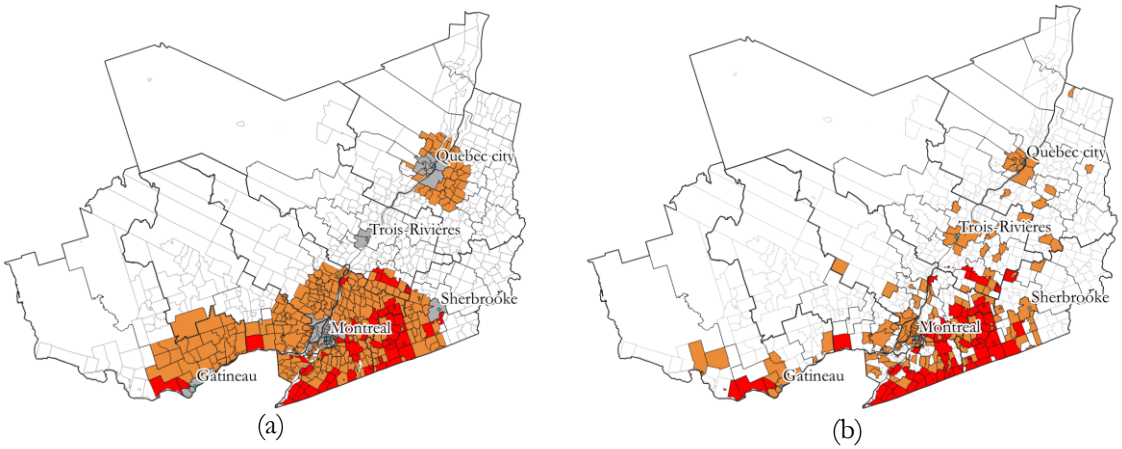

Figure 19. Maps comparing Lyme disease risk levels at the municipal scaled for 2019 as derived from a) sentinel surveillance model predictions (municipalities with >100 000 excluded) and b) the INSPQ (34). Legend: red: significant risk; yellow: present risk; white: possible risk. Criteria for determining risk levels are presented in Table 10.

Table 11. Sensitivity, specificity, positive and negative predictive values of predictions from models to classify municipal-level risk of Lyme disease in the south of Québec.

Risk level	Sensitivity (%)	Specificity (%)	PPV (%)	PPN (%)
Present	71.9	65.4	22.3%	94.3%
Significant	79.7	99.3	87.7%	97.5%

Discussion

In this study, we investigated the ability of sentinel tick surveillance to capture spatiotemporal variation in human Lyme disease risk across the emergence zone for this disease in southern

Quebec, Canada. We demonstrated that, even with limited sampling effort (21 sites sampled twice per year), sentinel surveillance reliably captured regional trends in LD risk over a large geographical area. Furthermore, we showed that risk maps generated from sentinel surveillance closely matched those derived from a more complex risk assessment based on multiple data sources. This first assessment of the application of sentinel surveillance in the context of emerging Lyme disease suggests that sentinel surveillance has the potential to provide a cost-effective approach for long-term monitoring of tick-borne disease risk over large geographic areas.

Our simple model, based on *I. scapularis* nymph densities alone as index of enzootic hazard, showed that an increase of 1 nymph per 100 m^2 was associated with an increase of 1.38 human LD cases for every logarithmic unit of the population. In the literature, many studies have used *B. burgdorferi* infected nymph densities (18, 19, 35, 36) as a measure of enzootic hazard, with similar positive associations with risk of LD. In contrast, our study was conducted on an area of emerging LD risk; nymph densities remain relatively low in active surveillance, and very few ticks test positive for *B. burgdorferi* s.s. Thus, our study supports the use of nymph density, as opposed to infected nymph density, as a representative enzootic hazard measure in areas where LD risk is emerging (9). Some information bias may be included due to interpolation of the data, as these estimations were used in our models to predict LD risk. Interpolation across the study zone will hide some of the finer scale heterogenous presence of ticks (37). While this bias is important to note, using the municipality as a random variable allowed for predicted and observed human LD cases to concord closely, thus limiting this source of bias. However, this leads to another limitation of our model: its applicability to other sentinel networks. Marginal R^2 was much smaller than the conditional R2, showing that although nymph density can contribute to spatiotemporal LD risk predictions, inclusion of the study context is vital within the model. Ticks and LD are subject to fine-scale heterogeneity due to the effect of the geographical and ecological context (22, 37); thus, in surveillance of the risk, these factors remain an important piece of the puzzle.

We used seasonality models to correct nymph densities collected across the field season. This allows comparability of the enzootic hazard measure, otherwise limited due to tick phenology (27). Development of seasonality models in the south of Quebec has made this adjustment possible (28), and public health authorities should evaluate the benefits of developing such

models in their respective areas or use those which are already available in the literature (28-40). We note that in previous studies conducted in eastern Canada, no such phenological adjustments had been carried out with active surveillance data to explain LD risk (9). Furthermore, by interpolating sentinel surveillance data, our analyses cover a greater proportion of our study zone, with the benefit of maximizing the use of resource-intensive data collected on the field.

Some limits are important to consider with the use of seasonality models, for example, they may not be able to fully capture the inter-annual phenological variations in tick life cycles. This limit is minimized as seasonality models used more than one year of data during construction (28). The phenology may also slightly differ across the study zone; however, as we used a model developed for data in Québec, the differences should be minimal. To overcome this limit further, timing sampling visits during the same period would overcome the need to correct nymph densities.

Using nymphal density model predictions, we were able to show that the model was able to match trends in human Lyme disease risk, both in time and space. Firstly, LD case predictions across different RSS through the study period capture the observed number of cases. Estrie was the region for which the model had the most difficulty in predicting observed case numbers. Estrie is also the region with the greatest number of human cases. However, LD incidence varies greatly across its area, and we had only two sentinel sites to capture this variation (41). We suggest adding a sentinel site in the endemic district of Brome-Missiquoi (29), which could potentially allow better annual predictions of human cases in this region. Without being able to predict the exact number of cases which will ensue, if from active surveillance data is representative of LD risk it can aid public health authorities to target areas for more in-depth public health inquiries and public health interventions.

The temporal concordance with the predicted LD risk is less strong than the spatial component; sentinel surveillance did not always reliably track interannual variation in human cases within a region. However, the overall trend predicted from the model was consistent with human cases at the provincial scale. Sentinel surveillance can thus serve as a broad indicator of human case trends, allowing sentinel surveillance to forecast the approximate LD risk for the year and can foreshadow a surge in human cases.

Every year, the INSPQ produces municipal-scale risk map-based surveillance data collected the previous year. Using the same criteria, we classified our model predictions into risk levels to create a comparable risk map. The modeling predictions were able to correctly identify significant risk municipalities, as classified by the INSPQ, in the south of the provinces with a sensitivity of 78.2% with a PPV of 87.7%. Sensitivity of the model predictions for categorizing municipalities as per the INSPQ risk map was lower for "present" and "possible" risk levels, suggesting that the model predictions are better at identifying areas with an increased and emerging risk of LD. The INSPQ has not validated their criterion based on the number of human cases to municipalities greater than 100,000 inhabitants and thus we could not include larger urban centers for our risk map (29). There is a need to develop other case-based criteria for establishing risk levels for densely populated urban areas. Nonetheless, the ability of sentinel surveillance to track spatiotemporal changes in risk of LD may complement information derived from other sources (e.g., passive surveillance). An annual "Sentinel Surveillance Risk Indicator" can provide a reliable estimate of human risk across all municipalities, and is strongly correlated with the more rigorous, but more costly, measure of risk provided by integrated surveillance (42, 43).

Our study shows that sentinel surveillance may provide a sustainable method to track spatiotemporal trends in LD risk over time. Such a network can support public health authorities in informing the public about LD risk within their region or municipality and this method could be extended or adapted to support LD risk assessment across broader spatial scales, such as the national level with sentinel sites distributed among provinces or states. More generally, our study provides evidence of the utility of sentinel surveillance for monitoring temporal changes in emerging disease risk (42), overcoming strategic or logistical challenges associated with other methods of surveillance (9) while still providing reliable information on regional disease risk over extensive geographic areas.

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Chapter III: A portrait of sentinel surveillance networks for vector-borne diseases: a scoping review supporting sentinel network design

Abstract

Vector-borne diseases (VBDs) are continuing to emerge globally, requiring new surveillance systems to follow increasing VBD risk for human populations. Sentinel surveillance is an approach that allows tracking of disease risk through time using limited resources. However, there is no consensus on how best to design a sentinel surveillance network in the context of vector-borne diseases. We conducted a scoping review to compare VBD sentinel surveillance systems worldwide with the aim of identifying key design features associated with effective networks. Overall, VBD surveillance networks were used most commonly for malaria, West Nile virus and lymphatic filariasis. A total of 45 criteria for the selection of sentinel unit location were identified. Risk-based criteria were the most often used, and logistic regression showed that using risk-based criteria dependent on host animals is particularly correlated with surveillance system sensitivity ($p<0.018$). We identify tools that could prove valuable for sentinel surveillance network design, including a standardized approach for evaluating surveillance systems and a tool to prioritize criteria for selecting optimal geographic locations for spatial sentinel units.

Introduction

In the last few decades, we have witnessed an expansion in the geographic distribution of many arthropod vectors of human disease such as mosquitoes, biting flies and ticks. Driving forces in vector range expansion include anthropogenic factors, such as urbanization and globalization, and climate change, which result in new environments becoming suitable for the survival of vectors (1-3). With expanding vector ranges, the emergence of vector-borne diseases (VBDs), diseases transmitted by hematophagous arthropods, is becoming a growing public health problem. VBDs now account for an estimated 17% of the worldwide infectious disease burden and cause more than 700 000 deaths annually (4, 5).

In many cases, VBD emergence requires public health authorities to develop new approaches to track VBD risk within their administrative boundaries. Public health surveillance is defined as the continuous and systematic collection of data in order to guide public health practice and interventions (6). In the surveillance of VBDs, additional complexities must be considered – their distribution in space is dependent on vector ecology and reservoir host ecology, and human exposure to vectors. This creates specific challenges for VBD surveillance: 1) as vector habitat range increases, public health authorities must survey an increasing geographic area with finite resources, 2) the presence of vectors and pathogens in the environment is often the target of surveillance since it is prerequisite to the emergence of human cases and 3) the spread of vectors and pathogens in space can be difficult to predict due to heterogeneity of habitat suitability and patchy introduction of the vector associated with stochastic events or host movement patterns.

Sentinel surveillance offers the opportunity to overcome some of these ecological and logistical challenges. Sentinel surveillance involves the selection of a sub-group of the population to be measured repeatedly to provide a time series of surveillance data. As it uses a targeted sample, costs are limited. Despite a restricted sample size, sentinels have been shown to permit the surveillance of the presence or absence of the vector and/or the pathogen in previous research, for instance as seen in sentinel chicken programmes for the prompt detection of West Nile virus circulation, to name a single example (7-9).

Although sentinel surveillance offers the possibility of establishing a cost-effective surveillance system for VBDs, its major limitation is the spatial interpolation of surveillance findings outside the sentinel units (10). Thus, to optimize the use of data obtained from the surveillance system, sentinel units must be carefully selected according to the aims of the surveillance program, taking into consideration the type of sentinel, its geographical location, sampling design and laboratory methods used. Sentinel units, which form individual parts of the sentinel surveillance network, refer to the geographical unit where a sentinel (hospital, clinic, laboratory, sentinel surveillance site) or a group of sentinel individuals (animals, mosquito traps) are located. In this manuscript, we use the term "sentinel unit location" to designate the selected geographic location of a sentinel unit. Animals (individuals or herds) are frequently used as sentinel units (11), and a review of the use of sentinel herds for the surveillance of

VBDs showed that sentinel unit location was a key factor determining the efficacy of the surveillance network (12).

Evaluation of surveillance systems is crucial to assess the efficacy and functionality of the network (13). With this information, public health authorities can evaluate the benefits and challenges of using certain surveillance structure prior to establishing a new network. The Centers for Disease Control and Prevention (CDC) has built a framework for surveillance network evaluation based on nine key characteristics (hereafter referred to as performance parameters). These performance parameters represent characteristics that a network should have to favor efficient and effective public health surveillance: simplicity, flexibility, data quality, acceptability, sensitivity, predictive value positive, representativeness, timeliness, and stability (14). Sentinel unit location will influence many of these parameters. Selecting appropriate locations for the surveillance units has the potential to favor the detection of disease occurrence (sensitivity), at an early stage in disease emergence (timeliness) and in a manner to capture the risk to human populations (representativeness).

To our knowledge, sentinel surveillance networks for VBDs have not been globally inventoried, as reviews have focused on specific types of sentinel units e.g., sentinel herds (12), or on VBDs in specific settings e.g., urban environment (15). Thus, a comprehensive review assessing the structure and performance of VBD sentinel surveillance networks worldwide could provide valuable insight into which criteria to consider when designing new surveillance networks of this kind. To respond to this knowledge gap, we carried out a scoping review to characterize the main features of past and existing surveillance networks. By extracting selection criteria involved in determining the spatial distribution of sentinel units, we were able to further describe the rationale underlying the spatial design of these networks. Lastly, by correlating the use of given selection criteria with the performance of the sentinel surveillance network, we aimed to examine whether certain criteria were more likely to result in the implementation of successful surveillance networks.

Methods

Search strategy

A systematic search was conducted in Ovid MEDLINE, Embase, CABAbstracts and Global Health and in the gray literature up to November 29, 2019. The search strategy, including searching terms related to sentinel surveillance and vector-borne diseases (terms for VBDs of major public health concern as determined by the WHO (16) are detailed in the supplementary materials. The search strategy was first validated by a public health librarian from the Public Health Association of Canada (PHAC). The second validation involved using a snowball strategy (manually screening references of relevant articles) and by cross-checking for the presence of 10 references provided by an expert in the field. Any references not found during these two validation steps and which met our inclusion criteria were added to the list.

Study selection

Titles and abstracts drawn from the literature search were screened for relevance independently by two reviewers, to determine whether the articles met each one the following inclusion criteria: 1) surveillance of a VBD, including vector, animal, human, or environmental surveillance 2) involved a network of at least two sentinel units, whereby a unit is an entity in a predetermined, fixed location 3) written in English, French or Spanish. Articles which did not contain primary data were excluded. Any disagreements were settled by reaching consensus after further discussion. During the screening step, the information was evaluated for relevance by using a standardized tool implemented in DistillerSR (Evidence Partners, ON). The screening tool was validated by pre-testing ten preselected scientific articles by three individual reviewers with agreements ≥85%. General study characteristics were also extracted, such as type of study and year of publication (Appendix 1).

Data extraction: Description of sentinel surveillance networks for VBDs

Articles which met the inclusion criteria in the relevance screening were brought forward to the data extraction step, consisting of a second standardized data extraction (DE) tool (Appendix 1). The DE tool was validated by three individual reviewers with agreements ≥85% on closed-ended questions from three preselected articles using the tool.

The DE tool contained three parts. The first involved extracting criteria that were used in the selection of the sentinel unit location. Articles which did not report this information were excluded. In the second part, general characteristics of the sentinel network where clarified, such as VBD investigated, vectors responsible for the disease, methods used for data collection, and type of data collected. Lastly, a global evaluation of the sentinel network was completed, following CDC framework, to gain an overall impression of the value of the surveillance network.

Evaluation of sentinel surveillance networks and their construction

Based on CDC guidelines, proxies for each performance parameters were developed, and associated questions were included in the data extraction form (Appendix 1). This allowed reviewers to evaluate the performance parameters of the surveillance in a categorical fashion (i.e., whether or not the sentinel network met the performance parameter proxies, or if it was unknown from reading the article).

The next step was to examine whether certain sentinel unit selection criteria influenced the success of the surveillance system. As aforementioned, sentinel location was deemed to impact directly three of the surveillance network performance parameters: sensitivity, representativeness, and timeliness. However, timeliness was excluded from this analysis as in most articles, it was not possible to evaluate whether the surveillance network had met this performance parameter.

Thus, surveillance network sensitivity and representativeness were independently inserted as answer variables into logistic regressions using the criteria used for sentinel unit selection as fixed effects. These models were run using the glm function within the R environment (17). Articles whose sensitivity or representativeness could not be evaluated by reviewers were excluded from these models. Fixed effects only included selection criteria which were used in ≥10 articles, which resulted in the exclusion of 28 criteria from the models. Collinearity between variables was excluded using Eigenvalues and variance decomposition proportion as calculated with the *eigpop* function (18) in R. An Akaike Informaiton Criterion (AIC) backward stepwise approach was used to identify the best fitting model. Finally, the fit of the models

were evaluated using standard regression diagnostics methods, including Pearsons' χ^2 test for overdispersion and distribution of residuals.

Results

Search outcome

Our search strategy yielded a total of 7309 articles, from the 4 databases and the gray literature searched. A total of 4674 duplicates were removed, and 3 articles were added after cross-checking references during the search strategy validation steps. A total of 2638 articles progressed to the title and abstract screening step.

During title and abstract screening, 1006 articles were not based on surveillance of VBD, and 861 did not focus on sentinel networks and were thus excluded. Seventy other articles were excluded as they were in a language other than English, French or Spanish (47 Chinese; 3 Croatian; 3 German; 3 Italian; 1 Korean; 10 Portuguese; 2 Serbian; 1 Turkish) and 64 articles were excluded as they did not present primary data. One article was both written in another language and did not contain primary data. This resulted in a total of 638 articles which progressed to the data extraction step (**Figure 20**).

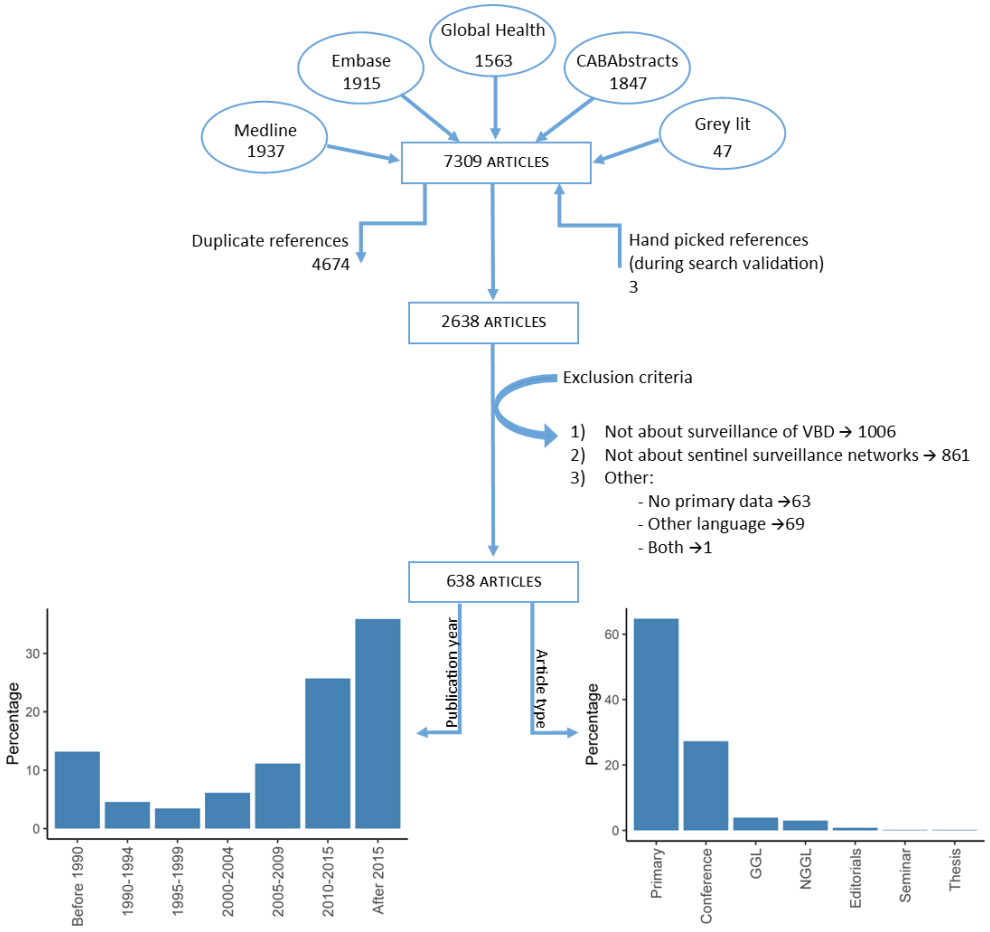

Figure 20. Search outcome from a scoping review aimed at investigating sentinel surveillance networks for vector-borne diseases, performed between September and November 2019. The search outcome is reported based on PRISMA guidelines. Legend: GGL, governmental gray literature; NGGL, non-governmental gray literature

Description of included articles

A total of 246 articles were eliminated either because they did not mention selection criteria used for sentinel site location (n = 186), or because the full text could not be found (n = 60). Thus, of the articles (n = 638) which passed the title and article screening step, 206 (32.2 %) passed the full data extraction step. From here on, only the articles which were retained through the data extraction step will be described.

The 206 articles retained were carried out in Africa (n=88, 42.7%), Asia (n=32, 15.5%), North America (n=27, 13.1%), Western Europe (n=18, 8.7%), Australia (n=14, 6.8%), Central or

South America (n=13, 6.3%), Oceania (n=8, 3.9%) and Eastern Europe (n=7, 3.4%). One study had sites both in Australia and Oceania. They presented results from sentinel networks operating at local (n=33, 16.0%), regional (n=73, 35.4%), national (n=94, 45.6%) or less commonly multinational (n=6, 2.9%) scale.

The principal VBDs monitored by sentinel networks included malaria (n=68, 33.0%), West Nile virus (n=32, 15.5%), lymphatic filariasis (n=22, 10.7%), and schistosomiasis (n=19, 9.2%) (**Table 12**). A total of 24 different viruses, 9 parasites and 3 bacteria were surveying across the articles.

Table 12. List of vector-borne diseases investigated within the articles included in the scoping review, including type of arthropod vector, type of pathogen and number of articles that studied each of these diseases

Disease	Vector	Pathogen	No. of articles
Malaria	Mosquitoes	Parasite	68
West Nile virus infection	Mosquitoes	Virus	32
Lymphatic filariasis	Mosquitoes	Parasite	22
Schistosomiasis	Snails	Parasite	19
Western equine encephalitis	Mosquitoes	Virus	15
Bluetongue	Midges	Virus	14
Murray Valley encephalitis	Mosquitoes	Virus	11
Onchocerciasis	Black flies	Parasite	11
Japanese encephalitis	Mosquitoes	Virus	10
Ross River virus	Mosquitoes	Virus	9
Arbovirus infection	Mosquitoes	Virus	7
Chikungunya	Mosquitoes	Virus	5
Zika	Mosquitoes	Virus	5
Barmah Forest virus infection	Mosquitoes	Virus	4
Yellow fever	Mosquitoes	Virus	4
Lyme disease	Ticks	Bacteria	4
Venezuelan equine encephalitis	Mosquitoes	Virus	3
Epizootic hemorrhagic disease	Midges	Virus	3
Arboviruses group A and B infection	Mosquitoes	Virus	2
Eastern equine encephalitis	Mosquitoes	Virus	2
Rift Valley fever	Mosquitoes	Virus	2
Utusu virus infection	Mosquitoes	Virus	2
Leishmaniasis	Phlebotomine sand flies	Parasite	2
Q Fever	Ticks	Bacteria	2
Saint Louis encephalitis	Mosquitoes	Virus	2
Bovine trypanosomiasis	Tsetse flies	Parasite	2
Chaga's disease	Triatomine bugs	Parasite	1

Edge Hill virus infection	Mosquitoes	Virus	1
Jamestown Canyon virus infection	Mosquitoes	Virus	1
Bovine ephemeral fever	Midges	Virus	1
Schmallenberg virus infection	Midges	Virus	1
Bartonella infection	Ticks	Bacteria	1
Crimean-Congo fever	Ticks	Virus	1
Powassan virus infection	Ticks	Virus	1
Tick-borne diseases	Ticks	NA	1
African trypanosomiasis	Tsetse flies	Parasite	1

Sentinel surveillance networks in the articles were largely active (n=181, 87.9%) and less commonly passive (n=14, 6.8%). Active surveillance[9] included methods such as field work to collect vectors (e.g., snail surveys, larval surveys, drag sampling), serologic or parasitologic testing (e.g., blood or stool testing in animals or human subjects), and syndromic surveillance through the administration of questionnaires. Meanwhile, examples of passive surveillance[10] were human case reporting, veterinary reporting of symptomatic animals and laboratory reporting of positive test results. Some articles (n = 11, 5.3%), used both active and passive surveillance within the sentinel network.

Description of the sentinel networks

Surveillance networks described in the articles operated for < 1 to > 20 years and comprised between two and > 50 sentinel units (**Table 13**).

Table 13. Number of sentinel surveillance units in surveillance networks described in articles considered in the scoping review, according to the duration of the surveillance network operation.

Number of sites	**Duration of network operation (years)**							**Total**
	<1	1 to 2	3 to 5	6 to 10	11 to 20	>20	Unknown	
2	7	3	0	0	0	0	0	10
3-5	15	15	10	1	1	0	1	43
6-10	20	22	13	4	4	0	0	63
11-20	7	11	8	1	1	0	0	28
21-50	9	9	8	3	0	1	0	30
>50	3	3	2	3	1	8	0	20

[9] Active surveillance involves data collection by the lead investigators or public health authorities.
[10] Passive surveillance involves putting structures in place to allow for existing data to be forwarded to public health authorities.

Unknown	3	2	3	2	1	1	0	12
Total	64	65	43	14	8	10	1	206

The sentinel units in the networks were villages (n=46, 22.3%), clinics (n=42, 20.4%), sites in an urban setting (n=1, 8.3%), sites in the countryside (n=16, 7.8%), farms (n=11, 5.3%), schools (n=9, 4.4%), sites in the suburbs (n=7, 3.4%), sites in the forest (n=4, 1.9%), health zones (n=4, 1.9%), houses (n=2, 1.0%), and laboratories (n=1, 0.5%), zoos (n=1, 0.5%)or kennels (n=1, 0.5%). However, 68 articles (33.0%) did not explicitly state or describe their sentinel site settings.

When animals were used within the network, and placed within the sentinel units, the most common animals used were chickens (n=32, 15.5%), bovine (n=22, 10.7%), wild birds (n=10, 4.9%), sheep (n=7, 3.4%), dogs (n=6, 2.9%), goat (n=4, 1.9%), horse (n=4, 1.9%), hamsters (n=3, 1.5%), mice (n=3, 1.5%), rodents (n=3), livestock (n=2, 1.0%), pigs (n=2, 1.0%), deer (n=1, 0.5%), donkeys (n=1, 0.5%) and zoo animals (n=1, 0.5%). A total of 132 articles (64.1%) did not use any animals as sentinels.

Aim of articles on sentinel networks

The broad aims of the articles are included following disease trends (n=128, 62.1%), testing intervention methods (n=72, 35.0%), profiling risk factors (n=32, 15.0%), acting as an Early Warning System (EWS) (n= 15, 7.3%) and evaluating the surveillance network (n=10, 4.9%).

Disease detection methods used

A total of 49 different sampling and laboratory methods were identified in the articles (**Table 14**) allowing the collection of various types of data (**Figure 21**).

Table 14. Data collection and lab analysis methods used for disease detection in sentinel surveillance systems described in the articles retained in our scoping review

Method	**No. of articles**
Mosquito trapping (any kind)	73

Blood sampling (human)	68
Symptom surveillance or questionnaire	60
Blood sampling (animal)	59
ELISA	51
PCR (vector)	42
Microscopy (human tissues)	40
Blood smear (thick and thin blood films)	36
Physical examination	27
PCR (human tissues)	24
Parasitology (excludes plasmodium)	21
PCR (animal tissue)	20
Sequencing	19
Microscopy (vectors)	16
Bioassay	15
Serum neutralization tests (SNT)	15
Rapid diagnostic tests (RDTs)	14
Stool sampling (human)	14
Human case reporting	12
Larval survey	12
Plaque reduction neutralization tests (PRNT90)	12
Hemagglutination test	11
Human landing catch	11
ICT card	11
Immunoassay	11
Classic isotopic 48-h test	9
Kato Katz methods	8
Serology (unspecified)	8
Snail survey	8
Urine sampling	8
Skin nip	7
Agar gel immunodiffusion (AGID)	6
Cerebrospinal fluid (CSF) sampling	5
Microscopy (animal tissues)	5
Stool sampling (animal)	5
Ophthalmic examination	4
Complete blood count (CBC)	3
Vector removal	3
Biochemistry	2
Rodent capture	2
Satellite imaging	2
Alere Filariasis Test Strip (FTS)	1
Biopsy	1
Isotope	1
Drag flannel sampling	1
Hot oligonucleotide ligation assay (HOLA)	1
Restriction fragment length polymorphism (RFLP)	1
Spot test	1
Ultrasonography	1

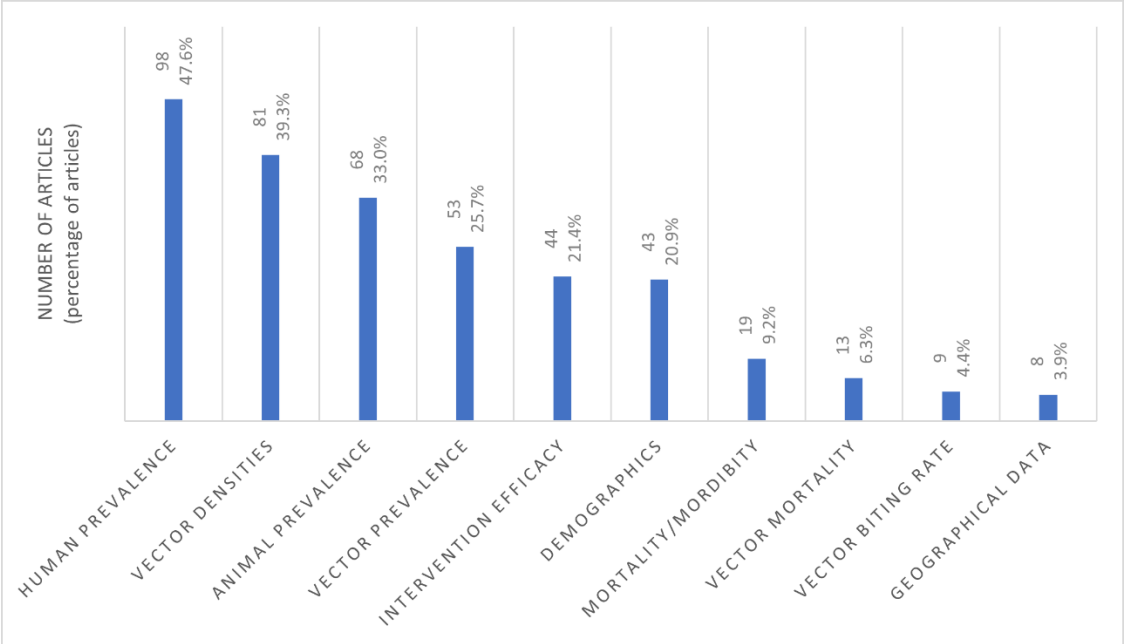

Figure 21. Type of data collected through the sentinel networks described in the articles retained in our scoping review. Articles could have more than one type of data collected. This included prevalence of pathogen/disease in humans (human prevalence), vectors densities, prevalence of pathogen/disease in animals (animal prevalence), prevalence of pathogen in vectors (vector prevalence), intervention or treatment efficiency (intervention efficacy), demographic data (demographics), mortality / mortality data for humans (mortality/morbidity), mortality data for vectors (vector mortality), vector biting rate and geographical data.

Selection criteria for sentinel unit locations

A total of 45 criteria involved in the selection of a sentinel locations were identified during the data extraction step (**Table 15**). These criteria were grouped into 6 broad categories: Risk, Environment, Population, Delimitation, Past information, and Logistics.

The category Risk includes criteria which evaluate the presence or absence of an indicator of risk within the selected sentinel units (e.g., presence of vectors, host animals or human cases). The Environment category take into consideration the natural features of the study zone, such as habitat suitability for vectors or host animals, based on ecological, meteorological, or

geographical data. The Population category is directly related to the human population of the study zone, either for demographic data, presence of human activity or population dynamics. The Distribution category refers to criteria guiding the spatial distribution of sentinel units across the study area. The Past information category incorporates previous knowledge, from former articles or surveillance programs, which supported the selection of sentinel unit locations. Finally, the Logistics category groups criteria which were used in order to maximize feasibility of the sentinel surveillance network, including access or diffusion of results. On average, articles used 2.4 criteria to determine sentinel unit locations.

The most common criteria category used to determine sentinel unit locations were Risk, Past information and Environment, with a total of 122 (59.2%), 79 (38.3%) and 74 (35.9%) articles using criteria from those categories, respectively. The Distribution, Logistics and Population categories were less commonly used, with a total of 51 (24.82%), 43 (20.9%) and 30 (14.6%) articles reporting using these criteria, respectively.

Table 15. Criteria extracted from the articles included in our scoping review, classified into broad categories: Risk, Environment, Population, Distribution, Past information, and Logistics

Type	ID	Criterion	Description	No. of articles
Risk	R1	Risk (human)	There is documented risk of disease due to the presence of human cases within the sentinel unit location (SUL)	55
	R2	Variation in risk	There is a variation in degree of risk of the disease between the SUL	25
	R3	Risk (vector)	There is documented risk of disease due to the presence of appropriate vector disease within the SUL	22
	R4	Risk (unspecified)	There is documented risk of disease, however the nature of the risk is not elucidated within the SUL	20
	R5	Risk (host animals)	There is documented risk of disease due to the presence of appropriate host species within the SUL	17
	R6	Proximity to risk	The SUL are in proximity to an area with document risk of disease	8
	R7	Risk (geography)	There is documented risk of disease due to geography (abiotic) within the SUL	5
	R8	Suspected risk	There is suspected risk of disease within the SUL	3
	R9	No risk	There is no document risk of disease within the SUL	2
	R10	Risk (interface)	There is documented risk of disease due to the presence of vector-human interface within the SUL	2
Environment	E1	Geographical features	The geography of the SUL has been taken into consideration during the selection	27
	E2	Ecology (vector)	The ecology of the SUL is appropriate for the presence of the vector	18
	E3	Variation in ecology	The SUL have been chosen due to variation in ecology between these units	23
	E4	Ecology (unspecified)	The ecology of the SUL has been taken into consideration during the selection, however authors have not specified how	6
	E5	Variation in geography	The SUL have been chosen due to variation in geographical features between these units	7
	E6	Ecology (host animal)	The ecology of the SUL is appropriate for the presence of the host species	7
	E7	Proximity to area of interest	The SUL is near an area of interest, such as a school	5
	E8	Livestock population	Selection of the SUL in order to maximise the volume of livestock within the units	4
	E9	Climate	Climate has been taken into consideration in the selection of the SUL	4
	E10	Ecology (disease)	The ecology of the SUL is appropriate for the presence of the VBD	2
	E11	Variation in farming practices	The SUL have been chosen due to variation in farming practices between these units	1
	E12	Variation in housing type	The SUL have been chosen due to variation in housing type between these units	1
Population	P1	Population numbers	Selection of the SUL in order to maximise the population reached within the units of the study zone	17
	P2	Population demographics	Population demographics are considered during the selection of SUL	10
	P3	Population stability	The populations within the SUL are stable (no immigration / emigration)	6
	P4	Population instability	The population within the SUL are unstable (immigration / emigration)	2
	P5	Presence of human activity	There is presence of a specific type of human activity (e.g. fishing, hunting, wild mushroom picking) within the SUL	3
	P6	Health clinic demographics	Demographics of the health clinics are considered during the selection of SUL	1
Distribution	D1	Administrative boundaries	Selection of SUL according to administrative boundaries	29

	D2	Random	Random distribution of SUL in the study zone	16
	D3	Even distribution	Even distribution of SUL through the study zone	9
	D4	Minimal distance	Separation of SUL by a minimal distance	2
Past information	I1	Past surveillance	The SUL were chosen as they had been used in previously in surveillance programmes	34
	I2	Previous studies	The SUL were chosen as they had been used in previously in scientific studies	21
	I3	Previous PH interventions	There are previous public health interventions carried out within the SUL	12
	I4	No previous PH interventions	There are no previous public health interventions carried out within the SUL	8
	I5	Variation in PH interventions	There is a variation in public health interventions carried out with the SUL	5
	I6	Areas of scientific interest	The SUL have been chosen as they represent areas of increased scientific interest	3
	I7	Modelling	The SUL were chosen as there is modeling data to support their selection	1
Logistics	L1	Logistics	Logistical constraints (e.g. travelling distance, access) are considered for the SUL	31
	L2	Voluntary	SUL are based on voluntary enrollment	14
	L3	Stakeholders	The SUL are selected according to stakeholder preferences, suggestions or recommendations	3
	L4	Specialist centers	There are specialists or a specialist centre within the SUL	2
	L5	Threshold of consultations	The SUL are selected in order to ensure that a minimal threshold of patient consultations is achieved	2
	L6	Communications	There are adequate communication facilities within the SUL	1

Evaluation of the sentinel surveillance networks

From the 206 articles, a vast majority were reported to be useful (n=200, 97.1%) by the authors. Furthermore, acceptability of the sentinel network was high (n=191, 92.7%), with sensitivity (n=187, 90.8%) and representativeness (n=157, 76.2%). Meanwhile, a large proportion of the articles had an obvious degree of complexity (n=105, 51.0%). Overall, data quality was high, with 99 articles (48.1%) reporting less than 10% of data missing.

Some of the evaluation parameters showed a higher degree of uncertainty. Overall, 182 (88.3%), 181 (87.9%), and 175 (85.0%) of the articles did not provide enough information to objectively assess stability, timeliness, or flexibility, respectively.

Table 16. Multinomial logistic models used for evaluation of criteria performance in sentinel surveillance networks, selected by an AIC stepwise approach.

Model	Model equation	AIC

1. Sensitivity	Sensitivity = $\beta_0 + \beta_1$D1 + β_2D2 + β_3E1 + β_4E2 + β_5E3 + β_6I1 + β_7I2 + β_8L1 + β_9L2 + β_{10}P1 + β_{11}R1 + β_{12}R2 + β_{13}R4+ β_{14}R5	132.6
2. Representativity	Representativity = $\beta_0 + \beta_1$D1 + β_2E3 + β_3I1 + β_4I2 + β_5I3 + β_6L1 + β_7L2 + β_8P1 + β_9R2 + β_{10}R3	232.3

D1 Administrative boundaries ; D2 random, E1 geographical features ; E2 ecology (vector) ; E3 variation in ecology ; I 1 Past surveillance ; I2 previous studies ; I3 previous public health interventions ; L1 logistics ; L2 voluntary participation ; P1 population numbers ; R1 risk based on human disease number ; R2 variation in risk ; R3 risk based on vector data ; R4 measure of risk used, but measure unspecified ; risk based on host animal data

Best fitting models, as determined by stepwise model selection, are reported in Table 16. Logistic regressions showed that choosing sites used in previous studies, based on population numbers or using a risk measure of host animals were strongly significantly associated with sensitive surveillance systems. Meanwhile, use of logistical constraints, population numbers, use of sites from previous studies or past surveillance initiatives, sites with previous public health intervention, and variation in ecology were criteria significantly associated with representative surveillance systems (**Table 17**).

Table 17. Logistic models investigating the effects of using specific sentinel site selection criteria on surveillance network sensitivity and representativeness

Criteria		Sensitivity				Representativeness			
		Value	**Std. Err.**	**|z|**	**P-value**	**Value**	**Std. Err.**	**|z|**	**P-value**
Intercept		4.433	0.962	4.610	<0.001	0.501	0.260	1.923	0.054
D1	Administrative boundaries	-1.632	0.864	-1.889	0.059	0.493	0.553	0.893	0.372
D2	Random	-0.350	1.195	-0.293	0.770				
E1	Geographical features	-0.700	0.982	-0.713	0.476				
E2	Ecology (vector)	-1.237	0.958	-1.291	0.197				
E3	Variation in ecology	-1.550	1.076	-1.441	0.150	0.869	0.330	2.630	0.009
I1	Past surveillance	1.055	1.172	0.900	0.368	0.836	0.332	2.519	0.012
I2	Previous studies	1.640	0.702	2.338	0.019	2.386	0.290	8.224	<0.001
I3	Previous PH interventions					2.417	0.289	8.355	<0.001
L1	Logistics	-0.245	0.965	-0.254	0.799	1.338	0.648	2.065	0.039
L2	Voluntary	-0.902	1.256	-0.719	0.472	0.675	0.819	0.824	0.410

P1	Population numbers	1.909	0.710	2.688	0.007	1.457	0.678	2.150	0.032
R1	Risk (human)	-1.685	0.939	-1.795	0.073				
R2	Variation in risk	-0.923	0.935	-0.988	0.323	1.115	0.652	1.710	0.087
R3	Risk (vector)					-0.149	0.536	-0.278	0.781
R4	Risk (unspecified)	-2.06	1.4	-1.47	0.142				
R5	Risk (host animals)	2.952	1.244	2.374	0.018				
McFadden's R^2		0.190				0.069			

Selection criteria which were used in over 15 articles were included in the models. The reference levels for the analyses were "not sensitive" and "not representative".

Discussion

Vector-borne diseases are rapidly emerging worldwide, a phenomenon precipitated by climate change (5,19,20). As vector habitat range expands, public health authorities see the need to survey large geographical areas to detect changes in the distribution of vectors and associated changes in the spatial distribution of VBD risk. Sentinel surveillance provides an attractive surveillance method by limiting costs and offering targeted insight into the disease cycle through time. Our scoping review offers a portrait of how sentinel surveillance networks for VBDs are designed, including the type of sentinels used, the number of sentinel units, and the disease detection methods used. Furthermore, we have been able to summarize key criteria used for the selection of sentinel unit location in the context of VBDs and provide a rudimentary evaluation of these networks.

The four VBDs most frequently targeted by sentinel surveillance systems in the reviewed literature were malaria, West Nile virus, lymphatic filariasis and schistosomiasis. Overall, mosquito-borne diseases accounted for two thirds (67%) of retained articles, possibly reflecting global concern that by 2050 half of the world's population could be exposed to disease-spreading mosquitoes such as *Aedes* spp., due to their expanding habitat range (1). Malaria represents a major global health burden, accounting for approximately 435 000 deaths annually (21) and it was therefore not surprising that one third (33%) of retained articles focused on this parasite. However, despite dengue showing the greatest increase in global incidence in the last 50 years, with a 30-fold rise, none of the articles included in our review targeted this disease (22). Meanwhile, sentinel surveillance has been shown effective in

monitoring transmission for other diseases spread by *A. aegypti*, such as Zika and chikungunya (23). As collection methods and laboratory techniques are often similar for analysis of pathogens transmitted by a specific vector species, we suggest that existing sentinel networks could increase their impact by diversifying surveillance targets to include a larger breadth of neglected tropical diseases in regions where they are emergent or endemic.

Mosquito trapping, blood sampling or symptom surveillance/questionnaires in humans, followed by blood sampling in animals were the most commonly used data collection methods. As for laboratory methods, ELISA and PCR tests were most often employed. These relatively simple methods require limited training and resources (in comparison to more extensive methods such as rodent capture, physical examinations, specialized laboratory tests) and may therefore have logistical advantages over more complex or expensive techniques in terms of network feasibility and sustainability.

A total of 45 selection criteria were identified from the different articles retained in our scoping review, reflecting the large variety of criteria considered by public health authorities when designing surveillance networks. This list of criteria provides a starting point for researchers and public health authorities seeking to identify selection criteria that will help design a sentinel network capable of fulfilling their surveillance objectives. Overall, an average of 2.4 criteria were used in the articles examined in this review, suggests that, in practical terms, working with a limited number of criteria may be sufficient to achieve satisfactory sentinel unit selection.

Risk-based criteria were the most frequently used for sentinel unit selection. Risk measures included incidence of human cases of VBD, presence of host animal, variation of risk between sentinel site locations, presence or abundance of the primary vector, or lastly, some unspecified measure of risk of disease. As sentinel surveillance utilizes a limited subset of the population, using risk to orientate the location of sentinel units should allow for more sensitive data collection. Logistic regression analysis showed that using a selection criterion based on risk as measured by the use host animals is significantly correlated with sensitive surveillance systems ($p=0.018$). This supports the use of sentinel animals as a sensitive initial indicator of risk (24-28), with the caveat that care must be taken to select an epidemiologically appropriate sentinel animal for the disease being studied (11).

Environment was the second most frequent category of criteria used in selection of sentinel unit locations – particularly geographical features. Variation in ecology (without explicit detail into which features were taken into consideration) were correlated with a more representative surveillance system ($p=0.009$). None of the environmental criteria were correlated with sensitive surveillance systems. Despite this finding, we argue the importance of considering environment and landscape features in the selection of a sentinel unit, as VBDs are known to be sensitive to environmental changes, including ecological, landscape and geographical characteristics (19,29). However, choosing sentinel unit locations based solely on environment may hinder representativeness if anthropogenically driven factors, such as human movement, urbanization and poverty, are not taken into consideration (30). Environmental criteria nonetheless play an increasingly important role in the era of climate change, and so we suggest that careful selection of sentinel unit locations based on both ecological and geographical criteria will help insure sensitivity and long-term relevance of the surveillance system, especially in the context of disease emergence.

Many surveillance networks used past information to select sentinel unit locations, taking advantage of sites used during previous surveillance initiatives (34 networks) or research projects (21 networks). These selection criteria are likely to lead to a longer time series and reduce resources required to establish new sentinel locations. Furthermore, surveillance systems that used past study sites (including past surveillance sites, or sites which have been previously targeted for public health interventions) as a selection criterion were significantly more representative ($p<0.001$). Considering this information, we suggest that using existing sites established in previous initiatives and converting these to sentinel unit locations may be advantageous, provided that the previous study's objectives and data collection methods are compatible with those of the new surveillance network. Meanwhile, surveillance networks that evaluate intervention methods represent a special subgroup; in this case it is also important to determine if sentinel unit locations are to be places in areas with or without application of the targeted public health interventions.

Researchers should evaluate the added value of considering the geographic distribution of their sites – administrative boundaries may have a slightly negative impact on sensitivity of the sentinel surveillance network ($p=0.059$) but could ensure equity in resource allocation across

a territory. This could be overcome by selecting an even distribution of sites within the study zone or random distribution of sites that do not appear to have a negative impact.

Taking into consideration population-based criteria, such as population numbers, for selection of sentinel unit location was associated with increased representativeness and sensitivity of the surveillance network ($p=0.032$; $p=0.007$). This is unsurprising since representativeness describes the accurate representation of the disease distribution in the population by place and person. Thus, targeting the right population, or maximizing the population reached by the sentinel units can provide a better portrait of the disease situation.

Finally, logistical criteria (for instance, taking into consideration travel distance and access to sentinel sites) was associated with representativeness of the surveillance network ($p=0.039$). This suggests that sound strategic planning of sentinel unit locations, taking into account logistical constraints and aiming for voluntary participation, is more likely to result in effective and feasible data collection, resulting in a better understanding of the disease and its repercussions on human populations.

One limit of this scoping review is that the literature search targeted VBDs that can be transmitted to humans. However, articles that reported on VBDs solely impacting animal health were not excluded, as they are still considered of public health importance, and can impact human populations indirectly. These diseases, such as bluetongue, are nevertheless under-represented in our results. Although many of the criteria identified will be broadly applicable to any type of sentinel network targeting VBDs, specific additional criterial may be important to consider when build sentinel surveillance networks for VBDs affecting principally animal populations, or even plants (31).

Our logistic regressions provided insight into ways of prioritizing criteria selection to optimize sentinel surveillance network performance. However, these regressions should be used as indicators, and limitations from this approach are important to note. Firstly, lack of sensitivity or representativeness may not necessarily be due to sentinel unit location, but due to the methods used (e.g., failing to use an appropriate species as sentinel animals) (32). Next, due to the complex nature of evaluating surveillance networks and the limited information available in the articles, we used simplified proxies in order to determine whether a particular surveillance network successfully met the CDC system attributes (14). However, there was still

a high volume of missing information, where the reviewers were unable to determine whether the parameter was fulfilled.

Our results from the descriptive analyses of evaluation parameters and the performance score highlight an important gap in thorough reporting of surveillance functionality in publications. In addition, in articles where the aim was specifically to evaluate the surveillance system, the evaluation usually focuses on a single key aspect of the overall performance of the network, such as sensitivity, representativeness, timeliness, or stability (28,32-39). The need for a comprehensive approach to evaluate surveillance systems, which should be complete, flexible, and operational has been identified in the past (40). We add to this conclusion that clear and concise reporting of surveillance network evaluations should be incorporated into this approach. This would allow researchers and public health authorities implementing new surveillance networks or adding new sentinel unit locations to their network to grasp potential benefits and challenges associated with different surveillance network designs.

Our scoping review characterized different elements required for the construction of a sentinel surveillance network for VBDs. Findings from the literature can act as a reflection exercise for those wishing to establish a new sentinel surveillance system. We have identified tools that could prove valuable for such aims, including a standardized and comprehensive approach to evaluating surveillance systems and a tool to prioritize criteria that pinpoint locations which would be most effective in sentinel unit dispersal for the establishment of sentinel networks. In particular, given the high number of criteria and the particularities of individual VBDs, the development of an algorithm which could be applied by researchers or public health authorities in order to prioritize criteria to meet surveillance objectives would be a useful future development in this area.

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Chapter IV: Criteria for selecting sentinel unit locations in a surveillance system for vector-borne disease: A decision tool

Abstract

With vector-borne diseases emerging across the globe, precipitated by climate change and other anthropogenic changes, it is critical for public health authorities to have well-designed surveillance strategies in place. Sentinel surveillance has been proposed as a cost-effective approach to surveillance in this context. However, spatial design of sentinel surveillance systems has important impacts on surveillance outcomes, and careful selection of sentinel unit locations is therefore an essential component of planning. A review of the available literature, based on arealist approach, was used to identify key decision issues for sentinel surveillance planning. Outcomes of the review were used to develop a decision tool, which was subsequently validated by experts in the field. The resulting decision tool provides a list of criteria which can be used to select sentinel unit locations. We illustrate its application using the case example of designing a national sentinel surveillance system for ticks and Lyme disease in Canada. The decision tool provides researchers and public health authorities with a systematic, evidence-based approach for planning the spatial design of sentinel surveillance systems, taking into account the aims of the surveillance system and disease and/or context-specific considerations.

Introduction

The geographical distribution of vector-borne diseases (VBDs) is increasing all around the world; some VBDs are re-emerging in areas where they had disappeared for some time (e.g., malaria in Asia) whilst others are appearing in new locations (e.g., West Nile Virus in North America) (1, 2). Factors including climate change and globalization have expedited the process of disease emergence, as they have created favorable conditions for these diseases to evolve (2). As these facilitating factors are impossible to control in a timely fashion to stop and reverse geographical expansion of VBDs, public health authorities must adapt their practices and act

further down the line of disease emergence – in preventing the transmission of pathogens from vectors to human populations.

To implement timely and efficient interventions against VBDs, public health authorities require surveillance systems which provide a defined spatio-temporal portrait of the disease and vectors on their territory, over a time period of sufficient length to assess trends and intervention outcomes. Concurrently, for surveillance system to stay sustainable, the surface area and granularity of the surveillance performed are limited by finite resources, requiring that specific areas be prioritized when the whole of the territory cannot be fully surveyed. This issue is further emphasized when disease prevalence increases. This phenomenon imposes additional stress on surveillance systems and resources, which may further restrict surveillance coverage of the study area e.g., passive tick surveillance in Canada, which was gradually reduced in endemic regions (3).

Sentinel surveillance offers the opportunity to target specific locations to inform about risk across larger study areas, thus reducing resources required by limiting sampling units and effort (3). Sentinels are a finite subunit of a population which are measured repeatedly through time. However, as the sample size is restricted, the sentinel units and their location must be carefully chosen during the planning phase to effectively answer surveillance objectives and avoid suboptimal use of resources or even inaccurate results. For instance, some locations may be better suited to following disease and pathogen trends, while others may be more effective at capturing early warnings of disease emergence. Furthermore, if vector surveillance is carried out in ecologically unsuitable environments, absence of vectors may falsely indicate low risk of VBDs across the surveillance zone.

In the context of VBDs, sentinel surveillance has been both successful and unsuccessful for monitoring disease risk to human populations. In some cases, the use of sentinel animals (e.g., chicken, horse, crow) has allowed for early detection of West Nile virus; however, this has not always been replicated and sentinels occasionally fail to emit a signal prior to the diagnosis of the first human cases (4-8). Dogs can also serve as effective sentinels to track the risk of Lyme disease (LD) in endemic regions, but research has shown that in non-endemic regions, canine seroprevalence is not a representative measure of the risk to humans in the context of emergence (9-11). These examples highlight the complexity of decision-making in sentinel

surveillance for VBDs and the fact that although surveillance may work in a particular setting, the application of the same protocol may not be effective in another context.

One of the first decisions to be taken by public health authorities in establishing a sentinel surveillance system is to determine which type of sentinel unit will be used. We will define a sentinel unit as the statistical unit of the surveillance system associated to a known geographical location. As such, sentinel units can be diverse and include individual animals, animal herds, medical/veterinary clinics, physicians, laboratories, zoos, etc. To support researchers in choosing the right sentinel species, a framework has been previously generated (12). Once the type of sentinel unit has been chosen, it must be distributed spatially across the study zone. The importance of geographical location of the sentinel units for the effectiveness of the sentinel system has been highlighted in a previous framework (13). For sentinel surveillance of influenza, the WHO has established guidelines for selection of sentinel sites (14). However, such guidelines (or similar decision tools) are missing for sentinel surveillance of VBDs.

In Canada, the emergence of Lyme disease is a public health priority (15, 16), and a national sentinel surveillance network for active acarological surveillance is being implemented. However, to ensure effective surveillance across a large study zone, a decision tool to support the selection of geographical locations of sentinel sites (from here on, this concept will be referred to as sentinel unit locations) should be utilized to ensure a systematic approach to surveillance system design; such an approach would ensure reproducibility of the surveillance design and homogeneity in the decision-making steps, encouraging comparability of results. In response to this problem, our research team previously conducted a scoping review to extract selection criteria used in choosing sentinel unit locations across different epidemiological contexts. As epidemiological context and surveillance objectives may influence spatial design of a sentinel surveillance system, we identified the need for a systematic approach to ensure key decision issues are addressed during the planning phases of the surveillance system.

The first aim of this study was to develop a decision aid tool to support the selection of sentinel unit locations, by identifying relevant criteria to consider for geographical distribution of sentinel units within the study zone. The second aim was to demonstrate the functionality of the decision tool by applying it to the design of a national sentinel surveillance system for emerging LD risk in Canada as a case study. Our research will support public health authorities

in transparent decision-making for planning of sentinel surveillance of VBDs, allowing the integration of spatially explicit information in surveillance design (17).

Methods

Development of the decision tool

To identify the decisional requirements to include in the spatial design of a sentinel surveillance system, based on the context of the surveillance initiative, we carried out a review based on a realist approach. Realist reviews have been used in the past to develop the conceptual basis and operations requirements for surveillance frameworks in vector-borne diseases, as these are designed to gain an understanding of how complex programs work in different settings. We adapted this approach to meet our review needs, to allow us to evaluate how different criteria for choosing sentinel site locations are used in different contexts.

A recent scoping review provided the scope and the exploratory background search for this current review (18). The database of articles built up during the scoping review was used for the purposive sampling steps, as the search strategy corresponded to the need of our review (18). The primary studies were appraised to extract key decision points related to sentinel surveillance planning. These findings were synthesized and integrated as foundational aspects of the decision tool. Full details of the realist-type approach are detailed in the supplementary material (Appendix 2).

Planning a surveillance system is a complex problem which requires several important decisions. Firstly, the type of sentinel unit should be decided upon e.g., site where vector surveillance will take place or where animal herd will be positioned, or a medical/veterinary clinic. Our decision tool will provide insight into how to distribute sentinel units across the study zone. However, determining the number of sentinel units which will form the sentinel surveillance system will be considered beyond the scope of the tool. Public health authorities and researchers may decide on this point based on resources available, surveillance objectives, and disease situation.

Validation of the decision tool

To ensure the functional validity of our decision tool, 14 experts in public health surveillance of VBDs were contacted and asked to assess the tool for functionality, as done in previous

methodological research (19). Experts were required to complete an individual web-based questionnaire, with the aim of assessing whether the proposed tool was relevant, complete, and self-explanatory. At the end of the questionnaire, text boxes were available for final comments and suggestions (Appendix 3). A total of six experts responded (43% response rate) and questionnaires were examined by the research team and the results were used to update and improve the decision tool. The final version includes findings from our literature analysis and modifications following the validation by experts.

Application of the tool: A case study

Lyme disease cases in Canada have shown a significant expansion during the 21st century; since its addition to the notifiable disease registry, the number of reported cases went from 144 cases reported in 2009 to close to 3000 cases in 2021 (20). In response to this increasing risk, the Canadian Lyme Disease Research Network (CLyDRN) was created in 2019. As part of its research objectives, the CLyDRN had the mandate to build a sentinel surveillance system to provide comparable LD risk measures across the country, based on active surveillance of ticks. A sentinel approach was advocated as it allows for a feasible surveillance strategy across a vast study zone. The selection of criteria to guide final geographical location of sites for this LD sentinel surveillance system at a national level was used as a case study to illustrate the application of the decision tool in supporting selection of sentinel unit locations.

Results

Identification of a decision path and key decisions issues

In the previously performed scoping review, criteria had been classified into six categories: past information, risk, environment, human population characteristics, distribution of sites, and logistics (18). This classification was kept as a skeleton for the decision tool and was used to identify key decisions that should be considered during sentinel site selection, to account for fundamental aspects of the epidemiological situation. The decision issues identified for each criterion, which constituted a key element of the tool were identified from the review (**Table 18**).

The starting point for the tool is to consider any previous studies (**past information**) or unit locations which have been used in the predetermined study area. We propose to include these sites as a starting basis if they have been used to answer objectives similar to those of the sentinel system being developed. This will contribute to a longer temporal sequence for surveillance and previously collected data could provide valuable insight into the current situation of the VBDs within the sites (21-31). Next, if the objective of the system will be to evaluate a public health intervention, it is important to know whether there have been previous interventions conducted within the sites and choose sites accordingly (32-40).

The next category of criteria to consider is **risk-level**, that is, the presence or absence of an indicator/measure of risk to determine priority areas for sentinel unit locations. Sentinel sites are often sampled using a risk-based approach targeting subgroups of a population where disease or the pathogen is more likely to be present (41). Many different types of sources of data can be used for evaluating risk to humans, e.g., using data from vectors, host animals, or human cases (21, 22, 42-48). Often, these can be integrated together to obtain an overall risk signal. Publicly available databases e.g., the Expanded Special Project for Elimination of Neglected tropical diseases (ESPEN) (49), can provide large scale risk data and can be used to understand the variation in risk across space. Early warning systems (EWS) constitute a special case for which human case data may not provide a signal in a timely manner and for which other data sources, such as host animal data should be prioritized; their use has been frequently reported in the literature and has resulted in sensitive surveillance systems (45-47, 50-53). Another valid alternative is vector data, including vector abundance or pathogen prevalence in vector populations. Data availability and accessibility may affect the selection of risk-based criteria.

Because **environment** plays such a crucial role in the transmission cycle of vector-borne pathogens, it constitutes an important category and criteria pertaining to it are involved in key decisions issues. Ecological suitability for presence of vectors and climatic conditions are predominant criteria (22, 48, 54-58). Larger variation in ecological features may allow for risk factor profiling (6, 36, 59-66). For use of surveillance systems as EWS, we recommend that the selection criteria be orientated towards a risk-based measure, as opposed to environmental criteria, to improve specificity.

In public health surveillance, population-oriented approaches are advocated. To get the best representativeness, surveillance system will aim to maximize population coverage (43, 47, 67-75). Other **human population** criteria which may be utilized by the researcher are dependent on the surveillance objectives and disease context (71, 72, 76-78). For instance, does the surveillance initiative target a particular population structure? Is population stability of key importance in the transmission cycle, as seen in lymphatic filariasis (69, 74, 77, 79-82)? Is the presence of certain human activities required for disease transmission, for instance human water reservoir contact for schistosomiasis (46, 83-85)?

In the **distribution** of sites category, the main criterion identified was equity of resources allocation for distribution of sentinel units across the study area. For instance, although risk may be concentrated in a particular area, it may be necessary to characterize and follow the risk in different areas. Administrative boundaries (e.g., municipal, county, or regional) can be used to ensure equity and presence of a sentinel unit in different or priority administrative sectors (61, 73, 86-95).

Logistics criteria were incorporated as a decision step within the decision path to enhance the feasibility and sustainability of the system. This last group of criteria can also be used as a discriminatory feature to select between multiple potential sites which meet equally the previous selection criteria. This group of criteria mostly deals with any logistical constraints related to the sentinel unit location including the need of voluntary participation, presence of specialist centers, stakeholder opinions, or adequate communication facilities (32, 43, 69, 96-112).

Table 18. Selection criteria for choosing sentinel unit locations within a surveillance system for vector-borne diseases; each criterion has associated decisions issues which public health authorities must consider in light of their surveillance context sentinel unit location

Criteria group	Criterion	Decision issues	Selected references
Past information Previous knowledge, from former studies or surveillance programs,	Sites used in previous studies or surveillance initiatives	• These sites can provide a longer temporal series • Data from these sites could provide valuable insight into the current	(21-31)

which support the selection of sentinel unit location		situation of the disease within the sites	
	Sites with previous interventions	• When testing public health interventions, there must have been documented interventions conducted at the sentinel sites; this can be a single or multiple types of interventions /intervention intensities	(32-40)
Risk The presence or absence of an indicator of risk or use of a measure of risk to determine priority areas for sentinel unit location	Risk measure from host animals	• For Early Warning Systems, risk measures from host animal data are commonly used to select sentinel sites • A combination of human case, vector and host animal data can be used to evaluate risk level if following disease trends	(45-47, 50-53)
	Risk measure from vector data	• Vector data, such as abundance of vectors, is often used to provide a measure of risk to target sentinel regions • May be appropriate in the context of EWS • A combination of human case, vector and host animal data can be used to evaluate risk level if following disease trends	(22, 46, 47, 53, 113-115)
	Risk measure from human case data	• Human case data can be used to target zones of higher risk and identify priority regions which should be monitored by sentinels • For EWS using a risk measure from human case data doesn't provide a timely signal • A combination of human case, vector and host animal data can be used to evaluate risk level if following disease trends	(21, 42-45, 47)
	Variation in risk	• When the purpose of the surveillance system was to test an intervention method, having sites with a variety of risk levels can evaluate intervention efficacy across different epidemiological contexts	(59, 71, 76, 116-120)
Environment Consideration of the ecological features of the study zone to	Ecology suitable for vectors	• Appropriate ecology for the establishment of vectors in a prerequisite for VBD circulation	(22, 48, 54-58, 112)
	Consideration of geographical features	• Certain geographical considerations, such as altitude and latitude, can be determinants of presence of VBDs	(21, 27, 47, 52, 57, 117, 121-123)

determine priority areas for sentinel unit location	Variation in ecological features	• A variation of ecological features across sentinel unit locations may be required if the surveillance system involves risk factor profiling	(6, 36, 59-66)
Human population Human population characteristics are used to determine priority areas for sentinel unit location	Consideration of population numbers or population density	• Surveillance systems will attempt to maximize their population cover	(43, 47, 67-75)
	Population demographics	• Population demographics can influence VBD disease cycles e.g., population structure • To target sentinel unit locations which are relevant to the surveillance objectives, considering population demographics may be of benefit e.g., where high risk groups reside	(71, 72, 76-78)
	Population mouvements	• In some disease contexts, population movements are important to consider as they support a better understanding of the epidemiological portrait • E.g., individuals emigrating from an area endemic for malaria may facilitate spread of the parasite across locations • E.g., mechanical movements of humans could bring vectors e.g., mosquitoes	(69, 74, 77, 79-82)
	Presence of human activities	• Depending on disease context, consideration of human activities can be important in the surveillance context • E.g., human activities in aquatic envrionments are required for the transmission of schistosomiasis • E.g., outdoor activities can increase exposure to vectors	(46, 83-85)
Distribution of sites Spatial considerations for distribution of sentinel units across the study area	Administrative boundaries	• To ensure equity of resource allocation, it may be desirable to consider administrative boundaries (municipal, regional, etc.)	(61, 73, 86-95)
Logistics Feasibility of the sentinel surveillance system, including access or diffusion of results	Site accessibility, voluntary participation, communication facilities, health centers, etc.	• To ensure sustainability and feasibility of the surveillance system, logistic criteria should be considered	(32, 43, 69, 96-112)

A decision tool for sentinel surveillance of vector-borne diseases

Broad criteria categories were organized in a decision path to form a logical sequence of checkpoints and act as the tool for criteria selection. The user can follow each step of the path, however it may be used in an iterative manner. Within each step, key considerations identified through the review are presented as decision issues; these strategic questions can be answered by users during the planning process. Finally, the decision tool was assessed by experts and adjusted accordingly to ensure its validity (**Figure 22**). The functionality of the decision tool is demonstrated using a case study (section 3.3).

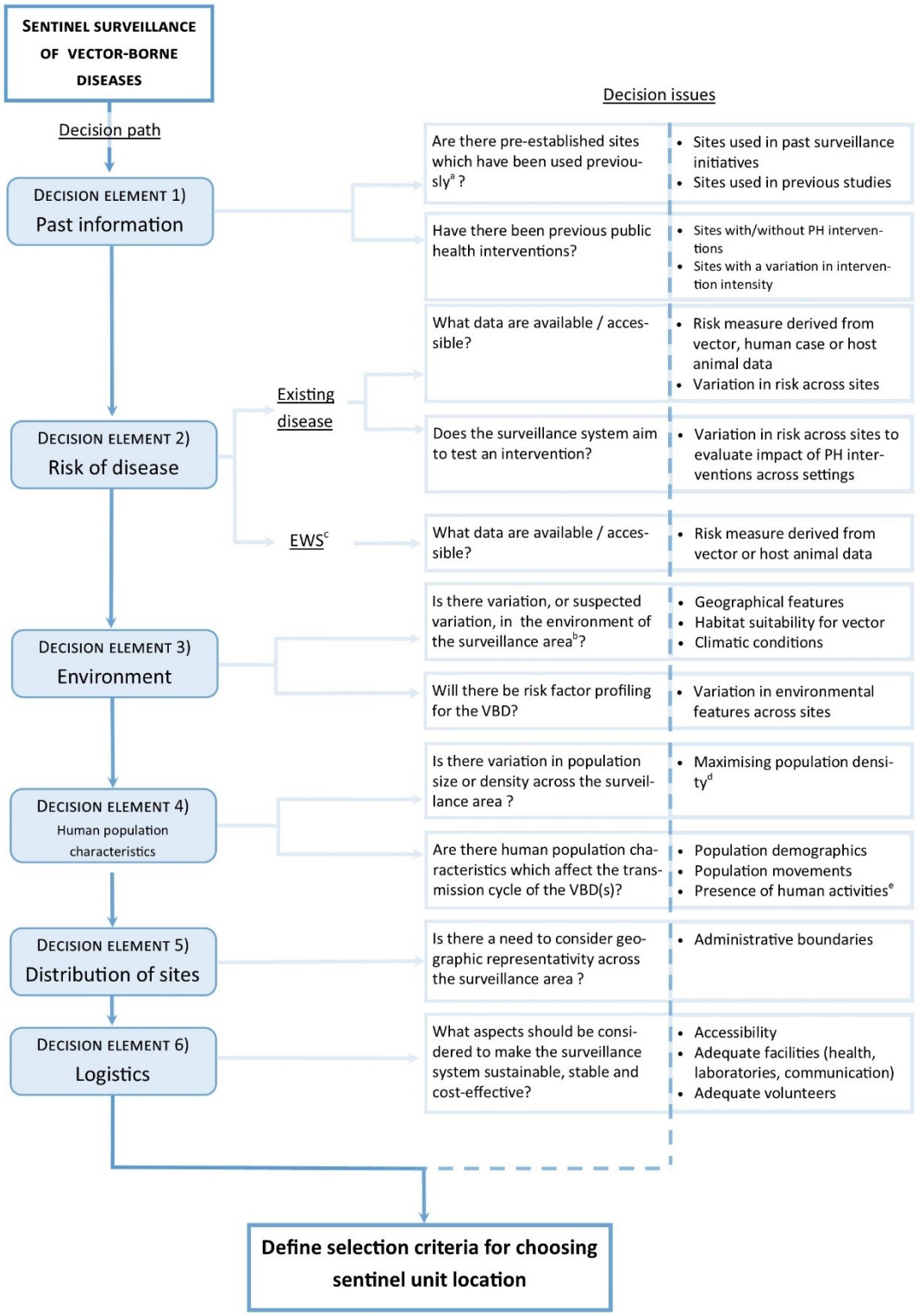

Figure 22. Key criteria to consider when developing a protocol for the selection of sentinel unit locations for vector-borne diseases

[a] Site should have been used for a similar objective

[b] The variation in the environment is judged significant by the investigators

[c] Early warning system
[d] It is also relevant to consider potential important population influx e.g., from tourism, occupational reasons
[e] Human activities which influence exposure to vectors / vector-borne diseases

Sentinel surveillance for Lyme disease in Canada: a case study

The objective of the CaLSeN is to follow spatiotemporal LD risk trends in Canada. Following the decision to build a sentinel surveillance network, the Surveillance Working Group began by deciding upon the basic network structure. The sentinel unit within the network will consist of a sentinel region., where active surveillance efforts (drag sampling for ticks) will be concentrated. Sentinel regions will consist of a 50km radius-wide area in proximity to a population center and will contain of 5 to 10 individual sampling sites. LD risk is very different across provinces and to provide a comparative portrait of LD, at least one sentinel region will be selected in each province. This will ensure that all provinces are represented, meeting CLyDRN's mission statement. The number of sentinel regions will depend on the size of the province, which varies greatly, and on each province's capacity to carry out fieldwork (human resources). As part of the initial planning phases for the surveillance network, we should consider how the spatial design of the network will be constructed.

The decision tool was used to determine how sentinel regions will be distributed across Canada. The decision path was used (**Figure 23**). At the first checkpoint (*past information*), we considered if previous sites have been used in similar surveillance initiatives. Although there has been past active surveillance done in most of the Canadian provinces, there are no sentinel regions established for more intensive active surveillance initiatives. There are no planned public health interventions as part of the surveillance system. Thus, at this checkpoint, no criteria were retained. For the second checkpoint (*risk*), we have decided to monitor the disease in regions where risk is the most significant (i.e., as existing disease). We did not aim for the network to act as an EWS, as we planned to select a finite number of sampling units, but rather to provide a representative epidemiological portrait across Canada. Human case data is difficult to obtain, due to its sensitive nature, and we have resorted to passive tick submissions, available across the territory. Passive tick submissions have been determined to be a good signal for LD risk in human population in past studies (124). This was the only criteria retained, as currently no interventions are planned within the surveillance system. For the third

checkpoint (*environment*), as we see important variations in environment-type within provinces, this criterion should be incorporated in the decision-making process. Furthermore, as climate change is an important factor for tick range expansion and tick population establishment, climate, in the form of temperature, was also retained. Risk factor profiling is not a primary aim of the surveillance system, hence variation in ecology was not kept as a criterion. For checkpoint 4 (*human population*), we wished to maximize the human population covered by the surveillance system i.e., we aimed to select sentinel regions with higher population density such as urban centers. We decided not to consider population particularities, as access to demographic data at the municipal level across the whole of Canada posed challenges. Nonetheless, this could also be retained e.g., to consider populations with higher risk of exposure to blacklegged ticks such as forest workers, indigenous communities, etc. (125, 126). For checkpoint 5 (*distribution*), the design of the sentinel system already covers how resources are allocated: we aim for at least one sentinel region per province. However, within the province, there is no need to consider administrative boundaries. Lastly, for checkpoint 6 (*logistics*), the main determinants of sustainability of the network are related to cost. Communication and laboratory facilities will not be impacted by the location of the sentinel region. Sampling material costs are not impacted by choice of sentinel region, but important variation of costs and time-resources will be associated with travel distance between CLyDRN collaborating centers and the sentinel region.

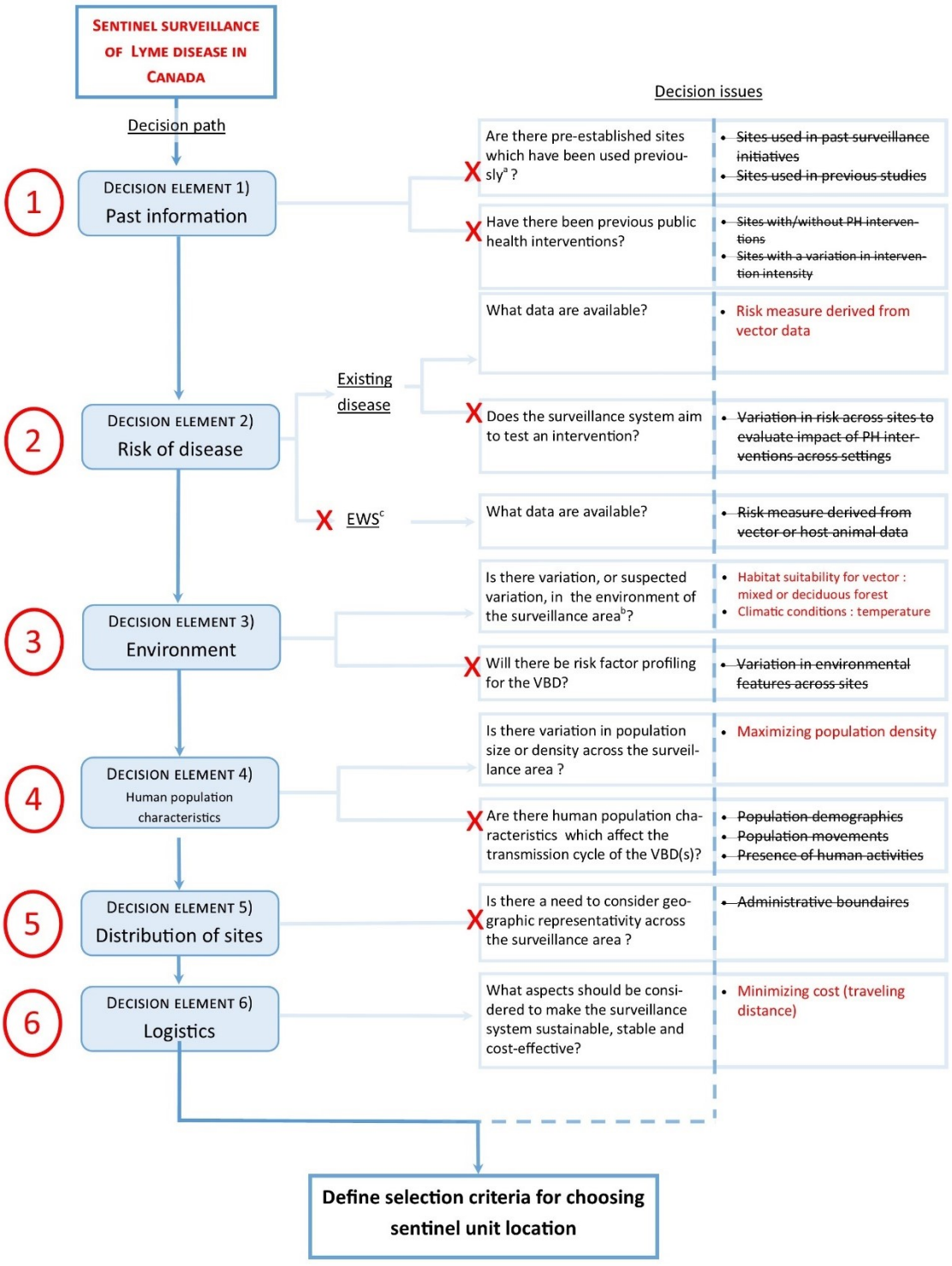

Figure 23. Demonstration of the functionality of the decision tool for determining key criteria for selecting spatial design for a national sentinel surveillance network for Lyme disease in Canada (case study)

Using the decision tool, a total of five criteria have been retained (**Table 19**). These criteria can subsequently be used within a multi-criteria decision analysis (MCDA). The MCDA encourages the participation of multiple stakeholders and provides a transparent decision-making approach. Such an analysis is the object of ongoing work in the context of this case study.

Table 19. Criteria to consider for planning the spatial design of a sentinel surveillance system for Lyme disease in Canada, retained after use of the decision tool

No.	Selection criterion
1.	Measure of risk of Lyme disease as represented by passive acarological surveillance data
2.	Ecological suitability within the sentinel region for the presence of *Ixodes spp.*, in the form of presence of mixed or deciduous forests
3.	Climatic suitability within the sentinel region for the presence of *Ixodes spp.*, in the form of accumulated degree days
4.	Population density covered by the sentinel regions
5.	Travelling distance between the sentinel region and CLyDRN collaborating centres

Discussion

Our study has permitted the development of a new decision tool to guide spatial design of sentinel surveillance systems. As sentinels are a limited sample of a population, careful selection of sentinel unit location is essential for the system to be effective. Although such decision tools were available for other types of infectious diseases, it was not the case for VBDs (127). As VBDs require complex interactions between pathogens, vectors and animal hosts, risk distribution becomes heterogenous in space (128). Careful selection of sentinel location becomes even more crucial to ensure data from sentinel sites is representative of the epidemiological portrait across the study area.

Conducting a review of the material obtained from previous work (18) allowed the identification of key decisions issues. We based our decision tool development approach on previous papers dealing with VBDs (13, 129). Being based on a broad literature search, a strength of our review was the inclusivity of research papers, providing insight into key decision issues to consider for elaborating the spatial design of VBD sentinel surveillance systems. Despite this inclusivity, it is important to note that many papers in the literature do not explicit the decisional process behind selection of sentinel unit location; thus, these papers would have been excluded in the original scoping review database (18). Furthermore, some VBDs e.g., malaria, West Nile virus, are overrepresented (18). However, validation by experts working on different VBDs helped strengthen the decision path.

VBDs represent a vast and heterogenous group of infectious diseases: their transmission cycles are complex and vary considerably from one disease to another. By keeping the scope of the decision tool wide, it is amenable to various VBDs but it could mean that some of the criteria suggested by the tool may not be relevant the specific disease or pathogen under surveillance. For instance, some VBDs do not rely on animal reservoirs e.g., malaria (130), whilst that others, such as West Nile Virus or LD, depend greatly on animal reservoirs to persist in the environment (131). Some criteria provided by the decision tool may be too broad for application and should be refined appropriately e.g., climatic conditions, habitat suitability. We acknowledge that to maximize the utility of the tool, users must have expertise in the field of the VBD under surveillance and also, knowledge about surveillance systems. Nonetheless, we believe the decision issues can be regarded as transversal: public health authorities or academics should follow the decision path regardless of the VBD(s) they are planning on surveying; this will ensure that key decision issues are not overlooked. The user must keep an open mind and flexible approach and use the tool as an aid as opposed to a strict procedural algorithm. The tool may be used in an iterative manner.

The inclusion of a vast scope of the literature has allowed the development of a decision tool that is not only adaptable to VBDs but also different contexts and surveillance objectives. However, the assessment of how the stage of the disease's emergence process may impact decision issues was not a focus of our realist-type review. The surveillance strategy may indeed diverge depending on whether a disease is absent, in emergence or endemic. Although this could have an impact on sentinel unit locations, we would recommend first to evaluate the

relevance of using a sentinel surveillance approach. Clow *et al.* have developed a framework for adapting surveillance approaches across different stages of the emergence process (129). Such frameworks are complementary to our work and should be used conjointly during the planning phases of the surveillance systems.

In planning a public health surveillance system, the surveillance objectives should be decided on initially as these will have an impact on the system structure (132, 133). Using sentinel surveillance as an EWS can be a difficult endeavor; due to restricted sampling, sentinel surveillance has more often been used for monitoring temporal changes in frequently occurring diseases/pathogens or to detect disease outbreaks (133). Indeed, from our review, a very small proportion of studies had the aim of acting as an EWS (18); therefore, we recommend that the tool be used with caution if the aim of the sentinel surveillance system is to act as an EWS. In this case, we advise that the decision tool could be used alongside literature dealing with sentinel surveillance as EWS, specific to the VBD under investigation (13, 102, 134).

The functionality of the decision tool was demonstrated using our case example of building a new sentinel surveillance system for LD in Canada. Using the decision tool, we believe we were able to extract all relevant decision issues related to our case study, which can be retained and incorporated into a systematic decision-making process e.g., multi-criteria decision analyses (MCDA). A total of five different criteria were retained from the decision tool (**Table 19**). Further use of the decision tool will contribute to validating its functionality, especially in differing contexts e.g., in developing countries, where access to data and research realities may be very different to the case study presented.

Although the tool does not integrate the relative importance of each criterion, additional processes can easily overcome this limitation. MCDA have been used to address complex problems relating to vector-borne diseases, such as the development of intervention plans, where multiple and conflicting criteria are applied (135, 136). MCDA has also been used to map out risk areas for infectious diseases, such as avian influenza (137); we suggest that a similar approach can be utilized, in conjunction with criteria obtained from our decision tool, to identify sentinel locations. Indeed, MCDA is an inclusive, transparent, and systematic approach for incorporating different levels of information and could be used to integrate retained criteria from the decision tool in a practical manner. Our decision tool has

consolidated information from global VBD sentinel surveillance systems worldwide and channeled it into a methodical diagram which can aid in the selection process of sentinel unit locations in versatile circumstances. The selected criteria can be integrated in an MCDA model, allowing a participative approach with stakeholders concerned by the surveillance issue. In the future, the use of the decision tool in the establishment of sentinel surveillance systems for VBDs should be evaluated to demonstrate its operational strengths and limitations; new surveillance systems created with the support of this decision tool will require evaluation to provide additional insight into spatial design of sentinel surveillance for VBD for optimization of the decision tool.

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Chapter V: Spatial multi-criteria decision analysis for the selection of sentinel regions in tick-borne disease surveillance

Abstract

The implementation of cost-effective surveillance systems is essential for tracking the emerging risk of tick-borne diseases. In Canada, where Lyme disease is a growing public health concern, a national sentinel surveillance network was designed to follow the epidemiological portrait of this tick-borne disease across the country. The surveillance network consists of sentinel regions, with active drag sampling carried out annually in all regions to assess the density of *Ixodes spp.* ticks and prevalence of various tick-borne pathogens in the tick population. The aim of the present study was to prioritize sentinel regions by integrating different spatial criteria relevant to the surveillance goals. We used spatially-explicit Multi-Criteria Decision Analyses (MCDA) to map priority areas for surveillance across Canada, and to evaluate different scenarios using sensitivity analyses. Results were shared with stakeholders to support their decision making for the selection of priority areas to survey during active surveillance activities. Weights attributed to criteria by decision-makers were overall consistent. Sensitivity analyses showed that the population criterion had the most impact on rankings. Thirty-seven sentinel regions were identified across Canada using this systematic and transparent approach. This novel application of spatial MCDA to surveillance network design favors inclusivity of nationwide partners. We propose that such an approach can support the standardized planning of spatial design of sentinel surveillance not only for VBDs, but more broadly for infectious diseases surveillance where spatial design is an important component.

Introduction

Tick-borne diseases (TBDs) represent a major concern for public health globally. The geographical expansion of tick populations has resulted in increased incidence of diseases such as Lyme disease (LD), anaplasmosis, and tick-borne flaviviruses (e.g., tick-borne encephalitis), to name a few (1-4). TBDs can affect humans, domestic animals, and wildlife, leading to far-

reaching impacts on our societies (4). Amongst TBDs, Lyme disease (LD) is the most common vector-borne disease found in the northern hemisphere (5-8).

LD is caused by a variety of genospecies of *Borrelia burgdorferi* senso lato (9). Tick vectors of LD belong to the *Ixodes* genus but differ in species according to geographical location. In North America, the principal vectors are *I. scapularis* and *I. pacificus,* in Europe they are *I. ricinus* and *I. persulcatus,* and in Asia, the main tick species of interest is *I. persulcatus* (9, 10). The spatial spread of ticks by host animals (e.g., deer, birds), leading to the local establishment of new tick populations, is a key mechanism driving the geographic expansion of LD risk (11, 12). Thus, the surveillance of ticks is used to monitor the increase in *Borrelia spp.* and other pathogens carried by blacklegged ticks in human and animal populations (13, 14).

Acarological active surveillance can be used to detect the presence of tick populations in the environment (15, 16). This method usually consists of drag or flag sampling in ecologically suitable sites (i.e., consisting of deciduous or mixed forests). The density of infected nymphs questing in the environment can be calculated, and this measure has been correlated with LD risk to human populations (14, 17). However, due to the intensive nature of active surveillance, the surveillance zone must be carefully targeted (7, 18). In Europe, several surveillance scenarios were assessed by Eurosurveillance to give insight into which methods would lead to more effective and efficient surveillance (19). In this review, active surveillance of ticks was deemed a complicated process, with difficulties involving timely, standardized sampling across a substantial study area (19).Large-scale standardized acarological active surveillance systems for LD (e.g., at the national or continental scales) are, to our knowledge, yet to be developed due to important feasibility issues, although extensive tick surveillance system have been put in place e.g., in the United States. However, such systems have the potential to provide a comparable measure of acarological hazard across space and give insight into the evolving portrait of tick population establishment and TBD risk emergence.

In Canada, human LD cases have been increasing exponentially in the last decade. In 2010, 143 cases were diagnosed and, by 2021, this number reached nearly 3000 (20). In parallel, *Ixodes* spp. tick populations have expanded their geographical range within Canada (16, 21, 22). As a result of this range expansion, the federal passive surveillance system initiated in the early 1990s experienced an increasing volume, which overwhelmed the national and provincial public health laboratories. Therefore, this passive surveillance system was discontinued in

2021. Thus, to survey the acarological risk of LD in Canada, active surveillance efforts now represent the main source of validated information. Currently, active surveillance efforts in Canada are coordinated at the provincial or regional level and performed by public health authorities or academia; therefore, funding, protocols and surveillance efforts vary greatly across the country. The expansion of the geographic range of infected-blacklegged ticks with several tick-borne disease pathogens and the risk that it poses for the health of the Canadian population highlights the need for developing a national level active surveillance network. Such a surveillance network should be able to track acarological hazard (i.e., changes in abundance of ticks) in space and time to alert public health authorities as to when and where hazard levels and can indicate the need for public health interventions. Furthermore, active surveillance permits PCR testing and can indicate that there is novel circulation of an emerging pathogen.

With the increasing public concern related to LD, the development of a Canadian Lyme Sentinel Network (CaLSeN) was proposed by the Canadian Lyme Disease Research Network (CLyDRN) as part of its 'Prevention and Risk Reduction' pillar. The objective of the network is to follow the epidemiological portrait of LD across the ten Canadian provinces, using active surveillance (drag sampling) to measure tick density and assess the occurrence of *B. burgdorferi* as well as other tick-borne pathogens in the environment. However, due to the vastness of the defined surveillance zone, active surveillance of this large territory represents a logistical challenge.

Canada has a surface area of nearly 10 million km^2, making it the second-largest country in the world by area, with a population of over 35 million (23). To survey large geographical areas using active surveillance, a sentinel approach can make the endeavour feasible. Sentinels are a fixed subset of units selected from the defined source population, sampled repeatedly through time to follow spatial and/or temporal disease trends. In the context of acarological active surveillance, sentinels take the form of sentinel sites; these sites are visited regularly so that tick densities are monitored spatio-temporally. A vast range of considerations fuel the reflection on how to distribute sentinels across the study zone, including known presence of risk, environmental suitability, and logistical constraints (24). However, during the decision-making step, the retained criteria are unlikely to all be of equal importance, a problem that needs be taken into consideration during the planning phases of the surveillance system.

Multi-criteria decision analysis (MCDA) approaches provide a systematic and objective strategy to deal with such a dilemma. MCDA is used in several fields, including economics, politics, and health, to support decision making in complex situations involving multiple and even conflicting objectives (25). MCDA has been used in the past for comparison of management plans for TBDs, including communication, surveillance, and control strategies (26, 27). Results highlighted the ability of MCDA to characterize the key issues and complexities regarding TBDs and include them in decision making. As an extension to classic MCDA, the incorporation of georeferenced data via Geographic Information Systems (GIS) can provide a spatial representation of the prioritization process emanating from the analysis. Such a strategy (GIS-MCDA) has been proposed for the public health management of vector-borne diseases in general and specifically for TBD surveillance (28, 29).

In this article, we apply a GIS-MCDA to prioritize surveillance regions across Canada for the spatial design of a new national sentinel surveillance system for ticks and tick-borne diseases (CaLSeN). This study aims firstly, to use GIS-MCDA to prioritize sentinel regions by integrating different spatial criteria relevant to the surveillance goals; and secondly, to use the resulting prioritization map to inform decision-making and selection of areas suitable for active tick surveillance. This method could be adapted to meet surveillance needs for other vector-borne diseases, or even other infectious diseases, in other geographical areas.

Methods

The Canadian Lyme Sentinel Network (CaLSeN)

CaLSeN uses a standardized protocol to map reported LD cases across Canada. Within the network, the surveillance units are "sentinel regions". Sentinel regions are circular areas with a radius of 50 km around a population center. Each node is composed of 5 to 10 sampling sites, which are visited yearly to collect ticks and ecological data. CaLSeN was first piloted in the summer of 2019 to assess the feasibility of sampling across Canada (30). Sampling did not go ahead in 2020 due to travel restrictions in place with response to the COVID-19 pandemic. The network was subsequently expanded for 2021 and 2022, using a spatial MCDA approach to support sentinel region selection.

Spatial MCDA Process

The MCDA process can be divided into ten systematic steps (Figure 24). It requires three main elements, or inputs, which must be defined: the decision makers, the criteria, and the alternatives (31). Several key concepts underpin the analysis: weighting, performance evaluation, and combination rules (or aggregation). The spatial extension to GIS-MCDA translates the data into georeferenced layers within a geographic information system to provide a spatially-explicit solution to the problem.

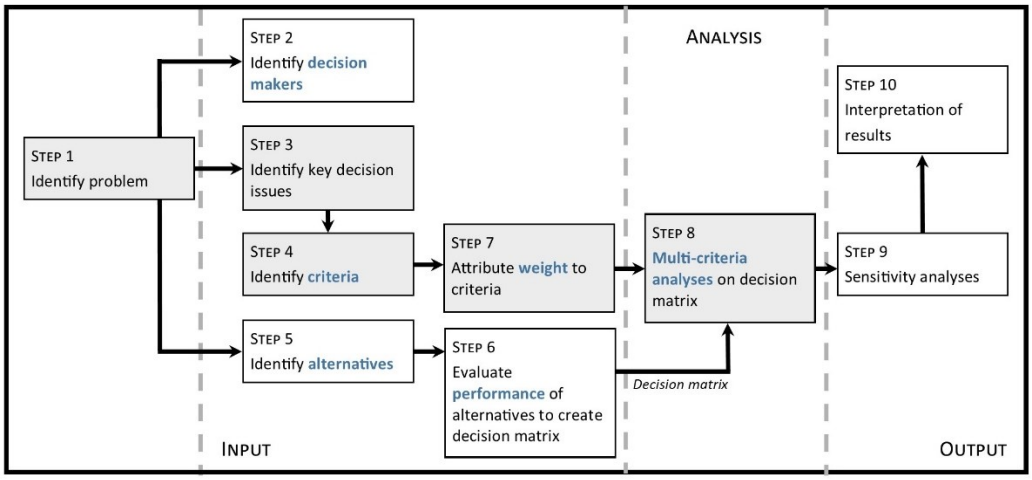

Figure 24. Diagram of general steps in multi-criteria analysis

Step 1. Identify the problem

First, the problem must be clearly identified to allow stakeholders to work towards a similar goal. This step allows project leads to identify relevant decision makers, criteria, and alternatives (see Steps 2 to 5). For CaLSeN, the problem retained was the need to identify relevant and feasible sentinel regions for the active surveillance of ticks across Canada, including presence and abundance of ticks and pathogen prevalence. Thus, it was determined that a spatial MCDA would use spatially explicit data and the output of the analysis would support decision making through the production of maps.

Step 2. Identify decision makers

Decision makers (DMs) were identified based on their participation in ongoing tick-borne disease research and their expertise in tick and LD surveillance. A total of 13 DMs were identified and agreed to participate in the study. Each province was represented by at least one decision maker. The panel of professionals was composed of academics and provincial and federal public health authorities.

Steps 3-4. Identify decision issues and criteria

A decision tool had been previously developed to help researchers and public health authorities decide on geographical positioning of sentinel locations for vector-borne diseases (32). The output of the tool is a list of criteria which should be considered during site selection. The tool was applied to our case study and performance measures were developed from the retained criteria (**Table 20**). Each criterion was translated into a vector layer in QGIS version 3.18.1 (33) using available georeferenced data (see Step 7).

Table 20. Criteria used in the MCDA for selection of sentinel regions of the Canadian Lyme Sentinel Network (CaLSeN) with performance measures

No.	MCDA criteria	Performance measure
1)	Maximize the human population reached within the units of the study zone	Logarithm of the population taken from Statistics Canada's Census 2016 data
2)	Documented risk of disease due to the presence of appropriate vector within the sentinel region	Number of passive tick submissions from federal passive surveillance system from 2010 to 2015 standardized by the logarithm of the population
3)	Ecological suitability for the presence of the vector, *Ixodes spp.* ticks	Habitat suitability indication for *Ixodes spp.* ticks using the product of the percentage of deciduous or mixed forest cover with temperature in the form of accumulated degree days above 0°C

4)	Logistical constraints	Distance traveled between the collaboration center to the center of the sentinel region in kilometers

Step 5. Identify alternatives

As stated in Steps 3-4, for each of the criteria used for the MCDA process, georeferenced data were used to measure the performance of each criterion. The use of georeferenced data layers permitted the use of all southern Canada for the consideration of sentinel regions, without being impeded by administrative boundaries. Southern Canada represents the area at a maximum of 600km from the United States border, where the risk of LD is present or emerging. The alternatives covered by the GIS-MCDA were also restriction to permit better visual differentiation between rankings in the high-risk area.

The vector layer for each criterion was converted to a raster layer with a cell size of 25 km in QGIS. The rasters contained a performance value for each cell size and the georeferenced cells were thus used as the geographical unit of the alternatives.

Step 6. Attribute weights

Each of the DMs was asked to weigh the criteria by allocating 100 points between them. Individual results were kept hidden from the group to ensure DMs were not influenced by each other. Final weights were presented to DMs during the consultation process to gain a consensus on final weights which would be applied to the MCDA. DMs decided that the final weight values for each criterion would remain the same for each model to support a standardized approach to sentinel unit selection.

Step 7. Evaluate performance

A performance score was attributed for each alternative for each of the criteria. The combination of the criteria performance scores for each of the alternatives is known as the decision matrix.

For the first criterion, human population data were obtained from Statistics Canada's 2016 Census (23). Polygons were created using publicly available census subdivision (CSD)

boundaries from Statistics Canada (23), with population data georeferenced to the centroid of the polygon.

The second criterion was addressed using passive surveillance data made available through data sharing agreements from each province. This database, created by the Public Health Agency of Canada (PHAC), specifies the number of ticks recorded per province through passive surveillance. Number of passive tick submission between 2005 and 2015 were used. The data are georeferenced to the CSD centroid of the municipality where the tick originated. For most of the provinces, a tick index was derived using these data (34) by summing the number of tick submissions from 2005 to 2015 and divided by the logarithm of the population. However, this measure was deemed inappropriate for provinces where passive surveillance was discontinued in regions of high submissions. These included Ontario, Quebec, and Nova Scotia. For these provinces, a second establishment period index was developed. Koffi *et al.* (2012) identified a threshold of passive tick submissions associated with the presence of questing ticks in the environment during active surveillance within a given CSD. Leighton *et al.* (2012) then applied this threshold to identify CSDs with a high likelihood of containing an established tick population as those which exceeded the threshold for two consecutive years, since persistent observations of high tick submissions provided stronger biological evidence of a locally reproducing tick population. We applied the approach of Leighton *et al.* (2012), analyzing the passive surveillance dataset to identify years from 2000-2015 in which tick submissions from each CSD exceeded a threshold of one tick submission per logarithm of the population and cumulating "years of establishment" following the second consecutive year in which the threshold was exceeded (35). This empirical cut-off was determined by evaluating the risk distribution across CSDs by province and selecting a threshold which was discriminatory, and which allowed within province comparisons (Appendix 4). The final index was thus a duration-of-establishment period, in years, which was used as a measure of risk for these provinces.

The third criterion, determining the ecology of the territory to allow for the establishment of ticks, was addressed using shapefile data of land cover across Canada. Ticks can establish in a range of habitats (36); however, woodlands are generally considered most suitable (37). To increase specificity of these criteria, we decided to include data on mixed or deciduous forest as these forest types are particularly associated with the presence of *Ixodes* spp. ticks (38). Land

cover data from 2015 (39) were used to calculate the percentage of forests for each 25km grid squares across the study zone. Annual accumulated degree days > 0° C (DD) were calculated for each 25km grid square using climate normal data (1981-2010 averages) from ClimateNA (40), and the product of percentage of forest with DD was used as a habitat suitability index for tick populations (41).

The fourth criterion considers the logistics of sampling in the form of the proximity between the potential sentinel regions and a collaboration center. The location of the CLyDRN center was added to the map and a distance matrix in kilometers was created between these collaboration centers and potential sentinel regions. For Newfoundland and Labrador and Prince Edward Island, partners available to carry out sampling activities were not identified at the time of the decision-making process. For these provinces, this last criterion was thus omitted.

According to the MCDA algorithm chosen, the decision matrix should be normalized (42). Thus, for each province, each of the criteria were standardized by mean and standard deviation according to Formula 1:

$$z = \frac{x - \mu}{\sigma} \qquad \textit{Formula 1.}$$

where z is the standardized number, x is the raw figure, μ is the group mean, and σ is the group standard deviation.

Step 8. Apply combination rules

Combination rules refer to the way the algorithm runs mathematically and is also referred to as aggregation. There are many different MCDA algorithms, and it has been shown that methods vary greatly between studies (43-45). Thus, frameworks have been developed to guide decision makers on which method they should use based on their research objectives and the level of uncertainty in their data (46). According to the framework developed by Wątróbski *et*

al., (46), the PROMETHEE II method for the MCDA should be used in our case study based on the decision problem descriptors.

The visual PROMETHEE Academic Edition (47, 48) was used to run the models. Ten models were created, with one for each province. This meant the outputs were more easily comparable within a province to select sentinel sites at the provincial level. PROMETHEE II complete rankings were chosen, to permit to compare all alternatives and includes no incompatibilities. Complete rankings were deemed appropriate as there were no strongly conflicting criteria (48). The chosen output of the analysis for the models was the global Phi score, where the highest Phi represents a better scoring alternative in the MCDA.

Step 9. Carry out sensitivity analyses

The final step prior to interpretation of results is the sensitivity analysis. Visual PROMETHEE allows changing of weights to see how it impacts the scores using the visual stability intervals function. This allows the evaluation of the robustness of the prioritization based on the weighting of the criteria. Furthermore, three alternative scenarios were created to provide a visual cartographic representation of the impact of each of the criteria including risk-based, environmental, and population scenarios (**Table 21**).

Table 21. Weights attributed to the three alternative scenarios for sensitivity analyses

	Weights (%)			
Scenario	Risk	Environment	Population	Distance
A) Risk-based	70	10	10	10
B) Environmental	10	70	10	10
C) Population	10	10	70	10

Step 10. Interpret results

Lastly, the Phi scores were imported into QGIS version 3.18.1 to create maps to represent the highest Phi score using the analyses. The SAGA Gaussian filter was used to smooth grid data and remove noise, where the degree of smoothing is dependent on standard deviation (49).

These maps were presented back to DMs during follow-up meetings for final decisions on sentinel region locations. Meetings were held in large groups, with all provinces attending, but

also at the provincial level. Using the maps, population centers were identified which consists of areas of key scientific interest for the establishment of a sentinel region. Sensitivity analyses were used to support decision making.

Results

Weighting

After individual criteria were weighted and an interactive session was held to obtain a consensus from all parties, final weights were calculated. These final weights are presented, along with the standard deviation, in Table 22.

Table 22. Final weights attributed to each of the criteria. Final weights were individually scored, then a mean was calculated, rounded to the nearest percentage, and presented back to the group to gain consensus on the final weights. Standard deviations are also shown to demonstrate the spread in weighting.

Criteria	Weight	Standard deviation
Acarological risk	40	9.81
Log of the population	25	7.34
Environmental index	25	8.86
The distance from collaborating research centers	10	3.08

Phi scores for MCDA

MCDA were run for each of the provinces, and the Phi values from the varying scenarios were used to create maps (**Figure 25**). These maps were presented to stakeholders to support decision making for the selection of sentinel regions.

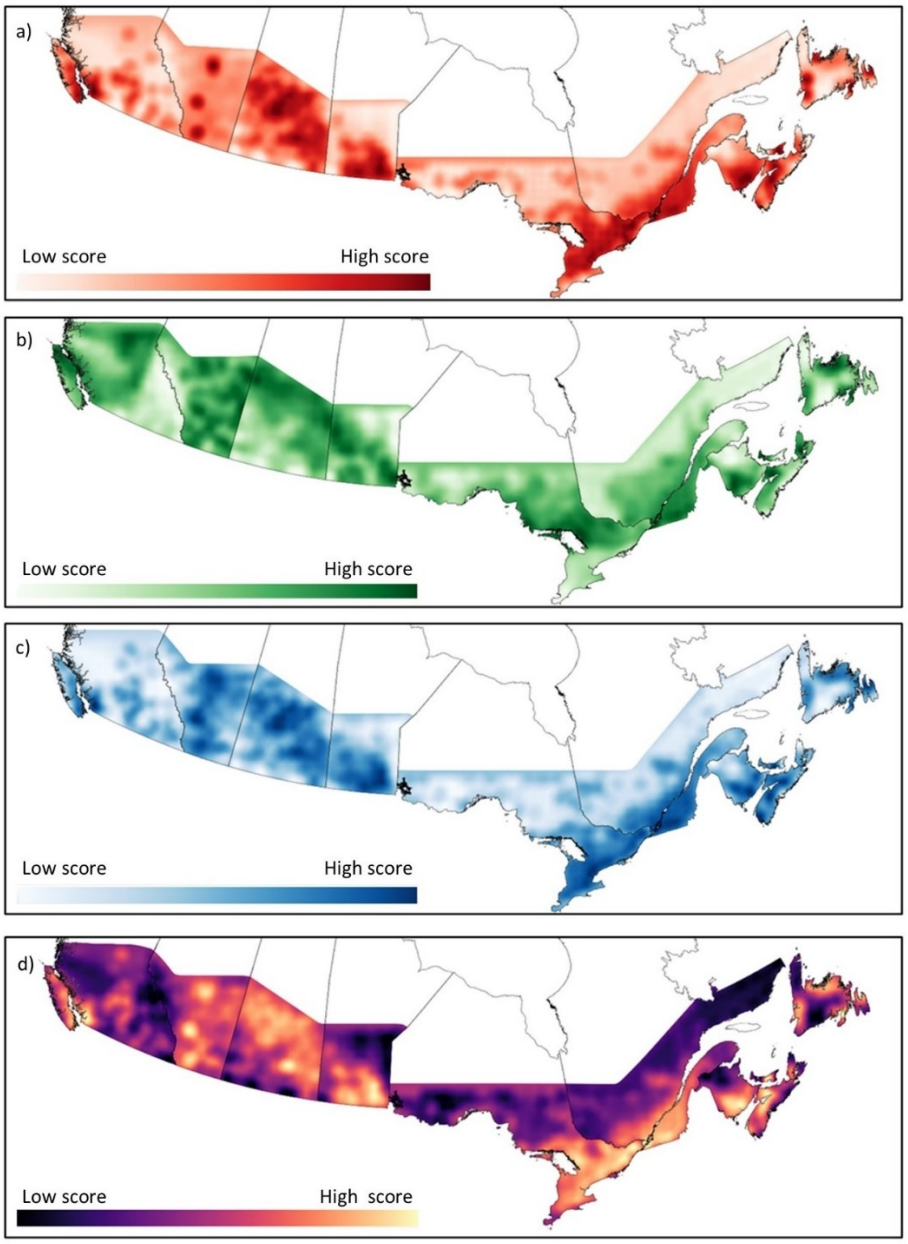

Figure 25. Maps projecting MCDA Phi scores from scenario a) risk-based, b) population, c) environment, and d) weighted. The shading indicates the relative performance across the set of alternatives – a higher score represents a better performance according to the criteria and weighting used within the models. Specifically, scores represent how performance is distributed across space at the provincial level according to the MCDA, depending on criteria weightings. These maps were presented back to stakeholders to support decision-making for selection of sentinel regions.

Sensitivity analyses

Sensitivity analyses were performed to assess the impact of weighting scores on the prioritization of sentinel regions by province. As an example of the exercise, we present visual stability intervals using results generated from the Prince Edward Island data (**Table 23**). The stability intervals are presented for each of the four evaluation criteria and permit the evaluation of how ranking would be affected if the weight attributed to the criterion in question was altered.

Table 23. Stability levels for results of Prince Edward Island for weighted scenario, with levels for all ranking to remain the same, and levels for half of the rankings to remain the same.

Criteria	Weight	**Stability levels for rankings to remain the same**		**Stability levels for 50% of rankings to remain the same**	
		Min weight	Max weight	Min weight	Max weight
Risk	40	29.41	42.86	29.41	46.27
Environment	25	17.81	34.78	17.81	34.78
Population	25	18.92	44.44	0	44.44
Distance	10	7.69	21.74	3.08	21.74

Interpretation of results

Three meetings with all DMs were held, in addition to one or two meetings for each province. During these meetings the maps were used as a decision support tool for selecting sentinel regions, focused around a population center. Following these multiple group discussions, a final map displaying which regions had been retained as part of the sentinel surveillance network (**Figure 26**) was presented to the whole Surveillance Working Group. A final consensus was gained for the spatial distribution of sentinel nodes across Canada.

Following the sensitivity analyses, results were presented to the DM group to provide visual support for decision making. For each province, the number of desired sentinel regions was decided by the group according to the resources that each province could attribute to sampling.

Figure 26. Sentinel regions for the Canadian Lyme Sentinel Network (CaLSeN)

Discussion

With the growing burden of vector-borne diseases, accelerated by climate and anthropogenic changes, effective surveillance systems must be put in place to track the associated evolving risk (50). We have employed a spatial MCDA approach to target thirty-seven areas of scientific interest for active tick surveillance of Lyme disease risk throughout Canada and inform stakeholders. This novel approach makes it possible to take into consideration multiple facets related to the complex life cycles of the tick-borne diseases, such as human population density, environmental suitability, and logistical constraints.

Emergence of vector-borne diseases is characterized by a complex epidemiological process, requiring an interaction between pathogens, vectors, susceptible animal hosts, and human populations; the portrait is further complicated by other driving factors such as climate and anthropogenic changes to the environment (51). With uneven distribution of suitable ecology for the vector and pathogen establishment process, and human populations centered around urban centers, the risk for vector-borne diseases is spatially heterogenous (52). This creates significant challenges in constructing informative and representative surveillance systems, especially at a large scale, and requires an important decision-making effort during the planning stages. The MCDA allows for a systematic, inclusive, and transparent approach for selecting sentinel regions whilst considering relevant, but sometimes conflicting, criteria (25, 26, 31).

By creating different scenarios, we can visually understand the impact of each criterion on the final MCDA output and use this information to inform decision makers. This approach has permitted us to see which geographical areas incorporate the facets most related to Lyme disease surveillance priorities and use the maps as a tool for the decision process. Through the sensitivity analyses, we were able to determine the stability of each of the sentinel regions. The criteria weightings can have a large impact on the Phi values of the subunits – thus this shows the importance of conducting these sensitivity analyses to understand the possible alternative outcomes, in addition to gaining unanimous consensus from DMs when determining weighting of the criteria.

As the MCDA exercise has permitted our group of decision makers to establish final sentinel region, next steps will be to distribute sampling sites throughout each sentinel region. Previous sentinel networks have used grid separation to gain even geographical representation of the study area. These sites will serve as transects for drag sampling and allow for multiple data points to be collected across the sentinel regions to obtain finer scale acarological risk data. A standardized sampling protocol will then be applied at each of the sampling sites.

An important aspect of using a MCDA approach is that the output of the analyses is used as a decision aid support tool, as opposed to simply creating a final decision map (28). This allows flexibility in the decision-making process and permits decision makers to reflect upon priorities and how to distribute sites across the study area to gain the best geographical representation whilst optimizing the relevance of the sentinel regions selected.

A limitation of using an MCDA approach in the decision-making process is the substantial effort required to recruit and involve a variety of experts. Although input from different decision makers represents a strength of the process, the coordination and numerous feedback loops of the process represent a significant investment of time for those involved. For the establishment of short-term surveillance networks, for instance for surveillance of outbreaks, this method may not be appropriate. However, in the context of establishing a long-term surveillance network, contribution from experts in the field assures that sentinel regions will be relevant for a long period of time.

Our study showcases an innovative application of spatial MCDA for the establishment of a nationwide surveillance system. This has allowed us to pinpoint areas of key surveillance interest across the country in a flexible manner, as the LD emergence status is not equivalent across the country. The results of this exercise have been applied to support DMs in the process of complex decision-making and continue to support decisions regarding the establishment of a sustainable national surveillance program for LD in Canada.

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General Discussion

This thesis has explored how sentinel surveillance can contribute to monitoring the risk of LD in human populations at two different scales: the provincial scale in Québec, and the national scale in Canada. In light of the evolving risk of VBDs in poleward regions, accelerated by climatic and anthropogenic changes, this research can guide other surveillance initiatives with similar objectives.

The decision to utilize sentinel surveillance as a tool to follow disease trends must be supported by a transparent and robust approach; the limited number of sampling units reinforces the need for them to be representative of the epidemiological process occurring.

Thus, this thesis provides a systematic approach which can be used to develop sentinel surveillance systems for VBDs. I first compared sentinel versus risk-based surveillance from an already existing active surveillance system to understand how these two approaches differ in the information that they provide. I analyzed sentinel surveillance data to assess its ability to follow spatiotemporal LD risk to human populations. Although these sites showed potential for following LD risk trends, it was hypothesized that a systematic approach to support sentinel system spatial design could optimize data generated from the sentinel active tick surveillance system and ultimately provide better representativity of LD risk. Thus, I scoped the literature to synthesize existing examples of sentinel surveillance, compared these, and extracted criteria, which were used in choosing where in space the sentinel units were placed. To follow on from this review, I constructed a decision tool to select relevant criteria, with the support of experts in the field of VBD surveillance, to systematize selection of criteria that are most relevant to consider when planning a new sentinel surveillance network. Finally, the output of the decision tool was integrated into a spatial MCDA to map out priority surveillance regions for a sentinel network for active surveillance of LD at the national scale in Canada,.

In the following sections, I highlight the main results from my research and their limits, discuss remaining knowledge gaps and identify how future studies can respond to these research needs.

Sentinel surveillance for risk of Lyme disease and other tick-borne diseases

Although surveillance of LD has greatly increased over the last twenty years in Canada, the increasing burden of the disease at the national level has meant that surveillance has had to be adjusted over time in response to intensification of resources required to maintain the surveillance system as it was.

Firstly, LD was added to the notifiable disease system nationwide in 2009. Although the case definition was revised in 2016, LD case reporting is the only source of surveillance information that has remained unchanged (185). Cases meeting the case definition (**Table 6**) are compiled and are subject to public health investigation to gather prerequisite information for the disease database. Although this surveillance system is standardized, the main limitation, as discussed in the introduction of this thesis, is its inability to serve as an EWS; as human cases have already occurred, only the later stages of the transmission cycle are captured. Surveillance which can capture earlier signals is desirable for public health authorities to allow time to implement intervention strategies to protect citizens e.g., communication campaigns aimed at promoting vigilance among health care providers (HPCs).

The ability of acarological passive surveillance to emit an early warning signal for the emergence of LD has been demonstrated in previous research. Launched in the 1990s, the federal passive surveillance programme initially analyzed ticks from both veterinary and human hosts. As the process of disease emergence continued, increasing densities of ticks resulted in higher volumes of tick submissions and required increasing resources including funding and laboratory personnel.

Active surveillance can provide another measure of enzootic hazard. Efforts invested in active surveillance in Canada, usually done through drag sampling, has historically varied across time. Some public health authorities at the provincial level have put in place their own active surveillance systems, which differ in sampling protocol and amount of sampling effort invested. Hence, it is difficult to compare the different measures obtained from these active surveillance initiatives.

These variations in acarological surveillance (in time and space) have resulted in a lack of a consistent early signal for enzootic hazard across the Canadian territory. Currently, the

emergence of LD risk cannot be captured in a uniform and timely manner across the country, as the only comparable measure (human case data) captures LD risk at a later stage. Developing sustainable surveillance systems with a stable surveillance effort is of great potential benefit to public health: this could result in a time series of the enzootic hazard through space by providing comparative measures of hazard. The sentinel structure can subsequently permit surveillance at a large geographical scale (at the Canadian level) by targeting areas of key scientific interest. However, the representativity of sentinel sites for active acarological surveillance has to be evaluated to support this hypothesis.

This thesis has explored the role of sentinel surveillance for LD to serve as a standardized measure of enzootic hazard. The first chapter compared sentinel sites and accessory sites, which are selected using a provincial risk-based algorithm (57). These sites serve different purposes; however, it was important to evaluate the information that was obtained from these differing sources. Québec's sentinel sites, established in 2015 with the support of the *Groupe d'experts sur les maladies transmises par les tiques*, were put in place to follow trends in LD endemic regions of Québec and to attempt to capture emerging risk in regions on the extremities of tick population distribution (**Figure 1**). Accessory sites were selected yearly in an to attempt to capture areas where risk is changing i.e., areas where the distribution of ticks is expanding. The outcome of our analysis was that sentinel sites were a better indicator of the spatial distribution of LD risk across the study period (2015-2019) compared with accessory sites. Thus, this provided a justification for the sentinel approach when we attempt to follow disease trends over a given geographic region across time. Such recommendations have also been brought forward by the ECDC which suggest that sentinel surveillance may be appropriate for monitoring changes in risk over time. (53).

A logistical benefit of sentinel surveillance is the feasibility and sustainability of the system if it is adequately planned. As sentinels involve a limited subset of the population, sampling efforts are concentrated in strategic sites. The resources needed to travel to the sentinel sites are also reduced, as there can be fewer sites to visit. Engaging surveillance collaborators may be easier, as they know precisely what effort is required from them year after year, and the locations of the field sites. As seen in a published surveillance report (Appendix 5), the sentinel approach was shown to be achievable in Canada through the successful establishment of the Canadian Lyme Sentinel Network (CaLSeN).

Planning for complementary surveillance initiatives around sentinel sites can supply additional information; working towards an integrated surveillance system is a possibility. For instance, adding sentinel veterinary clinics around sentinel surveillance sites could contribute building an enhanced surveillance system for tracking the evolving LD risk and monitor for the extended establishment of tick populations or the emergence of new tick-borne pathogens. Sentinel surveillance units can be designed to meet One Health goals, including environmental, animal, and human health components.

The second chapter of this thesis further highlighted the ability of sentinel surveillance sites to follow spatiotemporal risk patterns of LD. Sentinel surveillance systems must be built specifically for the geographical area that makes up the study zone; the ability of the density of nymphs to track the risk to the human population depended greatly on characteristics related to the municipality in our model. Therefore, although density of nymphs collected in sentinel regions can be translated into risk at a broad geographic scale, to account for the heterogeneous dispersion of ticks across space, ecological characteristics should be considered to accurately portray the risk at finer geographic scales.

Active acarological surveillance initiatives using a sentinel approach have been carried out elsewhere in Canada, e.g., in Ontario (36, 185), using repeated sampling of field sites over time to capture differential LD risk over space, to test time-to-establishment hypotheses in the region, and to demonstrate the northern expansion of ticks. However, these studies did not directly compare enzootic hazard and LD risk, as was done in the second chapter of this thesis.

The different uses of data derived from sentinel sites highlights the value of these sites. Nonetheless, sites where active surveillance is carried out in a recurrent fashion are often not referred to by researchers as sentinel sites. They may not always be integrated in a formal surveillance system and are often used for specific field studies. Labelling them as sentinels and incorporating them into a formal surveillance system could have important benefits. The site locations would not be subject to change due to the evolution of objectives of a research project, contributing to a longer time series. By formally designing sentinel surveillance systems, public health authorities are encouraged to define a surveillance zone and must carry out a structured planning process to select sentinel unit locations. In the case of establishing a new sentinel surveillance network of VBDs, the second part of my thesis has supported a systematic approach for the spatial design of such a system.

It is worth highlighting the advantages of maintaining surveillance in sentinel sites positioned within endemic areas. Clow *et al.* showed how, as the epidemiological portrait of TBD evolves, surveillance objectives shift (56). Once a TBD, such as LD, becomes endemic, although we ought to keep monitoring the portrait of the disease itself, surveillance within these endemic regions provides an opportunity to monitor for emergence of new pathogens (e.g., *Anaplasma phagocytophilum, Babesia microti,* and Powassan virus). Sentinel surveillance could support this objective. Firstly, it provides a standardized hazard measure, comparable through time – an increase in the infection prevalence of pathogens within endemic tick populations can be tracked. Secondly, as resources are saved by limiting sampling effort, conserved resources can be redirected toward parallel surveillance objectives e.g., increasing testing for other tick-borne or vector-borne pathogens.

Establishing sentinel surveillance systems for VBDs

With the dispersion of vectors in space and time, precipitated by climate and anthropogenic changes, public health authorities must put in place effective surveillance structures to provide a representative real-time portrait of the evolving epidemiological situation (6, 17). Faced with limited or changing/unsteady resources and the need to consider interacting ecological requirements of the transmission cycle of a VBD, planning an effective surveillance system becomes a complex decision problem. Thus, to aid in the planning phases of this decision problem, a structured and objective approach is ideal.

This thesis explores the role of sentinel surveillance for monitoring VBDs, more specifically LD. Sentinel surveillance has the advantage of limiting surveillance effort – a select number of sampling units are followed through time – to permit cost effective systems which can persist through time. However, sentinel surveillance comes with challenges; as we are using a limited subset of the population, the sample must be chosen carefully to ensure that it is representative of the population under study.

As VBD are dependent on multiple interactions between the environment, pathogens, vectors, and animal hosts, this leads to a geographically heterogenous distribution of enzootic hazard (206, 207). This has important repercussions for sentinel surveillance – sentinel unit locations

must be carefully chosen taking into consideration a range of criteria which may affect hazard distribution.

As the literature did not provide a framework to support this aspect of decision-making, one of the main outcomes of this thesis was to construct a systematic approach for the geographical design of sentinel surveillance systems for VBDs. The third chapter first lists current sentinel surveillance case studies for VBDs. From these case examples, it was possible to extract criteria which had been used by researchers and public health authorities for selecting the geographical design of the sentinel surveillance system. A vast range of criteria were extracted and could be grouped together in six main categories: Risk-based, human population, environmental, distribution, past information, and logistical criteria. Although this provided a preliminary basis for future planning of surveillance systems, due to the high number of criteria identified, a decision tool was constructed in chapter 4.

In the final chapter of the thesis, the criteria retained from the decision tool were used to structure a spatial MCDA to support the decision-making process for choosing the locations of sentinel units i.e., sentinel regions. The MCDA approach has the advantage of reaching out to a multitude of partners and ensures their participation during the planning phases of the surveillance network. Subsequently, these partners can promote the surveillance network at the national, provincial, or local level, depending on their jurisdiction of influence, and their active participation encourages their support towards final decisions. The involvement of partners is crucial of the operation of the network; due to the vastness of the study area, several teams must work in collaboration to carry out sampling activities.

The spatial element of the MCDA overcomes arbitrary separation of space caused by administration boundaries. Translation of data in georeferenced layers e.g., forest cover, population density, allows for subsequent results from the MCDA to be presented back to decision-makers in a visual, cartographical figure. This is particularly helpful when the research question involves deciding upon the spatial design of the network. Sensitivity analyses can also be used in the same manner, and various alternative scenarios, with different weights attributed to the criteria, can be presented alongside the weighted scenario to stimulate discussion, and give insight into the influence of each criterion for areas identified as priority regions for surveillance.

Apart from the spatial design of the sentinel network, other aspects remain important to consider during planning for surveillance of VBDs, as they can affect the data generated from the systems. Vectors display phenological changes, – for instance, densities of different stages of questing ticks (larvae, nymphs, adults) will change across the tick season (144). Phenology may also change depending on geographical location (208). Nymphs are generally most abundant between mid-June and early-July in Québec; however, in British Columbia, their peak is seen between mid-May and early June. Thus, timing of sampling activities should target a precise phenological period to allow for results to be comparable. For LD, nymphs have been shown to be associated with the highest risk: they are much smaller than adults, and therefore less likely to be detected by people during self-examination (145). Furthermore, they are most active during periods of outdoor activities in the summer months (209, 210). Lastly, they have the capacity to be infected, having taken their first blood meal as larvae. CaLSeN targeted nymphal peak as a sampling period, and so, the precise sampling interval was adjusted to match the nymphal questing phenology of each the sentinel region.

Limitations

Although the content of this thesis can support decision making for public health authorities working with VBD, in the context where their epidemiological portrait is evolving with climate change, several limitations must be carefully considered.

Firstly, chapter 1 described the benefits of sentinel surveillance over risk-based surveillance in Québec. Sentinel surveillance was shown to be more representative of LD risk across space during the 5-year study period. With climate and anthropogenic changes, and ongoing rise in tick abundance in southern Québec, this relationship may change as the epidemiological portrait evolves, and thius it will be worth repeating in future years to determine if the relationship remains constant.

Furthermore, we looked at a single aspect of the outcome of surveillance: whether enzootic hazard can predict LD risk in space and time. Although this is important to characterize, especially as the epidemiology of LD is rapidly changing, other relationships could be worth evaluating e.g., the time between presence of the first tick found in active surveillance and the first human case diagnosed in the same municipality. As sentinel surveillance sites are fixed,

this type of information may not be possible to achieve at the municipal level throughout the province, whereas risk-based selection of sites could permit this approach. This leaves public health authorities the need to carefully evaluate their surveillance priorities and determine if sentinel surveillance can meet them. In the second chapter, nymph densities were able to predict number of human cases reported at the municipal level. Nonetheless, the municipality code incorporated in the model as a random variable accounted for the majority of the R^2 i.e., most of the variation in LD risk was explained in relation with the municipality. This is not surprising; some geographic locations may have intrinsic factors which contribute to a higher risk of LD, even compared with adjacent municipalities e.g., a greater surface area of forests, population demographics which lead to more active lifestyles (211). This means that findings for this second chapter may not be as easily generalizable to other study areas. Models would have to be developed which are specific to each new region of application. Here again, as the portrait of LD is rapidly evolving, this study should be repeated to determine if the relationship between enzootic hazard and LD risk holds through time.

Although some general criteria (see section 4.4. Current surveillance strategies for Lyme disease in Canada) were used to select sentinel sites in chapters 1 and 2, a more rigorous process as described in the second half of the thesis was not utilized. The analysis of active surveillance data led to some challenges, as although tick densities were correlated with the number of LD human cases across the study period, the correlation was weak, and it was more difficult to use these data to predict LD risk at a finer geographic scale. Indeed, at the municipal level, the majority of the risk was explained by the municipality as a random variable. Some of the sentinel sites chosen may not have been optimal for the regions they were representing, for example, there were no sites in very high-risk regions in Estrie. Thus, I hypothesize that some of the limits and challenges encountered during analysis of the sentinel data may be addressed if such a process is used. This hypothesis remains to be tested.

Furthermore, although active tick surveillance with use of sentinel sites was shown to follow risk trends, it is possible that use of DIN would be a better indicator of LD risk compared with DON, as shown in previous studies (212). Pathogen data was not integrated within analysis as currently in Québec, relatively few nymphs are collected during active surveillance activites and even fewer are found positive for *B. burgdorferi* (213). Adding pathogen prevalence data to predictions could increase accuracy in models developed to monitor LD risk. Thus,

increasing abundance of *I. scapularis* ticks in Québec should lead to the revision of how tick surveillance data is analyzed, and surveillance strategies should be regularly revised.

The analyses in chapters 1 and 2 indicated that sentinel tick surveillance could follow LD risk trends to some extent, but it remains to be described how these results can be translated into public health action. We demonstrate that the data can be used to build risk maps which are similar to those produced by provincial public health authorities. Nonetheless, important questions remain to be answered. How can active surveillance data from sentinel sites impact on public health action in terms of public health interventions? As sentinel surveillance gives a limited insight into the overall epidemiological situation of LD emergence, how can it be optimized or integrated into surveillance strategies to increase representativity and usefulness of active surveillance? Chapters 3 to 5 describe a novel systematic approach for designing sentinel surveillance systems for VBDs. It was developed with the support of case examples from the literature (chapter 3) which were subsequently integrated into a decision tool (chapter 4). The decision tool is then used to determine which criteria are relevant for selection of sentinel unit location; its main purpose is to make the geographical positioning of sentinel units in space across the study area more objective. The tool has been validated by experts who work in tick-borne and mosquito-borne diseases; however, some relevant expertise may have been lacking e.g., experts working with diseases transmitted by midges, sandflies, snails, etc. I hypothesize that this bias is limited by the fact that the criteria which were used to build the decision tool were extracted from case examples related to VBDs in general, not only mosquito-borne or tick-borne diseases. As the tool was developed by our research team and validated by experts, the final product is based on personal interpretations of the literature and on each expert's own experiences with VBD surveillance. Though opinions from multiple well-established experts and support of a thorough literature review do add breadth and objectivity to the tool's development process, there remains an element of subjectivity within the tool due to the nature of its construction.

The literature review (chapter 3) focused on VBDs considered as diseases of medical importance, as defined by the WHO. Therefore, other diseases related to animal or plant health may be overlooked. This is an important limit to consider, as VBDs which affect plants or animals, but not humans directly, could nonetheless have important impacts on human health through indirect effects e.g., food security (214, 215). The One Health approach was

not explicitly applied within the construction of the tool. The need to consider the three spheres of One Health (humans, animals, and the environment) is not a prerequisite for use to the tool – users may decide to overlook environmental and animal health criteria if they judge them irrelevant. The inclusion of intersectoral partnerships, as advocated by One Health, is not referred to within the decision tool. The case study which illustrates the use of the tool does integrate some One Health notions, such as the use of a criterion for environmental suitability for tick establishment but does not extract criteria which are used to prioritize the surveillance of animal health or ecosystem health. Future use of the decision tool paired with a One Health vision could demonstrates the tool's ability to integrate One Health notions or identify ways it could be optimized to address any shortcomings.

Another aspect which is not explicitly expressed within the decision path of the tool is the importance of tackling socioeconomic health inequalities during surveillance activities. Indeed, social health inequalities remain a public health priority (216, 217). Within the decision element *Human population characteristics* (**Figure 30**), the tool suggests considering population factors that could affect the transmission cycle of VBDs. This offers the opportunity to target vulnerable or higher-risk groups e.g., people with high occupational exposure, immigrants, aboriginal communities, residents of low-income neighborhoods, individuals less likely to seek medical care or adopt preventive behaviors. This cue could nonetheless be interpreted differently according to users and there is a risk it could be overlooked. To address this potential weakness, specific criteria for targeting high-risk groups could be developed and integrated into the decision tool, either directly or as a transversal axis along the continuum of the decision path to remind actors to consider high risk groups throughout the criteria prioritization exercise. The literature used as a basis for the construction of the tool (i.e., the realist-type review) (chapter 4) did not uncover any criteria specifically used to target these populations. This could represent the lack of integration of social inequalities for surveillance of VBDs and should be explored in future research. During the validation step of the decision tool production, we recruited experts in the field of VBD surveillance. Thus, these experts are not particularly trained in social health inequalities, and this may be why more specific criteria aimed at social inequalities did not surface during the validation process. Including experts who work internationally with at-risk and/or vulnerable populations could have provided further insight into this issue.

One of the main limitations of the sentinel surveillance approach is the potential lack of representativity of the sentinels; as they are a limited subset of the population, they must be carefully chosen, and such an endeavour is no easy task. The approach proposed by this thesis, although supported by scientific evidence, remains to be evaluated in depth for validity and ensuing representativity of sentinel systems developed using this approach. As VBDs have complex transmission cycles and that their epidemiological situation evolves rapidly and heterogenously, it may mean that the sentinel approach is not appropriate in all contexts. Future work and application of the approach developed in this thesis will provide insight into how it can be improved.

Implications for public health

This thesis promotes the use of sentinel surveillance for LD, but also for VBDs in general. In Québec, surveillance strategies have involved active acarological surveillance of sentinel sites since 2015 in combination with accessory sites which are selected yearly, using a risk-based sampling strategy. We have evaluated the benefits of sentinel surveillance: it has been shown more reliable for following spatiotemporal trends for LD risk compared with risk-based accessory sites. As there is inter-annual variation in tick density, it is not surprising that risk trends are more difficult to follow using accessory sites. As they change every year, difference in tick densities across years is challenging to interpret – are the changes a result of the characteristics of the site itself, or due to variation between years? We stress the need to select a surveillance strategy based on surveillance objectives, however, to track evolving risk over time, returning to the same sites across years does represent a significant scientific and strategical advantage.

The final product of this thesis is the first pan-Canadian active surveillance network for LD. The sentinel structure has meant that such an initiative is feasible; feedback from collaborating research teams across the country confirms that it has been possible to add the sentinel surveillance sampling to their other research activities due to the limited sampling effort required. Sampling is facilitated as sites are kept constant through time and therefore, can more easily be planned in advance. The use of a standardized sampling protocol permits comparability of measures i.e., enzootic hazard in the form of nymph density, through time

and space. This gives the opportunity to compare the enzootic hazard across Canadian provinces and can aid in geographic targeting of public health interventions.

An immediate outcome for public health is the production of surveillance reports (Appendix 5) which are available for consultation and can track the enzootic hazard of LD across provinces and through time. Such reports can be used to inform public health authorities, so they are aware of the risk in their province, relative to others. Healthcare professional may also use the information to guide their diagnosis, by providing insight into which regions have a higher risk of LD, however with the caveat that the sentinel regions do not provide fine scale risk information and cannot rule out the existence of localized pockets of high risk. Surveillance reports can also be used in in knowledge translation to the general public and serve as a trigger for public health information campaigns and raising awareness.

The implementation of the network has relied on collaboration; nationwide partners have contributed to the establishment of the network, the sampling, the presentation of results, and the continuous improvement of surveillance activities. This results in a strong network of partners who work together towards a common goal and continue to develop expertise. This successful partnership model could help guide future surveillance initiatives when a large study zone must be monitored and when several jurisdictions are involved.

Overall, this thesis has provided an approach for spatial design of sentinel surveillance networks for VBD which can be replicated in other contexts. The approach is flexible in terms of scale – we have used it at the national scale; however, it could be applied at finer scales (provincial, regional, local) or even at the international scale, data permitting. We have used it to monitor TBDs, more specifically LD, however the same approach could be used for other VBDs, such as those transmitted by mosquitoes. Nonetheless, this approach must be applied in conjunction with other surveillance planning steps, such as development of clearly described protocols built to reflect surveillance objectives (218). The development of a centralized data collection and dissemination portal could encourage visibility of surveillance efforts and the data collected, as well as periodic evaluation of the association between acarological data and epidemiological outcomes with the aim of modified the surveillance system as appropriate (219).

Future research and recommendations

In the final chapter of the thesis, the spatial MCDA represents the final step in the systematic approach to planning the spatial design of a sentinel surveillance system for VBD. The Canadian Lyme Sentinel Network (CaLSeN) was originally piloted in the summer of 2019 (Appendix 5)

Activities were suspended in 2020 due to public health constraints imposed by the pandemic, which resulted in operational barriers for sampling. Sampling was restarted in 2021 at which point our systematic approach had been refined and was utilized to establish the final, expanded surveillance network. To ensure that our approach meets surveillance objectives and determines representative sentinel site locations, results originating from CaLSeN will have to be analyzed and used to evaluate the system.

The analysis of the data from the surveillance network could be similar to what has been conducted in chapters 1 and 2. However, more contextual information should be integrated into the models to represent the differences between regions. For instance, population demographics could impact the risk of LD acquisition e.g., age structure, employment type. Characteristics that vary among provinces should be explored: for instance, public awareness of LD may differ from one province to another. Furthermore, LD transmission risk may vary according to tick species. *I. pacificus* ticks are less likely to bite humans compared with *I. scapularis,* which would be expected to impact the relationship between enzootic hazard and LD risk in British Columbia (220). Such differences will be important to consider for building an accurate portrait of LD risk across Canada.

As highlighted in chapter 2, factors intrinsic to the municipality or region explained a greater proportion of variation in municipal LD risk than did enzootic hazard. Although some local environmental factors were explored in initial analyses (forest density, forest perimeter) these did not have a statistically significant effect on LD risk in models and were not retained. Thorough ecological and anthropological data measured at sampling sites and integrated into models could give a better portrait of risk factors that interact with enzootic hazard to contribute to LD risk. The sentinel structure could favor this approach, by limiting sites where additional parameters are measured.

Through CaLSeN, *Ixodes spp.* specimens are not only analyzed for *Borrelia burgdorferi* but a variety of other microorganisms including *Borrelia miyamotoi, Anaplasma phagocytophilum, Babesia microti, Babesia odocoilei* and Powassan virus. Although LD is currently more prevalent than these other pathogens in Canada, as these other pathogens are also carried by blacklegged ticks, their enzootic hazard is also likely to increase as a consequence of the range expansion of *Ixodes* spp. ticks. For instance, in the summer of 2021, the first perceived cluster or outbreak of human granular anaplasmosis (HGA) was identified in the Estrie region of Québec (221) and HGA incidence also increased in neighboring Ontario (222). Furthermore, climatic conditions are becoming more suitable not only for *Ixodes spp.* ticks but also for other tick species. A notable example in North America is the distribution of the lone-star tick, *Amblyomma americanum*, with established populations now recorded in the northeastern United States (200, 201). These other tick species may be vectors of diseases of public health concern, such as tularemia, Colorado tick fever, alpha-gal syndrome and Rocky Mountain spotted fever. By continuing surveillance not only for LD, but other related pathogens and tick species it becomes possible to track the enzootic risk of TBDs in an efficient way. Depending on secondary objectives e.g., surveillance of a specific pathogen or specific tick species, the surveillance network may have to be adapted, but the data collected from CaLSeN can nonetheless serve as baseline surveillance data for a broad range of emerging TBDs.

This thesis explored a single aspect of sentinel surveillance planning – the spatial distribution of sentinel unit across the study area. However, many other important considerations have been explored with the CLyDRN Surveillance Working Group. For instance, we have developed a standardized drag sampling protocol which is easy to replicate across different environments and by different teams. All activities e.g., data collection, specimen analysis, communication of result, must be carefully integrated one with another to ensure effective operationalization of the surveillance network.

The evaluation of CaLSeN remains to be completed. As it is a new network, a formal extensive evaluation should be conducted to ensure its sensitivity, representativeness, timeliness, simplicity, quality, flexibility, and stability (223). This will give insight into the success of the approach used to select sentinel unit location, but even more generally, will provide a throughout picture of the network's functionality and how it could be improved to ensure its sustainability.

Although this thesis has focused on TBDs, the proposed approach for spatial design of sentinel surveillance was conceived for VBDs in general. Thus, future work can include the use of our procedure for other vectors (e.g., mosquitoes, midges), and other VBDs (e.g., malaria, Zika, WNV).

Conclusions and Key Messages

1. Sentinel surveillance has the ability to track spatiotemporal risk of LD at the provincial scale in Québec.
    - Enzootic hazard derived from sentinel sites in the form of nymph density can distinguish between areas of higher LD risk across space.
    - Characteristics intrinsic to the municipality are a crucial determinant of LD risk, with municipality incorporated into models as random variables; thus, more research is required to evaluate these characteristics to permit sentinel surveillance to be more informative.
2. Sentinel surveillance is more reliable at predicting the risk of LD compared with risk-based surveillance during tick acarological surveillance.
    - Risk-based surveillance, whereby sampling sites vary yearly as a consequence of purposive sampling, was shown less capable of representing LD risk in the form of LD incidence in human populations across the study area and across the study period compared with sentinel site data.
    - Thus, surveillance objectives must be clearly defined to ensure that the surveillance structure can meet these objectives.
3. Sentinel surveillance has been used to monitor many different VBDs, in many contexts.
    - Our scoping review has described case examples from the literature which employed sentinel surveillance approaches.
4. To determine how sentinels are distributed across the surveillance zone, researchers and public health authorities utilized a wide range of selection criteria.
    - A need for a structured and objective method to select sentinel site locations was found; as sentinels are a select subgroup of the population, they must be representative of this population. To ensure this representativity, they must be carefully placed in space to be able to represent accurately the epidemiological situation under study.
5. A decision tool for selection of relevant criteria in the spatial design of sentinel surveillance system was developed.

- This tool is flexible for the context under study; it takes into account data availability, the VBD under study, and the human population under study.

6. The criteria which are extracted from the tool decision can be used to structure a spatially explicit MCDA.
    - This allows for collaboration between partners throughout the planning phases of the sentinel surveillance network, as required by the MCDA approach.
    - The spatial component of the MCDA overcomes challenges imposed by arbitrary administrative boundaries; priority maps can be produced which are a useful tool to present to partners during the decision-making process.
    - The feasibility of the sentinel network was demonstrated during the initial pilot year.
    - The sentinel surveillance systems resulting from this tool remain to be evaluated.

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Appendix 1

Title:
A portrait of sentinel surveillance networks for vector-borne diseases: a scoping review supporting sentinel network design

Scoping review protocol
Written September 2019
Last updated January 2020
Literature search completed November 2019

Contents

Background

In the last few decades, we have witnessed an expansion of the geographical distribution of arthropods such as mosquitoes and ticks to higher latitudes, resulting from climate change. As suitable vector habitat range continues to expand spatially, the emergence of mosquito- and tick-borne diseases is becoming a growing public health problem. General linear models evaluating the occurrence of emerging infectious disease (EID) events have seen a significant increase in the number of EID events caused by vector-borne disease in the last two decades ($p < 0.001$) (1). They are now estimated to represent a staggering 17% of all infectious disease burden, causing more than 700 000 deaths per year (WHO).

As vectors spread and become established further North and South, public health authorities require the capacity to track their emergence. Surveillance, as defined by the WHO, is the 'continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice'.

For vector-borne disease, we see additional complexities when dealing with their surveillance– their distribution in space is dependant on both vector and reservoir host ecology. The acquisition of the disease requires a vector-human interface in adequate circumstances. Thus, as we see three distinct populations interacting together (pathogen, vector, host), we need not only to consider the ecology of each, but also the relationship between these populations.

Surveillance networks for vector-borne must be able to overcome specific situations 1) as vectors' habitat ranges increase, public health authorities must survey large surface areas for risk of disease with limited resources 2) as the disease emerges, by the time disease cases are reported, the vector and the pathogen will already be established in the environment 3) a specified area may become endemic or see the disease begin to emerge, while the neighboring area shows no trace of the disease or its vectors due to, for example, lack of habitat suitability for the vector.

Sentinel surveillance offers the opportunity to overcome these ecological and logistical challenges.

Firstly, as surveillance is costly (especially when dealing with a large ground to cover), it must remain efficient. Sentinels are a sub-group of the population which are measured repeatedly

though time – this limits the selection process and the sample size. However, this sub-group must be representative of the population, and so careful selection of the sentinels is required. Secondly, surveying the presence or absence of the vector and/or the pathogen using sentinel surveillance has been shown effective; sentinel animals or sentinel study sites have been able to gather data that correlate with risk to human population and can act as Early Warning Systems (EWS) (2-4). Thirdly, by carefully selecting where these investigations are carried out, it is possible to areas of scientific interest i.e., where the diseases are more likely to emerge (5). This is particularly relevant for assessing disease risk at the regional or national level, when a large surface area must be monitored.

Although sentinel surveillance offers the possibility of establishing a cost-effective surveillance system for vector-borne diseases, its major limitation is the generalization of surveillance findings outside of the sentinel unit (6). Therefore, to optimize the use of data obtained from these sentinels, sentinels must be carefully selected. Often, sentinel surveillance for vector-borne disease involves use of animals, study sites or hospital/clinics/etc.— their locations must be accurately established to target areas of scientific interest.

Currently, the literature does not offer a framework for the selection process for sentinel locations in vector-borne disease surveillance. Using previous examples of sentinel surveillance in the literature, we will firstly characterize sentinel surveillance networks used for surveying VBDs. Then, by drawing out selection criteria used for choosing sentinel locations, and by evaluating these networks we can begin to determine which criteria are most relevant in selecting sentinel locations that answer surveillance objectives and are able to identify emergence of disease early, before the confirmation of the first human diagnoses.

Objectives

The aim of this scoping review is to scan the literature to determine in which contexts sentinel surveillance networks have been used for vector-borne diseases. Using these examples, it will be possible to evaluate which features of these surveillance programmes are beneficial, and which should be optimized. An optimized sentinel surveillance network will be able to better serve its purpose i.e., to signal disease trends, identify outbreaks and monitor the burden of disease within a population.

To allow our team to do this, it will be necessary to evaluate surveillance network within each article using guidelines provided from the Center for Disease Control (7).

This scoping review could help to formulate guidelines for future sentinel surveillance programs, by providing insight into the steps required for choosing appropriate sentinel site locations with the aim of optimising the sentinel surveillance network.

Review Team

Member	Organization	Project role
Camille Guillot	Université de Montréal	Project lead Participant First reviewer
Catherine Bouchard	Public Health Agency of Canada	Synthesis expertise
Mariola Mascarenhas	Public Health Agency of Canada	Synthesis expertise
Philippe Berthiaume	Public Health Agency of Canada	Synthesis expertise
Patrick Leighton	Université de Montréal	Advisory
Katherine Merucci	Public Health Agency of Canada	Participant Development of search algorithm
Carol-Anne Villeneuve	Université de Montréal	Participant Second reviewer
Caroline Sauvé	Université de Montréal	Participant Third reviewer

Methods

The scoping review protocol will be developed *a priori* to ensure consistency and reproducibility of the review. The general framework is drawn from Arksey and O'Malley's scoping review framework (8):

1) Establishing a research question
2) Conducting a literature search
3) Screening of relevant articles
4) Characterization of the selected article

5) Extracting data and summarising findings

1) Establishing a research question

1. In what contexts have sentinel surveillance networks been used in the past for vector-borne diseases?
2. From these case examples, which criteria have been used for planning the spatial design in sentinel surveillance networks which have been successful? Meanwhile, which criteria have been used for planning the spatial design in sentinel surveillance networks which have been less successful?

Follow up question:

3. Which recommendations can be drawn from the scoping review to help build guidelines for developing other sentinel surveillance projects, choosing sentinel sites locations and for optimizing sentinel surveillance for vector-borne diseases?

2) Conducting a literature search

a) Algorithm

#	Searches
1	exp Disease Vectors/ or Tick-Borne Diseases/ or (vector* adj2 disease*).tw,kf,kw.
2	((arthropod* or insect* or mosquito* or aedes or anopheles or culex or tick? or triatomine bug* or sandflies or sandfly or sand flies or sand fly or blackfly or blackflies or flea? or triatomine bug* or tsetse fly or tsetse flies or aquatic snail*) adj2 (disease* or infect* or vector* or transmi* or fever* or borne or carrier* or carry or carries)).tw,kf,kw.
3	Chikungunya virus/ or Chikungunya Fever/ or chikungunya.tw,kf,kw.
4	exp Dengue/ or Dengue Virus/ or (dengue* or (fever adj2 (Aden or bouquet or breakbone or dandy or red or solar or sun))).tw,kf,kw.
5	Rift Valley Fever/ or (rift valley adj2 (fever* or virus*)).tw,kf,kw.
6	Yellow Fever/ or yellow fever.tw,kf,kw.

7 Zika Virus Infection/ or Zika Virus/ or (zika or (zikv adj2 (virus* or infect* or fever*))).tw,kf,kw.

8 exp Malaria/ or (malaria* or paludism* or swamp fever*).tw,kf,kw.

9 Encephalitis, Japanese/ or (encephalitis adj2 japanese).tw,kf,kw.

10 Elephantiasis, Filarial/ or (lymph* adj2 (filari* or elephantias*)).tw,kf,kw.

11 West Nile virus/ or West Nile Fever/ or ((west nile or "Egypt 101") adj2 (fever* or virus* or flavivirus* or disease*)).tw,kf,kw.

12 leishmaniasis/ or leishmaniavirus/ or (leishmani* adj2 (virus* or infect* or fever*)).tw,kw. or leishmanias*.tw,kf,kw.

13 Phlebotomus Fever/ or ((sandfly or pappataci or phlebotomus) adj2 (fever* or febris)).tw,kf,kw.

14 Hemorrhagic Fever Virus, Crimean-Congo/ or Hemorrhagic Fever, Crimean/ or ((crimean or congo) adj2 (virus* or infection* or fever* or h?emmorrhagic)).tw,kf,kw.

15 exp Borrelia Infections/ or (lyme* adj2 (disease* or borrelios*)).tw,kf. or (borrelia or borrelios* or (relaps* adj2 fever*) or neuroborrelios*).tw,kf,kw.

16 Q Fever/ or (coxiella burnet* infect* or coxiellos* or ((Q or query) adj2 fever*) or (rickettsial adj2 pneumoni*)).tw,kf,kw.

17 Encephalitis, Tick-Borne/ or Encephalitis Viruses, Tick-Borne/ or ((encephalit* or meningoencephalit*) adj2 (central european or tick or russian spring summer or forest spring or russian or vernal or tick or woodcutter* or louping ill or powassan)).tw,kf,kw.

18 Tularemia/ or (tular?emi* or francisella tularensis infect* or ohara disease* or yato bya).tw,kf,kw.

19 exp Trypanosomiasis/ or (trypanosomos?s or trypanosomias?s or trypanosoma infect* or african lethargy or sleeping sickness or nelavan or Chagas*).tw,kf,kw.

20 Plague/ or ((plague adj2 (bacterial or oriental)) or (yersinia adj2 pest*)).tw,kf,kw.

21 exp Rickettsia Infections/ or ((rickettsial* adj2 (disease* or infect*)) or rickettsios?s).tw,kf,kw.

22 exp Onchocerciasis/ or (onchocercias* or onchocercos?s or onchoceros?s or (onchocerca adj2 infect*) or river blindness* or robles disease* or onchodermatos?s or (onchocercal adj2 (skin* or derma* or cutaneous*))).tw,kf,kw.

23 exp Schistosomiasis/ or (schistosomias?s or schistomias?s or schistosomos?s or bilharzias?s or bilharzios?s or (schistosom* adj2 infect*)).tw,kf,kw.

24 Tick paralysis/ or (tick adj (paralys* or toxicos*)).tw,kf,kw.

25	Typhus, Epidemic Louse-Borne/ or Typhus, Endemic Flea-Borne/ or Typhus.tw,kf,kw.
26	or/1-25
27	Sentinel Surveillance/
28	(sentinel adj4 (surveillance or network* or system*)).tw,kw,kf.
29	Sentinel*
30	or/27-29
31	26 and 30

* Vector-borne diseases to include in the search were selected according to the WHO's reported main vectors and diseases they transmit. (https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases)

b) Databases

The databases which will be searched include:

- CAB Abstracts
- Global Health
- Embase
- Medline

After deliberation, it was decided not to search Scopus. Scopus has many duplications between Embase and Medline, as these are both indexed within Scopus. Searching Scopus usually exponentially increases the number of results, and as the search is already catching all article with reference to "sentinel", we can anticipate retrieving a large number of articles. As it is a keyword only database it is not possible to search by subject headings. Thus, despite the adding workload, there is unlikely to bring forward many more relevant papers, not already grasped using Embase and Medline.

c) Grey literature

The grey literature searched includes:

- WHO

- WHO IRIS
- Harvard Think Tank
- Google
- TAHO
- ECDC
- Tropical Pathology and Infectious Diseases Association
- CDC
- PAHO
- Eurosurveillance

d) Search Verification

Firstly, a snowball strategy for search verification will be used: relevant paper references will be screened for potential relevance and if not already included in the scoping review database, they will be added to the review for screening. The addition of any papers after the literature search will be documented, including the date and reason for the addition.

Furthermore, we will an expert in the field to provide 10 references and verify that they are included in the scoping review database. As before, if these are not already present, they will be added to the review.

If the search strategy fails to capture over 10 relevant papers using these two strategies, it will be revised, and literature search repeated with the improved search terms.

3) Screening of relevant articles

The relevance screening level will be done on the title and abstract initially. If the abstract is not available, the relevance screening will be conducted on the title only, with a prudent approach and tend toward including irrelevant articles rather than excluding potentially relevant articles. Relevance screening will be used to determine if the papers describe

surveillance activities in the abstract, and sentinel surveillance in the abstract and/or text. Only documentation reporting primary data will be used for the review. The relevance screening tool can be found in Appendix I.

4) Extracting and characterizing data and summarising findings

A data characterization form will be applied to all relevant titles (see Appendix II).

The data extraction and characterization level of this scoping review is to confirm the relevance of the publication followed by extraction and characterization of important information around the criteria used in the selection of sentinel study sites. Information such as study design, surveillance methods used, reported prevalence of vector-borne diseases, risk factors or risk measures for developing these diseases, criteria for sentinel site selection, etc., will be captured and analyzed descriptively.

To evaluate the surveillance system, the criteria from the Center of Disease Control's criteria will be used (7). Firstly, the reviewer will describe and indicate the level of usefulness of the surveillance system, by describing the actions taken as a result of the activities from the surveillance system. Next, questions in the data extraction form will cover the following attributes of the system: simplicity, flexibility, data quality, acceptability, sensitivity, predictive value positive, representativeness, timeliness, stability. The framework of evaluation will be simplified, as to be able to evaluate as many criteria as possible for each paper.

To summarize the data, there will likely be a descriptive tabulation of all relevant information regarding sentinel site selection, in this case with a focus on the criteria used for the selection of the specific study area. Furthermore, the strengths and weaknesses of the surveillance network will be extracted from the text. Key points will be discussed to draw conclusions and recommendations for the establishment of a sentinel surveillance network.

Appendix I: Relevance Screening Tool

Questions	Options	Additional notes
RefID	Retrieved automatically from DistillerSR	
1.Does the abstract investigate surveillance of a **vector-borne disease**? Surveillance is the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice, and so, relevant papers/abstract can include: Surveillance of a vector-borne disease to quantify presence/absence of vector and/or pathogen and/or human cases OR Description of a surveillance system for a vector-borne disease	☐ Yes ☐ No (Exclude and submit form)	Vector-borne diseases are transmitted by arthropods when the skin barrier is ruptured to permit access to pathogens. Papers will be included if they consider surveillance of vector-borne diseases of public health interest, including, but not limited to: Chikungunya, Dengue fever, Lymphatic filariasis, Rift Valley fever, Yellow fever, Zika, Malaria, Lymphatic filariasis, Japanese encephalitis, Lymphatic filariasis, West Nile fever, Leishmaniasis, Sandfly fever (phelebotomus fever), Crimean-Congo haemorrhagic fever, Lyme disease, Relapsing fever (borreliosis), Rickettsial diseases (spotted fever and Q fever), Tick-borne encephalitis, Tularaemia, Chagas disease (American trypanosomiasis), Sleeping sickness (African trypanosomiasis), Plague (transmitted by fleas from rats to humans), Rickettsiosis, Onchocerciasis (river blindness), Schistosomiasis (bilharziasis), Typhus and louse-borne relapsing fever (If you are unsure whether to include the paper due to disease to it investigating, please contact lead investigator – in

OR Use of surveillance network for evaluation of public health intervention OR Pilot study for establishment of surveillance network OR Document the impact of an intervention, or track progress towards specified goals OR Monitor and clarify the epidemiology of health problems, to allow priorities to be set and to inform public health policy and strategies OR Serve as an early warning system for impending public health emergencies		general, include ALL human vector-borne diseases, common animal vector-borne disease) N.B.1. For this question, the term surveillance englobes the word "monitoring". N.B.2. Papers comparing laboratory tests used for surveillance **SHOULD NOT** be included. Also **exclude** papers in which diagnostic tests are being tested for the purpose of surveillance (not strictly surveillance in itself) N.B.3. E**xclude** papers in which the surveillance system is not primarily focused on vector-borne diseases e.g., neglected tropical diseases, febrile illnesses however **include** sentinel airports when they are used primarily to survey for VBDs N.B.4. **Exclude** papers that survey side effects of VBD, VBD treatments, or VBD drug safety. **Include** papers that investigate the surveillance of intervention efficacy for prevention/treatment of VBD or prevalence of resistance strains of VBD pathogens N.B.5. **Exclude** travel-associated, transfusion-associate and mother-to-child (trans-placental or breastfeeding) cases

2. Does the paper use a sentinel surveillance system/network in order to collect data, i.e. concept of repeated measures through time from a pre-selected unit/sample as part of a network (more than one isolated unit? This includes, but is not limited to: Sentinel physicians / healthcare professionals / laboratories / clinics / hospitals / airports OR Use of sentinel sites for sampling OR Use of groups sentinel animals in multiple locations	☐ Yes ☐ No (Exclude and submit form)	Within the article, is there mention of sentinel surveillance? This can include sentinel physicians/ healthcare profession, laboratories, sentinel sites where traps or where sampling is conducted or sentinel animals. Sentinels are specific cohorts (see above) that are used to estimate trends in a larger population. There are repeated measures at each sentinel unit. A network/system is composed of more than one sentinel unit which is subject to a uniform sampling protocol and at more than one location e.g. in several districts, villages, regions or countries to name a few examples. N.B.1 Pay particular attention to papers which investigate seroprevalence rates in animals; although multiple animals tested, they often represent only a single measure of seroprevalence one location. These papers should therefore be **excluded**. N.B.2 E**xclude** papers in which the unit (e.g. animal, population subgroup, site) was not originally selected as sentinel, but later determined to be an adequate sentinel i.e. papers which investigate the value of using the unit (e.g. animal, population subgroup, site) as a sentinel.
3. What year was the article published?	☐ 2015 – present ☐ 2010 – 2014	The year that the article was first available to the public (not including draft copies)

	☐ 2005 – 2009 ☐ 2000 – 2004 ☐ 1995 – 1999 ☐ 1990 – 1994 ☐ Before 1990	
4. Language of article	☐ English ☐ French ☐ Spanish ☐ Other (Exclude, complete form before submitting)	Specify Other language Please write with a capital first and write out full name in English
5. What type of document is this article?	☐ Primary research or model in peer-reviewed journal ☐ Thesis ☐ Conference proceeding without primary data (Exclude, complete form before submitting) ☐ Conference proceeding with primary data ☐ Literature review (Exclude, complete form before submitting) ☐ Literature review (Exclude, complete form before submitting) ☐ Governmental gray literature with primary data ☐ Governmental gray literature without primary data (Exclude, complete form before submitting)	**Primary research: O**riginal research/investigation/study carried out by the researcher (incl. surveys, interviews, outbreak reports, observations, etc.) **Thesis: A** long paper/essay or dissertation involving personal research (usually written for a university degree) **Conference proceeding abstract/short paper:** A collection of published academic papers **Literature review:** Examination of published literature **Systematic review/meta-analyses:** Analysis and interpretation of primary research **Grey literature:** Research that is unpublished or published in a non-commercial form (governmental / non-governmental)

	☐ Non-governmental gray literature with primary data ☐ Non-governmental gray literature without primary data (Exclude, complete form before submitting) ☐ Editorials/Commentaries without primary data (Exclude, complete form before submitting) ☐ Editorials/Commentaries with primary data ☐ Other (specify	**Editorial/Commentaries**: Short, invited opinion pieces that discuss an issue of immediate importance to the research community

Appendix II: Data characterisation Form

Question	Options	Additional notes
1. Is the full text available?	☐ Yes ☐ No (Exclude and submit)	Is the text available through the investigator's institution? Otherwise, can it be ordered? Please contact main investigator before selection No and submitting form
2. What has been used to select study area (may use more than one)?	☐ None identified (Exclude and submit) ☐ Based on population numbers ☐ Based on previous studies ☐ Randomized sample ☐ Known risk of disease (environmental data) ☐ Known risk of disease (human case data) ☐ Known risk of disease (not specified) ☐ Identification of stakeholders ☐ Areas without previous PH interventions ☐ Areas of scientific interest ☐ Based on passed surveillance ☐ Logistical reasons ☐ Economical reasons ☐ Voluntary enrollment ☐ Ecology (vector) ☐ Ecology (disease) ☐ Geographical characteristics	**None identified:** no clear reasoning for selection of the sentinel area; these papers therefore not contribute to answer the research question – the form should be submitted without completion **Based on population numbers:** Sentinel sites have been selected based on population numbers **Based on previous surveillance studies:** surveillance studies have already used these sentinel sites in the past e.g., a pilot study **Random:** Random selection of study sites **Known risk of disease (environmental data):** environmental data has shown there is risk of disease e.g., from presence of vector, or presence of pathogen **Known risk of disease (human case data):** There is risk of disease as shown from diagnosis of human cases

	☐ Modeling studies (vector) ☐ Modeling studies (climate change) ☐ Administrative boundaries ☐ Other (specify)	**Known risk of disease (not specified):** article states study site has been placed in an area of increased risk, however no statement of evidence of increased risk **Identify stakeholders:** selection of study site is influenced by stakeholders in the area **Areas without previous PH interventions:** study sites have not been subject of previous intervention to reduce vector / pathogen / disease prevalence **Area of scientific interest:** Researchers have an interest of going to this study area (may be specified or not) e.g., other studies have been previously done there **Based on passed surveillance:** Surveillance data has been gathered in the past (*this option may go along with 'Known risk of disease' option; however, the data has been gathered in a formal surveillance system) **Logistic reason:** Practical reasons e.g., close to research base, where permits were gained, presence of healthcare professionals etc. **Voluntary enrollment:** enrollment of healthcare professionals, clinics etc. on a voluntary basis **Ecology (vector)**: the ecology of the study site is appropriate of the establishment of the vector species

		Ecology (disease): the pathogen which causes the disease is able to become established in the environment **Geographical characteristics:** the site has been selected due to geographical characteristics e.g., presence of water, altitude, etc. **Modeling studies (vector):** Modeling studies have predicted expansion of the vector in this area **Modeling studies (climate change):** Modeling studies have predicted appropriate climate conditions for establishment of vector / pathogen in this area **Modelling studies (human cases):** Modelling studies have predicted human cases in this area **Administrative boundaries:** sentinel sites are chosen to fit within administrative boundaries i.e., one site par municipality / regional / etc. **Other: Please contact project lead if adding option "other" to ensure that wording is consistent, and option does not already fall within another checkbox**
3. What year was the sentinel network set up?	☐ Before 2000 ☐ 2000-2004 ☐ 2005-2009 ☐ 2010-2015 ☐ After 2015	

	☐ Not specified	
4. Does the surveillance network have a name?	[enter text]	Please enter full name first followed by acronym if applicable This will add to the option list If network does not have a name, write/check NA
5. How many years has the surveillance network been used? (Up to present)	☐ Less than one ☐ 1-2 ☐ 3-5 ☐ >5 ☐ ≥10 ☐ ≥20 ☐ Unknown	
6. Where does the study take place?	☐ North America ☐ Central-South America ☐ Eastern Europe ☐ Western Europe ☐ Africa ☐ Australia ☐ Asia ☐ Polynesia	**North America:** Canada, United States, Mexico **Eastern Europe:** Lithuania, Estonia, Latvia, Bulgaria, Ukraine, Poland, Romania, Czech Republic, Hungary, Belarus, Slovakia, Moldova **Western Europe:** Italy, Spain, France, UK, Germany, Norway, Sweden, Finland, Switzerland
7. At what level is the sentinel network used?	☐ Local ☐ Regional ☐ National ☐ Multinational	**Local:** study sites in one municipality **Regional:** study sites in multiple municipalities within the same region i.e., in proximity to each other

		National: study sites in multiple different regions across the country **Multinational:** study sites in multiple countries
8. What vector-borne disease does the paper investigate? (Select all that apply)	☐ Malaria ☐ Lymphatic filariasis ☐ Chikungunya ☐ Dengue fever ☐ Rift Valley fever ☐ Yellow fever ☐ Zika ☐ Japanese encephalitis ☐ West Nile fever / West Nile Virus ☐ Leishmaniasis ☐ Sandfly fever / phlebotomus fever ☐ Crimean-Congo haemorrhagic fever ☐ Lyme disease ☐ Relapsing fever (borreliosis) ☐ Rickettsial disease (spotted fever / Q fever) ☐ Tick-borne encephalitis ☐ Tularaemia ☐ Bluetongue disease ☐Chagas disease / American trypanosomiasis ☐ Sleeping sickness (African trypanosomiasis) ☐ Plague (all types)	

	☐ Onchocerciasis / river blindness ☐ Rickettsiosis ☐ Schistosomiasis / bilharziasis ☐ Typhus and louse-borne relapsing fever ☐ Other (specifiy)	
9. What vector is responsible for the disease?	☐ Ixodes spp. (tick) ☐ Dermacentor spp. (tick) ☐ Rhipicephalus spp. (tick) ☐ Amblyomma spp. (tick) ☐ Aedes spp. (mosquito) ☐ Anopheles spp. (mosquito) ☐ Culex spp. (mosquito) ☐ Sandflies ☐ Triatomine bugs ☐ Tsetse flies ☐ Fleas ☐ Black flies ☐ Aquatic snails	

	☐ Lice	
10. What sentinel animal is being used? (Select all that apply)	☐ None ☐ Chicken ☐ Other bird ☐ Cow ☐ Horse ☐ Other (specifiy)	**Other bird:** not chicken
11. What kind of surveillance is used? (Select all that apply)	☐ Active ☐ Passive	
12. Are human cases being reported within the sentinel network?	☐ Yes ☐ No	
13. What stage(s) of the disease cycle is being investigated in the surveillance system? i.e. what stage is being measured through the collection of data (Select all that apply)	☐ Vector ☐ Host animal ☐ Human ☐ Pathogen ☐ Unknown	**Vector:** The arthropod vector e.g., drag flannel sampling, mosquito traps. **Host animal:** A host for the vector other that humans, e.g., density of reservoir host. Note does not include host serology/density of infected ticks/mosquito, these will be accounted for in pathogen

		Human: Number of human cases reported. Note does not include human serology, this will be accounted for in pathogen **Pathogen:** quantification of presence of pathogen e.g., serology, density of infection ticks / mosquitoes
14. What methods are being used to gather data in the sentinel surveillance network? (Select all that apply)	☐ Blood test (animal) ☐ Blood test (human) ☐ Mosquito traps ☐ Flannel sampling (drag / flag) ☐ CO2 traps ☐ Questionnaires ☐ Human case reporting ☐ CSF test ☐ Parasitological survey ☐ Other (specifiy)	
15. What raw data have been gathered in the sentinel surveillance network? (Select all that apply)	☐ Serology (animal) ☐ Serology (human)	**Other: Please contact project lead if adding option "other" to ensure that wording is consistent, and option does not already fall within another checkbox**

	☐ Vector densities ☐ Symptoms ☐ Number of human cases ☐ Positive CSF ☐ Parasitology ☐ Other (specifiy)	
16. What is the study area? (Select all that apply)	☐ Field (urban centre) ☐ Field (countryside) ☐ Field (suburb) ☐ Hospital ☐ Laboratory ☐ Airport ☐ Clinic ☐ Other (specifiy)	**Clinic**: e.g., if sentinel is a family doctor (sentinel physician) select clinic **Other: Please contact project lead if adding option "other" to ensure that wording is consistent, and option does not already fall within another checkbox**
17. What was the broad aim of the study? (Select all that apply)	☐ Test intervention method ☐ Follow disease trend ☐ Early Warning System ☐ Risk factor profiling ☐ Other (specify)	**Test intervention method:** investigators are carried out public health invention as a means of disease control **Follow disease trends:** network is used to follow prevalence of disease / vector / pathogen, including investigation of areas for new signs of disease (either in

		human populations, animal populations or presence of pathogen in the environment) **Early warning system:** network used as early warning system to warm public health authorities of first signs of emergence of a disease **Other: Please contact project lead if adding option "other" to ensure that wording is consistent, and option does not already fall within another checkbox**
18. What strengths in the surveillance system have been identified in the paper? (copy paste from article)	[enter text]	Copy and paste from article Write NA if no strengths have been found/identified
19. What weaknesses in the surveillance system have been identified in the paper? (copy paste from article)	[enter text]	Copy and paste from article Write NA if no weaknesses have been found/identified
20. <u>Usefulness</u> (as defined by the WHO for evaluation of surveillance initiatives) Is the system able to be used for any the following purposes? (Check all that apply)	☐ Detect diseases, injuries, or adverse or protective exposures of public importance in a timely way to permit accurate diagnosis or identification, prevention or treatment, and handling of contacts when appropriate? ☐ Provide estimates of the magnitude of morbidity and mortality related to the health-related event under	

	surveillance, including the identification of factors associated with the event ☐ Detect trends that signal changes in the occurrence of disease, injury, or adverse or protective exposure, including detection of epidemics (or outbreaks) ☐ Permit assessment of the effect of prevention and control programs ☐ Lead to improved clinical, behavioral, social, policy, or environmental practices ☐ Stimulate research intended to lead to prevention or control ☐ Unknown ☐ Does not fulfill any of the suggested uses of surveillance initiatives (defined by WHO)	
21. Complexity (as defined by the WHO for evaluation of surveillance initiatives) Does the surveillance network require any of	☐ Special or follow-up laboratory tests to confirm the case ☐ Investigation of the case, including telephone contact or a home visit by public health personnel to collect detailed information;	

the follow (select all that apply)?	☐ Multiple levels of reporting (e.g., with the National Notifiable Diseases Surveillance System, case reports might start with the health-care provider who makes the diagnosis and pass through county and state health departments before going to CDC [29]) ☐ Integration of related systems whereby special training is required to collect and/or interpret data ☐ Surveillance network does not require any of these aspects ☐ Unknown	
22. Flexibility (as defined by the WHO for evaluation of surveillance initiatives) Has the surveillance network been able to expend with minimal resources?	☐ Yes (enrollment of voluntary sentinel physicians) ☐ No (increasing network has required intensive resources) ☐ No (network not expended) ☐ Unknown ☐ Yes (specify how the network has been expended)	**Definition.** Can public health surveillance system can adapt to changing information needs or operating conditions with little additional time, personnel, or allocated funds e.g.,–- more sentinel sites without increasing workforce - more physicians involved on a voluntary basis .
23. Data quality (as defined by the WHO for evaluation of surveillance initiatives)	☐ Low (≤20%) ☐ High (>80%) ☐ Unknown	**Definition.** Does data quality reflect the completeness and validity of the data recorded in the public health surveillance system

What is the percentage of“"unknow”" or“"blan”" responses to items on surveillance forms?		Good data quality has a low percentage of ‘blank’ responses
24. Acceptability (as defined by the WHO for evaluation of surveillance initiatives) Has there been proof of acceptability of surveillance initiatives? (Select all that apply)	☐ Subject or agency participation rate high ☐ Good physician, laboratory, or hospital/facility reporting rate ☐ The network has been able to recruit its desired number of voluntary physicians / health-care workers in the area wanted ☐ No ☐ Unknown ☐ Other markers of public acceptability (please specify)	
25. Sensitivity (as defined by the WHO for evaluation of surveillance initiatives)	☐ Yes (tracking numbers of human cases through time)	The sensitivity of a surveillance system can be considered on two levels. First, at the level of case reporting, sensitivity refers to the proportion of cases of a disease (or

Was the surveillance system able to track increases or decreases of human cases in time? OR Was the surveillance system able to track increases or decreases in vector populations vectors in time? OR Was the surveillance system able to track increases or decreases in the prevalence of the pathogen in time (e.g. serology, density of infection vectors) ?	☐ Yes (tracking numbers of vector populations through time) ☐ Yes (tracking numbers of prevalence of pathogen through time) ☐ No ☐ Unknown	other health-related event) detected by the surveillance system – this would be difficult to assess with our study method. Thus, we will use the **second definition**: sensitivity can refer to the ability to detect outbreaks, including the ability to monitor changes in the number of cases over time *This may be difficult to find from articles / publicly available data
26. Predictive value positive (as defined by the WHO for evaluation of surveillance initiatives) Predictive value positive (PVP) is the proportion of reported cases that	☐ High (> 50%) ☐ Intermediate (25-50%) ☐ Low (<25%) ☐ Presumed suboptimal (due to test chosen as supported by the literature without exact figures)	What is the proportion of cases reported in the surveillance network that were actually cases $\frac{\text{True positive}}{\text{True positive + false positive}}$ *This may be difficult to find from articles / publicly available data

actually have the health-related event under surveillance	☐ Presumed high (due to test chosen e.g. ELISA / PCR, as supported by the literature without exact figures) ☐ Unknown	
27. Representativeness (as defined by the WHO for evaluation of surveillance initiatives) Was the surveillance system able to distinguish between high risk and lower risk areas for human health?	☐ Yes ☐ No ☐ Unknown	**Definition**. A public health surveillance system that is representative accurately describes the occurrence of a health-related event over time and its distribution in the population by place and person
28. Timeliness (as defined by the WHO for evaluation of surveillance initiatives) Was the surveillance system able to act as an Early Warning System? OR Was the surveillance system able to pick up increase in vector / pathogen / cases before an outbreak?	☐ Yes ☐ No ☐ Unknown	**Early warning system:** network used to warm public health authorities of first signs of emergence of a disease (before diagnoses of disease) Does the paper state that the network was able to (or has the potential to) detect early signs of a disease outbreak with supporting evidence?

29. Stability (as defined by the WHO for evaluation of surveillance initiatives) Was the surveillance system able to manage the data, including transfer, entry, editing, storage, and back-up of data within expected delays? AND Was the surveillance system able to release data within expected delays?	☐ Yes ☐ No ☐ Unknown	**Definition**. Stability refers to the reliability (i.e., the ability to collect, manage, and provide data properly without failure) and availability (the ability to be operational when it is needed) of the public health surveillance system.

Appendix III: Results from literature search

Database(s): **All Ovid MEDLINE(R) ALL** 1946 to Present
Date of search: 29 November 2019

Search Strategy:

#	Searches	Results
1	exp Disease Vectors/ or Tick-Borne Diseases/ or (vector* adj2 disease*).tw,kf,kw.	42312
2	((arthropod* or insect* or mosquito* or aedes or anopheles or culex or tick? or triatomine bug* or sandflies or sandfly or sand flies or sand fly or blackfly or blackflies or flea? or triatomine bug* or tsetse fly or tsetse flies or aquatic snail*) adj2 (disease* or infect* or vector* or transmi* or fever* or borne or carrier* or carry or carries)).tw,kf,kw.	42961
3	Chikungunya virus/ or Chikungunya Fever/ or chikungunya.tw,kf,kw.	5065
4	exp Dengue/ or Dengue Virus/ or (dengue* or (fever adj2 (Aden or bouquet or breakbone or dandy or red or solar or sun))).tw,kf,kw.	21679
5	Rift Valley Fever/ or (rift valley adj2 (fever* or virus*)).tw,kf,kw.	1878
6	Yellow Fever/ or yellow fever.tw,kf,kw.	6444
7	Zika Virus Infection/ or Zika Virus/ or (zika or (zikv adj2 (virus* or infect* or fever*))).tw,kf,kw.	6825
8	exp Malaria/ or (malaria* or paludism* or swamp fever*).tw,kf,kw.	92314
9	Encephalitis, Japanese/ or (encephalitis adj2 japanese).tw,kf,kw.	5351
10	Elephantiasis, Filarial/ or (lymph* adj2 (filari* or elephantias*)).tw,kf,kw.	3933
11	West Nile virus/ or West Nile Fever/ or ((west nile or "Egypt 101") adj2 (fever* or virus* or flavivirus* or disease*)).tw,kf,kw.	7471
12	leishmaniasis/ or leishmaniavirus/ or (leishmani* adj2 (virus* or infect* or fever*)).tw,kw. or leishmanias*.tw,kf,kw.	25312
13	Phlebotomus Fever/ or ((sandfly or pappataci or phlebotomus) adj2 (fever* or febris)).tw,kf,kw.	538
14	Hemorrhagic Fever Virus, Crimean-Congo/ or Hemorrhagic Fever, Crimean/ or ((crimean or congo) adj2 (virus* or infection* or fever* or h?emmorrhagic)).tw,kf,kw.	1592

15	exp Borrelia Infections/ or (lyme* adj2 (disease* or borrelios*)).tw,kf. or (borrelia or borrelios* or (relaps* adj2 fever*) or neuroborrelios*).tw,kf,kw.	17841
16	Q Fever/ or (coxiella burnet* infect* or coxiellos* or ((Q or query) adj2 fever*) or (rickettsial adj2 pneumoni*)).tw,kf,kw.	5543
17	Encephalitis, Tick-Borne/ or Encephalitis Viruses, Tick-Borne/ or ((encephalit* or meningoencephalit*) adj2 (central european or tick or russian spring summer or forest spring or russian or vernal or tick or woodcutter* or louping ill or powassan)).tw,kf,kw.	5598
18	Tularemia/ or (tular?emi* or francisella tularensis infect* or ohara disease* or yato bya).tw,kf,kw.	4150
19	exp Trypanosomiasis/ or (trypanosomos?s or trypanosomias?s or trypanosoma infect* or african lethargy or sleeping sickness or nelavan or Chagas*).tw,kf,kw.	28394
20	Plague/ or ((plague adj2 (bacterial or oriental)) or (yersinia adj2 pest*)).tw,kf,kw.	7062
21	exp Rickettsia Infections/ or ((rickettsial* adj2 (disease* or infect*)) or rickettsios?s).tw,kf,kw.	8876
22	exp Onchocerciasis/ or (onchocercias* or onchocercos?s or onchoceros?s or (onchocerca adj2 infect*) or river blindness* or robles disease* or onchodermatos?s or (onchocercal adj2 (skin* or derma* or cutaneous*))).tw,kf,kw.	4935
23	exp Schistosomiasis/ or (schistosomias?s or schistomias?s or schistosomos?s or bilharzias?s or bilharzios?s or (schistosom* adj2 infect*)).tw,kf,kw.	27195
24	Tick paralysis/ or (tick adj (paralys* or toxicos*)).tw,kf,kw.	372
25	Typhus, Epidemic Louse-Borne/ or Typhus, Endemic Flea-Borne/ or Typhus.tw,kf,kw.	5846
26	or/1-25	296360
27	Sentinel Surveillance/	6166
28	(sentinel adj4 (surveillance or network* or system*)).tw,kw,kf.	2842
29	Sentinel*.tw,kw,kf.	26101
30	or/27-29	30401
31	26 and 30	1937

Database(s): **Embase** 1974 to 2019 November 27
Date of search: 29 November 2019

Search Strategy:

#	Searches	Results
1	*vector borne disease/ or exp *arthropod vector/ or *parasite vector/ or *tick borne disease/	4448
2	(vector* adj2 disease*).tw,kw.	7087
3	((arthropod* or insect* or mosquito* or aedes or anopheles or culex or tick? or triatomine bug* or sandflies or sandfly or sand flies or sand fly or blackfly or blackflies or flea? or triatomine bug* or tsetse fly or tsetse flies or aquatic snail*) adj2 (disease* or infect* or vector* or transmi* or fever* or borne or carrier* or carry or carries)).tw,kw.	46130
4	*chikungunya/ or *chikungunya virus/ or chikungunya.tw,kw.	6141
5	exp *dengue/ or (dengue* or (fever adj2 (Aden or bouquet or breakbone or dandy or red or solar or sun))).tw,kw.	26888
6	*rift valley fever/ or *rift valley fever virus/ or (rift valley adj2 (fever* or virus*)).tw,kw.	1974
7	*Yellow fever/ or yellow fever*.tw,kw.	5790
8	*zika fever/ or *zika virus/ or (zika or (zikv adj2 (virus* or infect* or fever*))).tw,kw.	8431
9	exp *malaria/ or (malaria* or paludism* or swamp fever*).tw,kw.	100126
10	*japanese encephalitis/ or *japanese encephalitis virus/ or (encephalitis adj2 japanese).tw,kw.	5408
11	*lymphatic filariasis/ or (lymph* adj2 (filari* or elephantias*)).tw,kw.	3832
12	*west nile fever/ or *west nile virus/ or ((west nile or "Egypt 101") adj2 (fever* or virus* or flavivirus* or disease*)).tw,kw.	8142
13	*leishmaniasis/ or *leishmaniavirus/ or leishmani*.tw,kw. or ((leishmani* adj2 (virus* or infect* or fever*)) or leishmanias*).tw,kw.	37965
14	*sandfly fever/ or *sandfly fever naples virus/ or *sandfly fever sicilian virus/ or ((sandfly or pappataci or phlebotomus) adj2 (fever* or febris)).tw,kw.	299
15	*crimean congo hemorrhagic fever/ or *crimean-congo hemorrhagic fever virus/ or ((crimean or congo) adj2 (virus* or infection* or fever* or h?emmorrhagic)).tw,kw.	1918

16	exp *Borrelia infection/ or exp *Borrelia/ or (lyme* adj2 (disease* or borrelios*)).tw,kw. or (borrelia or borrelios* or (relaps* adj2 fever*) or neuroborrelios*).tw,kw.	20335
17	*Q fever/ or (coxiella burnet* infect* or coxiellos* or ((Q or query) adj2 fever*) or (rickettsial adj2 pneumoni*)).tw,kw.	4327
18	*Rickettsialpox/ or *rickettsiosis/ or ((rickettsial* adj2 (disease* or infect*)) or Rickettsi* or spotted fever*).tw,kw.	11079
19	*tick borne encephalitis/ or ((encephalit* or meningoencephalit*) adj2 (central european or tick or russian spring summer or forest spring or russian or vernal or tick or woodcutter*)).tw,kw.	4414
20	*tick paralysis/ or (tick adj (paralys* or toxicos*)).tw,kw.	216
21	*tularemia/ or (tular?emi* or francisella tularensis infect* or ohara disease* or yato bya).tw,kw.	3105
22	exp *trypanosomiasis/ or (trypanosomos?s or trypanosomias?s or trypanosoma infect* or african lethargy or sleeping sickness or nelavan or Chagas*).tw,kw.	26224
23	*Plague/ or ((plague adj2 (bacterial or oriental)) or (yersinia adj2 pest*)).tw,kw.	5751
24	exp *Schistosomiasis/ or (schistosomias?s or schistomias?s or schistosomos?s or bilharzias?s or bilharzios?s or (schistosom* adj2 infect*)).tw,kw.	22950
25	exp *onchocerciasis/ or (onchocercias* or onchocercos?s or onchoceros?s or (onchocerca adj2 infect*) or river blindness* or robles disease* or onchodermatos?s or (onchocercal adj2 (skin* or derma* or cutaneous*))).tw,kw.	4645
26	*Typhus/ or *epidemic typhus/ or Typhus.tw,kw.	3798
27	or/1-26 [Vector borne diseases]	302174
28	*sentinel surveillance/	948
29	(sentinel adj4 (surveillance or network* or system*)).tw,kw.	3653
30	Sentinel*.tw,kw.	39662
31	28 or 29 or 30	40202
32	27 and 31	1915

Database(s): **Global Health** 1910 to week 47
Date of search: 29 November 2019

#	Searches	Results
1	disease vectors/ or vector-borne diseases/ or mosquito-borne diseases/ or tickborne diseases/ or ((vector* adj2 disease*) or ((arthropod* or insect* or mosquito* or aedes or anopheles or culex or tick? or triatomine bug* or sandflies or sandfly or sand flies or sand fly or blackfly or blackflies or flea? or triatomine bug* or tsetse fly or tsetse flies or aquatic snail*) adj2 (disease* or infect* or vector* or transmi* or fever* or borne or carrier* or carry or carries))).tw,id.	104596
2	exp Chikungunya virus/ or chikungunya.tw,id.	4140
3	exp Dengue virus/ or (dengue* or (fever adj2 (Aden or bouquet or breakbone or dandy or red or solar or sun))).tw,id.	19455
4	exp Rift valley fever virus/ or (rift valley adj2 (fever* or virus*)).tw,id.	1844
5	exp Yellow fever virus/ or yellow fever.tw,id.	4352
6	exp zika virus/ or (zika or (zikv adj2 (virus* or infect* or fever*))).tw,id.	4057
7	exp malaria/ or (malaria* or paludism* or swamp fever*).tw,id.	76488
8	Japanese encephalitis/ or (encephalitis adj2 japanese).tw,id.	5152
9	elephantiasis/ or filariasis/ or (lymph* adj2 (filari* or elephantias*)).tw,id.	12741
10	exp west nile virus/ or ((west nile or "Egypt 101") adj2 (fever* or virus* or flavivirus* or disease*)).tw,id.	6503
11	exp leishmaniasis/ or exp Leishmaniavirus/ or (leishmani* adj2 (virus* or infect* or fever*)).tw,id. or leishmanias*.tw,id.	25787
12	exp sandfly fever/ or ((sandfly or pappataci or phlebotomus) adj2 (fever* or febris)).tw,id.	431
13	exp Crimean-Congo haemorrhagic fever virus/ or ((crimean or congo) adj2 (virus* or infection* or fever* or h?emmorrhagic)).tw,id.	1577
14	exp lyme disease/ or (lyme* adj2 (disease* or borrelios*)).tw,id. or (borrelia or borrelios* or (relaps* adj2 fever*) or neuroborrelios*).tw,id.	13372
15	q fever/ or (coxiella burnet* infect* or coxiellos* or ((Q or query) adj2 fever*) or (rickettsial adj2 pneumoni*)).tw,id.	3310

16	exp Tick-borne encephalitis virus/ or ((encephalit* or meningoencephalit*) adj2 (central european or tick or russian spring summer or forest spring or russian or vernal or tick or woodcutter* or louping ill or powassan)).tw,id.	3152
17	tularaemia/ or (tular?emi* or francisella tularensis infect* or ohara disease* or yato bya).tw,id.	2155
18	exp Trypanosomiasis/ or (trypanosomos?s or trypanosomias?s or trypanosoma infect* or african lethargy or sleeping sickness or nelavan or Chagas*).tw,id.	21429
19	plague/ or Yersinia pestis/ or ((plague adj2 (bacterial or oriental)) or (yersinia adj2 pest*)).tw,id.	4292
20	exp rickettsia/ or rickettsial diseases/ or ((rickettsial* adj2 (disease* or infect*)) or rickettsios?s).tw,id.	6485
21	onchocerciasis/ or (onchocercias* or onchocercos?s or onchoceros?s or (onchocerca adj2 infect*) or river blindness* or robles disease* or onchodermatos?s or (onchocercal adj2 (skin* or derma* or cutaneous*))).tw,id.	4923
22	exp schistosomiasis/ or (schistosomias?s or schistomias?s or schistosomos?s or bilharzias?s or bilharzios?s or (schistosom* adj2 infect*)).tw,id.	30323
23	tick paralysis/ or (tick adj (paralys* or toxicos*)).tw,id.	171
24	exp typhus fevers/ or Typhus.tw,id.	2797
25	or/1-24	250290
26	sentinel surveillance/ or sentinel.tw,id.	5654
27	25 and 26	1563

Database(s): **CABAbstracts**
Date of search: 29 November 2019

#	Searches	Results
1	disease vectors/ or vector-borne diseases/ or mosquito-borne diseases/ or tickborne diseases/ or ((vector* adj2 disease*) or ((arthropod* or insect* or mosquito* or aedes or anopheles or culex or tick? or triatomine bug* or sandflies or sandfly or sand flies or sand fly or blackfly or blackflies or flea? or triatomine bug* or tsetse fly or tsetse flies or aquatic snail*) adj2 (disease* or infect* or vector* or transmi* or fever* or borne or carrier* or carry or carries))).tw,id.	147065
2	exp Chikungunya virus/ or chikungunya.tw,id.	4096
3	exp Dengue virus/ or (dengue* or (fever adj2 (Aden or bouquet or breakbone or dandy or red or solar or sun))).tw,id.	19033
4	exp Rift valley fever virus/ or (rift valley adj2 (fever* or virus*)).tw,id.	2082
5	exp Yellow fever virus/ or yellow fever.tw,id.	4129
6	exp zika virus/ or (zika or (zikv adj2 (virus* or infect* or fever*))).tw,id.	4062
7	exp malaria/ or (malaria* or paludism* or swamp fever*).tw,id.	75731
8	Japanese encephalitis/ or (encephalitis adj2 japanese).tw,id.	5000
9	elephantiasis/ or filariasis/ or (lymph* adj2 (filari* or elephantias*)).tw,id.	13573
10	exp west nile virus/ or ((west nile or "Egypt 101") adj2 (fever* or virus* or flavivirus* or disease*)).tw,id.	6511
11	exp leishmaniasis/ or exp Leishmaniavirus/ or (leishmani* adj2 (virus* or infect* or fever*)).tw,id. or leishmanias*.tw,id.	26407
12	exp sandfly fever/ or ((sandfly or pappataci or phlebotomus) adj2 (fever* or febris)).tw,id.	410
13	exp Crimean-Congo haemorrhagic fever virus/ or ((crimean or congo) adj2 (virus* or infection* or fever* or h?emmorrhagic)).tw,id.	1538
14	exp lyme disease/ or (lyme* adj2 (disease* or borrelios*)).tw,id. or (borrelia or borrelios* or (relaps* adj2 fever*) or neuroborrelios*).tw,id.	13412
15	q fever/ or (coxiella burnet* infect* or coxiellos* or ((Q or query) adj2 fever*) or (rickettsial adj2 pneumoni*)).tw,id.	3361
16	exp Tick-borne encephalitis virus/ or ((encephalit* or meningoencephalit*) adj2 (central european or tick or russian spring summer or forest spring or russian or vernal or tick or woodcutter* or louping ill or powassan)).tw,id.	3048

17	tularaemia/ or (tular?emi* or francisella tularensis infect* or ohara disease* or yato bya).tw,id.	2127
18	exp Trypanosomiasis/ or (trypanosomos?s or trypanosomias?s or trypanosoma infect* or african lethargy or sleeping sickness or nelavan or Chagas*).tw,id.	25982
19	plague/ or Yersinia pestis/ or ((plague adj2 (bacterial or oriental)) or (yersinia adj2 pest*)).tw,id.	4282
20	exp rickettsia/ or rickettsial diseases/ or ((rickettsial* adj2 (disease* or infect*)) or rickettsios?s).tw,id.	7710
21	onchocerciasis/ or (onchocercias* or onchocercos?s or onchoceros?s or (onchocerca adj2 infect*) or river blindness* or robles disease* or onchodermatos?s or (onchocercal adj2 (skin* or derma* or cutaneous*))).tw,id.	5041
22	exp schistosomiasis/ or (schistosomias?s or schistomias?s or schistosomos?s or bilharzias?s or bilharzios?s or (schistosom* adj2 infect*)).tw,id.	30176
23	tick paralysis/ or (tick adj (paralys* or toxicos*)).tw,id.	393
24	exp typhus fevers/ or Typhus.tw,id.	2682
25	or/1-24	298131
26	sentinel surveillance/ or sentinel.tw,id.	6359
27	25 and 26	1847

Gray literature

Site Searched	Search Terms	# of results retrieved	# of results screened	# of results retained
WHO https://www.who.int/	Vector AND sentinel	1555	4 pages	0
	Health Topics → Vector Control → Publications	1 page	1 page	0
**used Google to search WHO site	(vector AND sentinel) site:who.int	3720	6 pages	0

WHO IRIS https://apps.who.int/iris/simple-search?query=	vector AND sentinel	1831	4 pages	2
Harvard Think Tank https://guides.library.harvard.edu/hks/think_tank_search	Vector AND sentinel	20	20	2
Google	Vector AND (sentinel AROUND(3) surveillance)	548 000	7 pages	4
	Vector AND (sentinel AROUND(3) site)	6 900 000	5 pages	2
PAHO https://www.paho.org/hq/index.php?lang=en	Sentinel	4530	5 pages	0
Eurosuveillance https://www.eurosurveillance.org/	Sentinel	573	8 pages	9
Tropical Pathology and Infectious Diseases Association http://tpida.org/tpida/	Research → cases	1 page	1 page	0
CDC h ttps://www.cdc.gov/	Sentinel AND vector	1605	12 pages	22
NSW Public Health Bulletin	Sentinel AND vector	103	5 pages	6

ECDC https://ecdc.europa.eu/en/home	sentinel surveillance	2072	6 pages	0

Appendix IV: Search verification

Article provided by expert

Done 5th December 2019

Article no.	Reference	Captured?
1	Racloz V, Griot C, Stärk KD. (2006). Sentinel surveillance systems with special focus on vector-borne diseases. *Anim Health Res Rev*, 7(1-2):71-9	Yes
2	Paterson BJ, Mackenzie JS, Durrheim DN, Smith D. (2011). A review of the epidemiology and surveillance of viral zoonotic encephalitis and the impact on human health in Australia. *N S W Public Health Bull*, 22(5-6):99-104	Yes
3	Harvey K, Esposito DH, Han P, Kozarsky P, Freedman DO, Plier DA, Sotir MJ, Center for Disease Control and Prevention (CEC). (2013). Surveillance for travel-related disease-GeoSentinel Surveillance System, United States, 1997-2011. *MMWR Surveill Summ*, 62:1-23.	Yes
4	May L, Chretien JP, Pavlin JA. (2009). Beyond traditional surveillance: applying syndromic surveillance to developing sett–gs--opportunities and challenges. *BMC Public Health*, 9:242.	No -added
5	Harvey K, Esposito DH, Han P, Kozarsky P, Freedman DO, Plier DA, Sotir MJ, Center for Disease Control and Prevention (CEC), (2013). Surveillance for travel-related disease-GeoSentinel Surveillance System, United States, 1997-2011. *MMWR Surveill Summ* , 62:1-23.	Yes
6	Griffiths KM, Savini H, Brouqui P, Simon F, Parola P, Gautret P. (2018). Surveillance of travel-associated diseases at two referral centres in Marseille, France: a 12-year survey. *J Travel Med*, 25(1).	Yes
7	Braks M, van der Giessen J, Kretzschmar M, van Pelt W, Scholte EJ Reusken C, Zeller H, van Bortel W, Sprong H. (2011). Towards an integrated approach in surveillance of vector-borne diseases in Europe. *Parasit Vectors*, 4:192–No - added	No-added
8	Barrera R, Mackay A, Amador M, Vasquez J, Smith J, Diaz A, Acevedo V, Caban B, Hunsperger EA, Munoz-Jordan JL. (2010). Mosquito vectors of West Nile virus during an epizootic outbreak in Puerto Rico. *J Med Entomol*, **47**(6): 1185-1195.	Yes
9	Giovannini A, Calistri P, Conte A, Savini L, Nannini D, Patta C, Santucci U, Caporale V. (2004). Bluetongue virus surveillance in a newly infected area. *Vet Ital*, 40(3):188-97	Yes
10	Touch S, Hills S, Sokhal B, Samnang C, Sovann L, Khieu V, Soeug SC, Toda K, Robinson J, Grundy J. (2009). Epidemiology and burden of disease from Japanese encephalitis in Cambodia: results from two years of sentinel surveillance. *Trop Med Int Health*, 14 (11):1365-73	Yes

Four of the ten articles were then used for the snowball strategy.

Snowball strategy

Carried out between 4– 5th December 2019

Seven different review articles were used in the snowball strategy, to capture different elements of sentinel surveillance. As the topic of the scooping review is specific and englobes several elements, many of the references within review articles were not appropriate to capture by the search strategy, and one review article could not be found to capture all the necessary articles. Therefore, the article were chosen to ensure the search strategy capture the main aspects of sentinel surveillance networks for vector-borne diseases, notably:

Article 1) Sentinel surveillance focusing on vector-borne diseases
Article 2) Integrated surveillance for vector-borne diseases
Article 3) Syndromic surveillance
Article 4) Animals as sentinels
Article 5) the GeoSentinel network, Dengue (second most common vector-borne disease worldwide) and Malaria (most common vector-borne disease worldwide)
Article 6) West Nile virus (third most common vector-borne disease worldwide)
Article 7) Lyme disease (most common vector-borne disease in North America)

Article 1: Sentinel surveillance for vector-borne diseases

Racloz V, Griot C, Stark KD. (2006). Sentinel surveillance systems with special focus on vector-borne diseases. *Animal health research reviews*, 7(1-2), 71–79.

Article no.	Reference	Captured?
1	Anonymous (2002). National Arbovirus Monitoring Program (NAMP). [Available online at www.namp.com.au.]	Yes
2	Bauer B, Kabore I, Liebisch A, Meyer F and Petrich-Bauer J. (1992). Simultaneous control of ticks and tsetse flies in Satiri, Burkina Faso, by the use of flumethrin pour on for cattle. *Tropical Medicine and Parasitology* , 43: 41–46.	Added
3	Duncan AW, Correa MT, Levine JF, Breitschwerdt EB. (2005). The dog as a sentinel for human infection: prevalence of Borrelia burgdorferi C6 antibodies in dogs from southeastern and mid-Atlantic States. *Vector-borne Zoonotic Diseases*, 5: 101–109.	Yes

4	Eidson M, Komar N, Sorhage F, Nelson R, Talbot T, Mostashari F, McLean R. (2001). Crow deaths as a sentinel surveillance system for West Nile virus in the northeastern United States, 1999. *Emerging Infectious Disease s*, 7: 615–620	Yes
5	McCluskey BJ, Mumford EL, Salman MD and Traub-Dargatz JJ. (2002). Use of sentinel herds to study the epidemiology of vesicular stomatitis in the state of Colorado. *Annals of the New York Academy of Sciences*, 969: 205–209.	Yes
6	Mohammed ME, Aradaib IE, Mukhtar MM, Ghalib HW, Riemann HP, Oyejide A, Osburn BI. (1996). Application of molecular biological techniques for detection of epizootic hemorrhagic disease virus (EHDV-318) recovered from a sentinel calf in central Sudan. *Veterinary Microbiology* , 52: 201–208.	Yes
7	Paling RW, Leak SG, Katende J, Kamunya G, Moloo SK, (1987). Epidemiology of animal trypanosomiasis on a cattle ranch in Kilifi, Kenya. *Acta Tropica* , 44: 67–82	Yes
8	Ward MP, Flanagan M, Carpenter TE, Hird DW, Thurmond MC, Johnson SJ, Dashorst ME. (1995). Infection of cattle with bluetongue viruses in Queensland, Australia: results of a sentinel herd study, 1990–1992. *Veterinary Microbiology* , 45: 35–44.	Yes

Article 2: Integrated surveillance

Braks M, van der Giessen J, Kretzschmar M, van Pelt W, Scholte EJ Reusken C, Zeller H, van Bortel W, Sprong H. (2011). Towards an integrated approach in surveillance of vector-borne diseases in Europe. *Parasit Vector s*, 4:192.

Article no.	Reference	Captured?
1	Calistri P, Giovannini A, Hubalek Z, Ionescu A, Federica Monaco F, Savini G, Lelli R. (2010). Epidemiology of West Nile in Europe and in the Mediterranean Basin. *Open Viro l*, 4: 29–37.	Yes
2	Scholte E, Den Hartog W, Dik M, Schoelitsz B, Brooks M, Schaffner F, Foussadier R, Braks M, Beeuwkes J. (2010). Introduction and control of three invasive mosquito species in the Netherlands, July-October 2010. *Euro Surveill*, 15(45). pii: 19710.	Yes
3	Schmidt PL, (2009). Companion animals as sentinels for public health. *Vet Clin North Am Small Anim Prac* , 39:241-250	Yes

Article 3: Syndromic surveillance

May L, Chretien JP, Pavlin JA. (2009). Beyond traditional surveillance: applying syndromic surveillance to developing settings--opportunities and challenges. *BMC Public Health*, 9: 242.

Article no.	Reference	Captured?
1	Cox J, Abeku T, Beard J, Turyeimuka J, Tumwesigye E, Okia M, Rwakimari J. (2007). Detecting epidemic malaria, Uganda. *Emerg Infect Dis*, 13(5): 779-80.	No – not added
2	Ceccato P, Ghebremeskel T, Jaiteh M, Graves PM, Levy M, Ghebreselassie S, Ogbamariam A, Barnston AG, Bell M, del Corral J, Connor SJ, Fesseha I, Brantly EP, Thomson MC. Malaria stratification, climate, and epidemic early warning in Eritrea. Am J Trop Med Hyg. 2007;77: 61–8.	No – not added
3	Rockx B, van Asten L, Wijngaard C van den, Godeke GJ, Geohring L, Vennema H, Avoort H van der, van Pelt W, Koopmans M. (2006). Syndromic surveillance in the Netherlands for the early detection of West Nile virus epidemics. *Vector Borne Zoonotic Dis*, 6: 161–9.	No – not added

Article 4: Animals as sentinels

Halliday JEB, Meredith AL, Knobel DL, Shaw DJ, Bronsvoort BM, Cleaveland S. (2007). A framework for evaluating animals as sentinels for infectious disease surveillance. *J R Soc Interface*, 4(16): 973-84.

Article no.	Reference	Captured?
1	Eidson M, Komar N, Sorhage F, Nelson R, Talbot T, Mostashari F, Mclean R. (2001). Crow deaths as a sentinel surveillance system for West Nile virus in the Northeastern United States, 1999. *Emerg Infect Dis*, 7, 615–620.	Yes
2	Eidson M, Kramer L, Stone W, Hagiwara Y, Schmit K. (2001). Dead bird surveillance as an early warning system for West Nile virus. *Emerg Infect Dis*, 7, 631–635	Yes
3	McCluskey BJ. (2003). Use of sentinel herds in monitoring and surveillance systems. In Animal disease surveillance and survey systems: methods applications (ed. M. D. Salman). Iowa , IA: Iowa State Press, pp. 119–133.	Yes
4	Mostashari F, Kulldorff M, Hartman JJ, Miller JR, Kulasekera V. (2003). Dead bird clusters as an early warning system for West Nile virus activity. *Emerg Infect Dis*, 9, 641–646.	Yes

5	Ward MR, Stallknecht DE, Willis J, Conro, MJ, Davidson WR. (2006). Wild bird mortality and West Nile virus surveillance: biases associated with detection, reporting, and carcass persistence. *J Wildl Dis*, 42, 92–106.	Yes

Artic le 5: Geosentinel network, Dengue, Malaria

Griffins KM, Savini H, Brouqui P, Simon F, Parola P, Gautret P. (2018). Surveillance of travel-associated diseases at two referral centres in Marseille, France: a 12-year survey. *Journal of travel medicine*, 25(1), tay007.

Article no.	Reference	Captured?
1	Leder K, Torresi J, Brownstein JS, Wilson ME, Keystone JS, Barnett E, Schwartz E, Schlagenhauf P, Wilder-Smith A, Castelli F, von Sonnenburg G, Freedman DO, Cheng AC, GeoSentinel Surveillance Network. (2013). Travel-associated illness trends and clusters, 2000–2010. *Emerg Infect Dis*, 19(7):1049–73	Yes
2	Harvey K, Esposito DH, Han P, Kozarsky P, Freedman DO, Plier DA' Sotir MJ, Centers for Disease Control and Prevention. (2013). Surveillance for travel-related disease—GeoSentinel Surveillance System, United States, 1997–2011. *Morb Mortal Wkly Rep Surveill Summ*, 62: 1–23.	Yes
3	Gautret P, Botelho-Nevers E, Charrel RN, Parola P. (2010). Dengue virus infections in travellers returning from Benin to France, July-August 2010. *Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull 2010*, 15 (36):pii: 19657:1–2.	Yes
4	Neumayr A, Munoz J, Schunk M et al. (2017). Sentinel surveillance of imported dengue via travellers to Europe 2012 to 2014: TropNet data from the DengueTools Research Initiative. *Eurosurveillance*, 22(1).	Yes
6	Hamer DH, Barbre KA, Chen LH, Grobush MP, Shlagenhauf P, Goorhuis A, van Genderen PJJ, et al. (2017). Travel-associated zika virus disease acquired in the Americas through February 2016: a GeoSentinel analysis. *Ann Intern Med*, 166(2):99–108.	Yes
7	Dia A, Gautret P, Adheossi E, Bienaimé A, Gaillard C, Simon F, Parola P, Brouqui P. (2010). Illness in French travelers to Senegal: prospective cohort follow-up and sentinel surveillance data. *J Travel Med*, 17(5):296–302.	Yes

.

Article 6: West Nile Virus

Grossner CM, Marrama L, Carson M, Allerberger F, Calistri P, Dilaveris D, Lecollinet S, Morgan D, Nowotny N, Paty MC, Pervanidou D, Rizzo C, Roberts H, Schmoll F, van Bortel W, Gervelmeyer A. (2017). West Nile virus surveillance in Europe: moving towards

an integrated animal-human-vector approach. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin*, 22(18), 30526.		
Article no.	Reference	Captured?
1	Leblond A, Hendrikx P, Sabatier P. (2007). West Nile virus outbreak detection using syndromic monitoring in horses. *Vector Borne Zoonotic Dis*, 7(3):403-10.	Yes
2	Murgue B, Murri S, Zientara S, Durand B, Durand JP, Zeller H. (2001). West Nile outbreak in horses in southern France, 2000: the return after 35 years. *Emerg Infect Dis*, 7(4):692-6.	Yes
3	Rizzo C, Napoli C, Venturi G, Pupella S, Lombardini L, Calistri P, et al. (2016). Italian WNV surveillance working group. West Nile virus transmission: results from the integrated surveillance system in Italy, 2008 to 2015. *Euro Surveill*, 21(37):30340	Yes
4	European Centre for Disease Prevention and Control (ECDC). Annual epidemiological report 2014 – emerging and vector-borne diseases. Stock holm: ECDC; 2014.	Yes
5	European Centre for Disease Prevention and Control (ECDC). VectorNet: A European network for sharing data on the geographic distribution of arthropod vectors, transmitting human and animal disease agents. Stock holm: ECDC	Yes
6	Healy JM, Reisen WK, Kramer VL, Fischer M, Lindsey NP, Nasci RS, et al. (2015). Comparison of the efficiency and cost of West Nile virus surveillance methods in California. *Vector Borne Zoonotic Dis*, 15(2):147-55.	Yes

Article 7: Lyme disease

Sprong H, Azagi T, Hoornstra D, Nijhof A, Knorr S, Baarsma ME, Hovius JW. (2018). Control of Lyme borreliosis and other *Ixodes riicinus*-borne diseases. *Parasites & vectors*, 11(1), 145.

Article no.	Reference	Captured?
1	Septfons A, Goronflot T, Jaulhac B, Roussel V, De Martino S, Guerreiro S, Launay T, Fournier L, De Valk H, Figoni J, Blanchon T, Couturier E. (2019). Epidemiology of Lyme borreliosis through two surveillance systems: the national Sentinelles GP network and the national hospital discharge database, France, 2005 to 2016. *Euro Surveill*, 24 (11):1800134.	Yes
2	van den Wijngaard CC, Hofhuis A, Simões M, Rood E, van Pelt W, Zeller H, et al. (2017). Surveillance perspective on Lyme borreliosis across the European Union and European Economic Area. *Euro Surveill*, 22 (27):30569.	Yes

References

1. Jones K, Patel N, Levy M, Storeygard A, Balk D, Gittleman J, et al. (2008). Global Trends in Emerging Infectious Diseases. *Nature*, **451**:990-3.
2. Bahuon C, Marcillaud-Pitel C, Bournez L, Leblond A, Beck C, Hars J, et al. (2016). West Nile virus epizootics in the Camargue (France) in 2015 and reinforcement of surveillance and control networks. *Revue Scientifique et Technique - Office International des Épizootie*, **35**(3):811-24.
3. Petrić D, Petrovic T, Hrnjakovic I, Zgomba M, Milosevic V, Lazic G, et al. (2016). West Nile virus 'circulation' in Vojvodina, Serbia: Mosquito, bird, horse and human surveillance. *Molecular and Cellular Probes*; **31**:28-36.
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Appendix 2

Criteria for selecting sentinel unit locations in a surveillance system for vector-borne disease: A decision tool

Realist-type review protocol

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Based on:

Pawson R, Greenhalgh T, Harvey G, Walshe K. (2005). Realist review - a new method of systematic review designed for complex policy interventions. *J. Health Serv. Res. Policy*, **10**:21–34

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Our research team utilized a review approach based on the realist review (1) and modified the approach to suit our research objectives. All steps described below (Appendix) follow recommendations from Pawson *et al.* (1).

Step 1: Classify scope

a. Identify the review question

i. Nature and content of the intervention

The intervention under study for this realist review is the implementation of **sentinel surveillance systems for vector-borne diseases** (VBDs) of public health importance, as defined by the WHO (2). Some diseases determined to be of public health importance by the review team where included, despite not being on the WHO's list e.g., Bluetongue virus. Public health importance was determined by significant impact of human and/or animal health[11].

An initial scoping review (3) was used to list the various contexts where sentinel systems were used for surveillance of these VBDs.

ii. Circumstances or contexts for its use

A total of 36 various VBDs (or groups of VBDs e.g., tick-borne diseases) where surveyed across the articles retained in the scoping review (**Table 24**). The most frequently surveyed diseases included malaria, West Nile virus infection, lymphatic filariasis, and schistosomiasis.

Table 24. List of vector-borne diseases investigated within the articles included in the scoping review, including type of arthropod vector, type of pathogen and number of articles that studied each of these diseases

Disease	Vector	Pathogen	No. of articles

[11] Vector-borne diseases of plants were not captured with the search strategy

Malaria	Mosquitoes	Parasite	68
West Nile virus infection	Mosquitoes	Virus	32
Lymphatic filariasis	Mosquitoes	Parasite	22
Schistosomiasis	Snails	Parasite	19
Western equine encephalitis	Mosquitoes	Virus	15
Bluetongue	Midges	Virus	14
Murray Valley encephalitis	Mosquitoes	Virus	11
Onchocerciasis	Black flies	Parasite	11
Japanese encephalitis	Mosquitoes	Virus	10
Ross River virus	Mosquitoes	Virus	9
Arbovirus infection	Mosquitoes	Virus	7
Chikungunya	Mosquitoes	Virus	5
Zika	Mosquitoes	Virus	5
Barmah Forest virus infection	Mosquitoes	Virus	4
Yellow fever	Mosquitoes	Virus	4
Lyme disease	Ticks	Bacteria	4
Venezuelan equine encephalitis	Mosquitoes	Virus	3
Epizootic hemorrhagic disease	Midges	Virus	3
Arboviruses group A and B infection	Mosquitoes	Virus	2
Eastern equine encephalitis	Mosquitoes	Virus	2
Rift Valley fever	Mosquitoes	Virus	2
Utusu virus infection	Mosquitoes	Virus	2
Leishmaniasis	Phlebotomine sand flies	Parasite	2
Q Fever	Ticks	Bacteria	2
Saint Louis encephalitis	Ticks	Virus	2
Bovine trypanosomiasis	Tsetse flies	Parasite	2
C'aga's disease	Triatomine bugs	Parasite	1
Edge Hill virus infection	Mosquitoes	Virus	1
Jamestown Canyon virus infection	Mosquitoes	Virus	1
Bovine ephemeral fever	Midges	Virus	1
Schmallenberg virus infection	Midges	Virus	1
Bartonella infection	Ticks	Bacteria	1
Crimean-Congo fever	Ticks	Virus	1
Powassan virus infection	Ticks	Virus	1
Tick-borne diseases	Ticks	NA	1
African trypanosomiasis	Tsetse flies	Parasite	1

Other circumstances of the use of sentinel surveillance networks have been documented in a previous scoping review, including:

1) Number of sentinel sites / number of locations where sentinels were places (**Table 25**)
2) Number of years of operation (currently) of the sentinel surveillance system (**Table 25**)
3) Geographical location of the sentinel surveillance systems (Table 26)
4) Scale of operations of the sentinel surveillance systems (**Table 27**)

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Table 25. Number of sentinel surveillance units in surveillance systems detailed in articles retained during a previous scoping review, according to the duration of the surveillance network operation.

Number of sites	Duration of network operation (years)							Total
	<1	1 to 2	3 to 5	6 to 10	11 to 20	>20	Unknown	
2	7	3	0	0	0	0	0	10
3-5	15	15	10	1	1	0	1	43
6-10	20	22	13	4	4	0	0	63
11-20	7	11	8	1	1	0	0	28
21-50	9	9	8	3	0	1	0	30
>50	3	3	2	3	1	8	0	20
Unknown	3	2	3	2	1	1	0	12
Total	64	65	43	14	8	10	1	206

Table 26. Geographical locations of sentinel surveillance systems detailed in articles retained during a previous scoping review and number of articles where the geographical location was elicited

Geographical location	Number of articles (%)
Africa	88 (42.7)
Asia	32 (15.5)
North America	27 (13.1)
Western Europe	18 (8.7)
Australia	15 (7.1)
Central or South America	13 (4.2)
Oceania	9 (3.9)
Eastern Europe	7 (3.4)

Table 27. Geographical scale of sentinel surveillance systems detailed in articles retained during a previous scoping review and number of articles where the geographical scale was elicited

Geographical scale of sentinel surveillance system	Number of articles (%)
Local	33, (16.0)
Regional	73 (35.4)
National	94 (45.6)
Multinational	6 (2.9)

The broad objectives of the sentinel surveillance systems in the articles retained in the previous scoping review included: following disease trends, testing intervention methods, profiling risk factors, and acting as an Early Warning System (EWS)[12,13] (**Table 28**).

Table 28. Objectives of sentinel surveillance systems detailed in articles retained during previous a scoping review and number of articles which elicited each of the surveillance objectives

Objective of sentinel surveillance systems	Number of articles (%)
Following disease trends	128 (62.1)
Testing intervention methods	72 (35.0)
Profiling risk factors	32 (15.0)
Acting as an Early Warning System	15 (7.3)

iii. Policy intentions or objectives

Our previous scoping review has allowed to describe the contexts in which sentinel surveillance systems have been developed for vector-borne diseases. These are diverse e.g., different geographical locations, different scales and different vectors/VBDs under surveillance.

The Canadian Lyme Disease Research Network (CLyDRN) has the mandate to construct a sentinel surveillance network for Lyme disease across Canada. The network will be constituted of sentinel nodes; these nodes will be defined as sentinel regions consisting of a circular area with a radius of 50km around a population center. Active surveillance in the form of drag flannel sampling will be conducted at sites within these regions.

A key consideration in planning the surveillance system was to decide where in space should the sentinel regions be located. There were no precise guidelines to answer this question, which lead to the following **review question**:

[12] In the scoping review, some articles had the objectives of evaluating the sentinel surveillance system; as this is not an objective of the current realist review, which aims to investigate the establishment of new surveillance systems, this objective was not retained

[13] Some sentinel surveillance systems had more than one objective e.g., following disease trends and risk factor profiling

b. Refine the purposes of the review

In this step, the purpose of the review is refined to capture an explanatory theme, based on a programme theory which has a clear impact on policy and can offer the potential for change. Pawson *et al.* (1) describe four different approaches:

1. **Theory integrity:** Purpose by theories of change evaluation, where complex programmes as viewed as sequency of stepping stones, which each of the step needed to be achieved successfully to reach the intended outcome
2. **Theory adjudication:** As many different interventions can be described in the literature, a realist review can uncover evidence to adjudicate between rival theories or identify which permutation of mechanisms is most successful.
3. **Comparison:** Here, it is assumed that programmes only work under certain circumstances and so, the review will uncover many studies of the 'same' intervention and can attempt to identify patterns of successful versus unsuccessful outcome.
4. **Reality testing:** This approach uses opposition between policy-makers and practitioners, grounds for political friction, to generate rival theories that may be put to empirical adjudication via a realist review.

For the currently review, a **comparison approach** of the contents within the literature was used[14].

c. Articulate key theories to be explored

To set the stage for the realist review, the reviewer must familiarize themselves with current intervention theories found in the literature. From a long list of intervention theories, a short list will be drawn up and investigated in depth.

[14] As recommended by Pawson *et al.* (1), the final decision of which approach to use was finalized later during the review process; it is documented that realist review use iterative process and thus, pre-publication of realist review protocols are not recommended.

For our review questions, which consists of:

How to choose appropriate sentinel sites locations for a sentinel surveillance system for vector-borne diseases?

published reviews have identified diverse criteria which have been used to select geographical locations of sentinel surveillance systems. In previous work, these criteria where extracted (**Table 29**).

Table 29. List of criteria used during planning the spatial design of sentinel surveillance systems and number of times different sentinel surveillance systems used each of the criteria

Criterion	Description	No. of articles
Risk (human)	There is documented risk of disease due to the presence of human cases within the sentinel unit location (SUL)	55
Past surveillance	The SUL were chosen as they had been used in previously in surveillance programmes	34
Logistics	Logistical constraints (e.g., travelling distance, access) are considered for the SUL	31
Administrative boundaries	Selection of SUL according to administrative boundaries	29
Geographical features	The geography of the SUL has been taken into consideration during the selection	27
Variation in risk	There is a variation in degree of risk of the disease between the SUL	25
Variation in ecology	The SUL have been chosen due to variation in ecology between these units	23
Risk (vector)	There is documented risk of disease due to the presence of appropriate vector disease within the SUL	22
Previous studies	The SUL were chosen as they had been used in previously in scientific studies	21
Risk (unspecified)	There is documented risk of disease, however the nature of the risk is not elucidated within the SUL	20
Ecology (vector)	The ecology of the SUL is appropriate for the presence of the vector	18
Risk (host animals)	There is documented risk of disease due to the presence of appropriate host species within the SUL	17
Population numbers	Selection of the SUL in order to maximize the population reached within the units of the study zone	17
Random	Random distribution of SUL in the study zone	16
Voluntary	SUL are based on voluntary enrollment	14
Previous PH interventions	There are previous public health interventions carried out within the SUL	12
Population demographics	Population demographics are considered during the selection of SUL	10
Even distribution	Even distribution of SUL through the study zone	9
Proximity to risk	The SUL are in proximity to an area with document risk of disease	8
No previous PH interventions	There are no previous public health interventions carried out within the SUL	8

Variation in geography	The SUL have been chosen due to variation in geographical features between these units	7
Ecology (host animal)	The ecology of the SUL is appropriate for the presence of the host species	7
Ecology (unspecified)	The ecology of the SUL has been taken into consideration during the selection, however authors have not specified how	6
Population stability	The populations within the SUL are stable (no immigration / emigration)	6
Risk (geography)	There is documented risk of disease due to geography (abiotic) within the SUL	5
Proximity to area of interest	The SUL is near an area of interest, such as a school	5
Variation in PH interventions	There is a variation in public health interventions carried out with the SUL	5
Livestock population	Selection of the SUL in order to maximize the volume of livestock within the units	4
Climate	Climate has been taken into consideration in the selection of the SUL	4
Suspected risk	There is suspected risk of disease within the SUL	3
Presence of human activity	There is presence of a specific type of human activity (e.g., fishing, hunting, wild mushroom picking) within the SUL	3
Areas of scientific interest	The SUL have been chosen as they represent areas of increased scientific interest	3
Stakeholders	The SUL are selected according to stakeholder preferences, suggestions or recommendations	3
No risk	There is no document risk of disease within the SUL	2
Risk (interface)	There is documented risk of disease due to the presence of vector-human interface within the SUL	2
Ecology (disease)	The ecology of the SUL is appropriate for the presence of the VBD	2
Population instability	The population within the SUL are unstable (immigration / emigration)	2
Minimal distance	Separation of SUL by a minimal distance	2
Specialist centers	There are specialists or a specialist centre within the SUL	2
Threshold of consultations	The SUL are selected in order to ensure that a minimal threshold of patient consultations is achieved	2
Variation in farming practices	The SUL have been chosen due to variation in farming practices between these units	1

Variation in housing type	The SUL have been chosen due to variation in housing type between these units	1
Health clinic demographics	Demographics of the health clinics are considered during the selection of SUL	1
Modelling	The SUL were chosen as there is modeling data to support their selection	1
Communications	There are adequate communication facilities within the SUL	1

Next, as part of the realist review process, previous criteria were grouped together based on the nature of each criterion (**Table 30**) and used to formulate general theories (**Table 31**) from which the review will explore in further depth. Afterwards, a theoretically-based evaluative framework was build as the backbone of the realist review (**Figure 27**).

Table 30. Criteria for selecting geographical locations of sentinel units grouped by nature of the criterion.

Group	Criterion	Description
Risk-level	Risk (human)	There is documented risk of disease due to the presence of human cases within the sentinel unit location (SUL)
	Variation in risk	There is a variation in degree of risk of the disease between the SUL
	Risk (vector)	There is documented risk of disease due to the presence of appropriate vector disease within the SUL
	Risk (unspecified)	There is documented risk of disease, however the nature of the risk is not elucidated within the SUL
	Risk (host animals)	There is documented risk of disease due to the presence of appropriate host species within the SUL
	Proximity to risk	The SUL are in proximity to an area with document risk of disease
	Risk (geography)	There is documented risk of disease due to geography (abiotic) within the SUL
	Suspected risk	There is suspected risk of disease within the SUL
	No risk	There is no document risk of disease within the SUL
	Risk (interface)	There is documented risk of disease due to the presence of vector-human interface within the SUL
Environment	Geographical features	The geography of the SUL has been taken into consideration during the selection
	Ecology (vector)	The ecology of the SUL is appropriate for the presence of the vector
	Variation in ecology	The SUL have been chosen due to variation in ecology between these units
	Ecology (unspecified)	The ecology of the SUL has been taken into consideration during the selection, however authors have not specified how
	Variation in geography	The SUL have been chosen due to variation in geographical features between these units
	Ecology (host animal)	The ecology of the SUL is appropriate for the presence of the host species
	Proximity to area of interest	The SUL is near an area of interest, such as a school
	Livestock population	Selection of the SUL in order to maximize the volume of livestock within the units
	Climate	Climate has been taken into consideration in the selection of the SUL
	Ecology (disease)	The ecology of the SUL is appropriate for the presence of the VBD
	Variation in farming practices	The SUL have been chosen due to variation in farming practices between these units
	Variation in housing type	The SUL have been chosen due to variation in housing type between these units
Population	Population numbers	Selection of the SUL in order to maximize the population reached within the units of the study zone
	Population demographics	Population demographics (e.g., population-level, health clinic) are considered during the selection of SUL
	Population stability	The populations within the SUL are stable / unstable (immigration / emigration)
	Presence of human activity	There is presence of a specific type of human activity (e.g., fishing, hunting, wild mushroom picking) within the SUL
Distribution	Administrative boundaries	Selection of SUL according to administrative boundaries
	Random	Random distribution of SUL in the study zone
	Even distribution	Even distribution of SUL through the study zone

	Minimal distance	Separation of SUL by a minimal distance
Past information	Past surveillance	The SUL were chosen as they had been used in previously in surveillance programmes
	Previous studies	The SUL were chosen as they had been used in previously in scientific studies
	Previous PH interventions	There are previous public health interventions carried out within the SUL
	No previous PH interventions	There are no previous public health interventions carried out within the SUL
	Variation in PH interventions	There is a variation in public health interventions carried out with the SUL
	Areas of scientific interest	The SUL have been chosen as they represent areas of increased scientific interest
	Modelling	The SUL were chosen as there is modeling data to support their selection
Logistics	Logistics	All logistical consideration which will help the feasibility of the surveillance system, including: - Logistical constraints (e.g., travelling distance, access) are considered for the SUL - SUL are based on voluntary enrollment - The SUL are selected according to stakeholder preferences, suggestions, or recommendations - There are specialists or a specialist centre within the SUL - The SUL are selected in order to ensure that a minimal threshold of patient consultations is achieve - There are adequate communication facilities within the SUL

Table 31. Theories developed, using preliminary literature search, to explain how spatial distribution of sentinel surveillance networks for sentinel surveillance systems have worked or not worked

Theory one	- Choosing sites where previous studies or previous surveillance initiatives have been done in the past can ensure that these sites are representative of the epidemiological portrait[15]
Theory two	- Evaluating risk level (using a known data e.g., vector densities, human case data) can assist in identifying sites of key scientific interest for surveillance of vector-borne diseases
Theory three	- Using environmental data can further assist in identifying sites of key scientific interest for surveillance of vector-borne diseases
Theory four	- As public health surveillance is population-orientated, considering human population densities is an important aspect for identifying sites of key scientific interest for surveillance of vector-borne diseases
Theory five	- Considering human population characteristics e.g., demographics, human activities, could be of particular importance for surveillance of specific vector-borne diseases

[15] These sites should have served a similar surveillance objective

Theory six	- Using criteria to distribute sites across space could help to ensure that the entire study area is surveyed
Theory seven	- Using logistical considerations could support feasibility and durability of the surveillance network

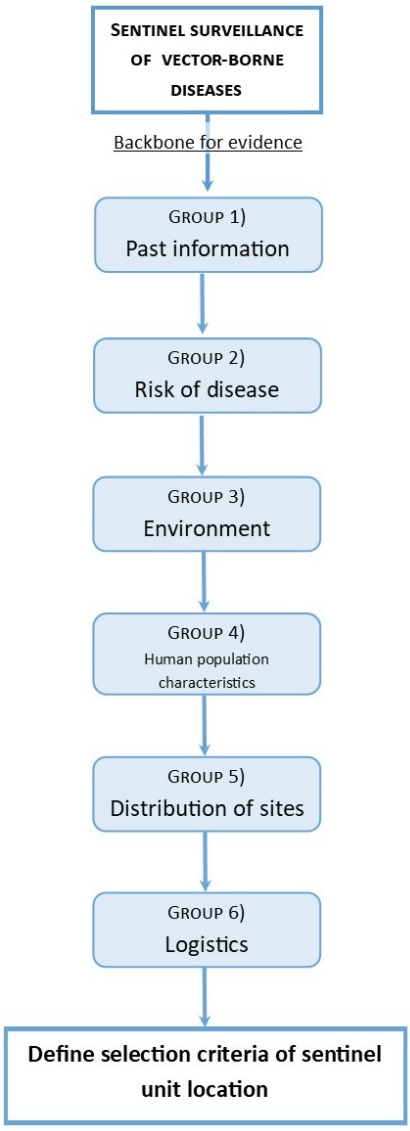

Figure 27. Evaluative framework for realist-type review ; the order of the criteria groups was determined through discussion with review team and validated by experts in the field of vector-borne surveillance

Step 2: Search for evidence

a. Exploratory background search

This step has the utility of 'getting a feel' for the literature of the subject. This has been done during our previous scoping review (**Figure 28**). The search strategy used for the scoping review was developed to be inclusive: search terms related to (1) sentinel surveillance and (2) vector-borne diseases. Relevance screening was subsequently used on title and abstracts to keep only relevant articles.

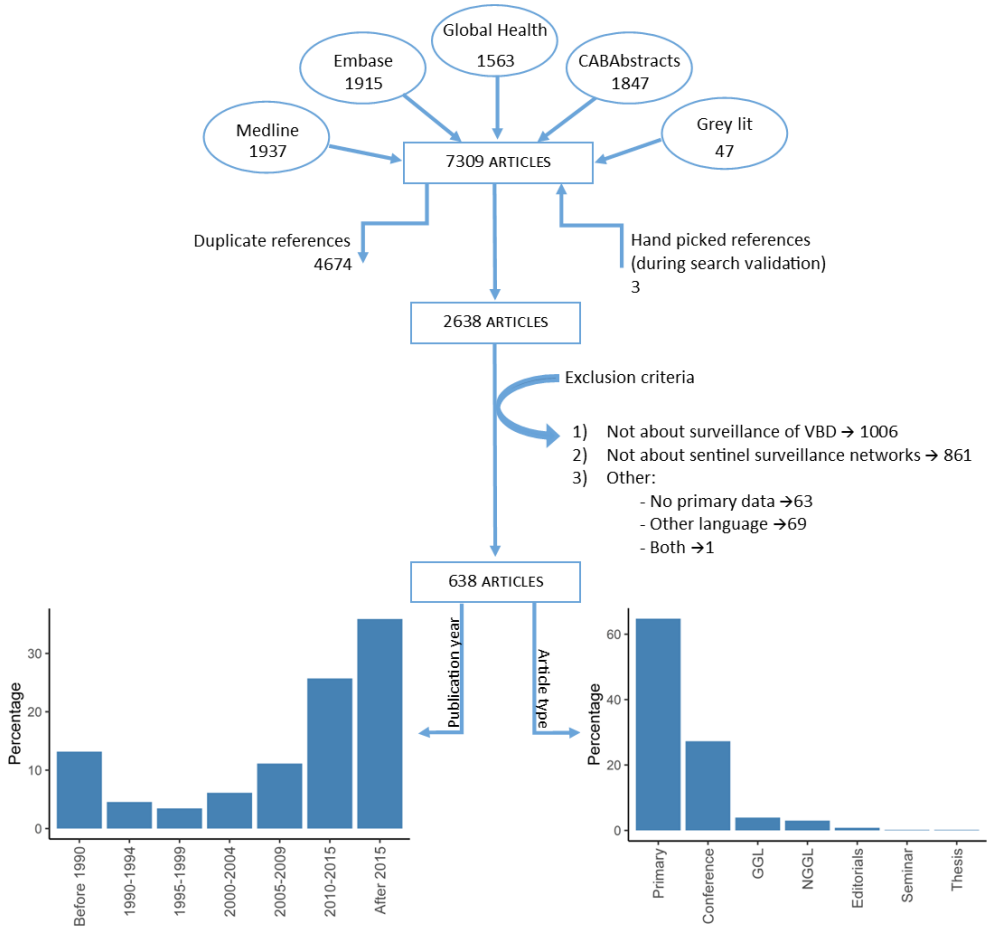

Figure 28. Search outcome from a scoping review aimed at investigating sentinel surveillance networks for vector-borne diseases, performed between September and November 2019. The search outcome is reported based on PRISMA guidelines. GGL, governmental gray literature; NGGL, non-governmental gray literature

b. Progressive focusing to identify key programme theories

Key program theories had been identified whilst speaking with key actors in the field (through CLyDRN surveillance group meetings) and through browsing of review papers including:

- Halliday JE, Meredith AL, Knobel DL, Shaw DJ, Bronsvoort BM, Cleaveland S. (2007). A framework for evaluating animals as sentinels for infectious disease surveillance. *J R Soc Interface*, 4(16):973-84.
- McCluskey, BJ. (2008). Use of Sentinel Herds in Monitoring and Surveillance Systems. In: Animal Disease Surveillance and Survey Systems: Methods and Application : 119-133.
- Racloz V, Griot C, Stärk KD. (2006). Sentinel surveillance systems with special focus on vector-borne diseases. *Anim Health Res Rev* 7(1-2):71-9.

c. Purposive sampling

This has been described as the 'search proper' by Pawson *et al.* (1), where the reviewer moves on from browsing the literature (primary research), and a formal audit trail is provided. In the case of this review, a sensitive strategy was used to capture articles pertaining to sentinel surveillance for VBDs (**Table 32**). Database searched included CAB Abstract, Global Health and Embase and Medline. A total of 8 hours were spent looking at the gray literature.

Table 32. Search strategy for articles pertaining to sentinel surveillance and vector-borne diseases. The search strategy was modified for various databases

#	Searches
1	exp Disease Vectors/ or Tick-Borne Diseases/ or (vector* adj2 disease*).tw,kf,kw.
2	((arthropod* or insect* or mosquito* or aedes or anopheles or culex or tick? or triatomine bug* or sandflies or sandfly or sand flies or sand fly or blackfly or blackflies or flea? or triatomine bug* or tsetse fly or tsetse flies or aquatic snail*) adj2 (disease* or infect* or vector* or transmi* or fever* or borne or carrier* or carry or carries)).tw,kf,kw.
3	Chikungunya virus/ or Chikungunya Fever/ or chikungunya.tw,kf,kw.
4	exp Dengue/ or Dengue Virus/ or (dengue* or (fever adj2 (Aden or bouquet or breakbone or dandy or red or solar or sun))).tw,kf,kw.
5	Rift Valley Fever/ or (rift valley adj2 (fever* or virus*)).tw,kf,kw.

6 Yellow Fever/ or yellow fever.tw,kf,kw.

7 Zika Virus Infection/ or Zika Virus/ or (zika or (zikv adj2 (virus* or infect* or fever*))).tw,kf,kw.

8 exp Malaria/ or (malaria* or paludism* or swamp fever*).tw,kf,kw.

9 Encephalitis, Japanese/ or (encephalitis adj2 japanese).tw,kf,kw.

10 Elephantiasis, Filarial/ or (lymph* adj2 (filari* or elephantias*)).tw,kf,kw.

11 West Nile virus/ or West Nile Fever/ or ((west nile or "Egypt 101") adj2 (fever* or virus* or flavivirus* or disease*)).tw,kf,kw.

12 leishmaniasis/ or leishmaniavirus/ or (leishmani* adj2 (virus* or infect* or fever*)).tw,kw. or leishmanias*.tw,kf,kw.

13 Phlebotomus Fever/ or ((sandfly or pappataci or phlebotomus) adj2 (fever* or febris)).tw,kf,kw.

14 Hemorrhagic Fever Virus, Crimean-Congo/ or Hemorrhagic Fever, Crimean/ or ((crimean or congo) adj2 (virus* or infection* or fever* or h?emmorrhagic)).tw,kf,kw.

15 exp Borrelia Infections/ or (lyme* adj2 (disease* or borrelios*)).tw,kf. or (borrelia or borrelios* or (relaps* adj2 fever*) or neuroborrelios*).tw,kf,kw.

16 Q Fever/ or (coxiella burnet* infect* or coxiellos* or ((Q or query) adj2 fever*) or (rickettsial adj2 pneumoni*)).tw,kf,kw.

17 Encephalitis, Tick-Borne/ or Encephalitis Viruses, Tick-Borne/ or ((encephalit* or meningoencephalit*) adj2 (central european or tick or russian spring summer or forest spring or russian or vernal or tick or woodcutter* or louping ill or powassan)).tw,kf,kw.

18 Tularemia/ or (tular?emi* or francisella tularensis infect* or ohara disease* or yato bya).tw,kf,kw.

19 exp Trypanosomiasis/ or (trypanosomos?s or trypanosomias?s or trypanosoma infect* or african lethargy or sleeping sickness or nelavan or Chagas*).tw,kf,kw.

20 Plague/ or ((plague adj2 (bacterial or oriental)) or (yersinia adj2 pest*)).tw,kf,kw.

21 exp Rickettsia Infections/ or ((rickettsial* adj2 (disease* or infect*)) or rickettsios?s).tw,kf,kw.

22 exp Onchocerciasis/ or (onchocercias* or onchocercos?s or onchoceros?s or (onchocerca adj2 infect*) or river blindness* or robles disease* or onchodermatos?s or (onchocercal adj2 (skin* or derma* or cutaneous*))).tw,kf,kw.

23 exp Schistosomiasis/ or (schistosomias?s or schistomias?s or schistosomos?s or bilharzias?s or bilharzios?s or (schistosom* adj2 infect*)).tw,kf,kw.

24 Tick paralysis/ or (tick adj (paralys* or toxicos*)).tw,kf,kw.

25 Typhus, Epidemic Louse-Borne/ or Typhus, Endemic Flea-Borne/ or Typhus.tw,kf,kw.

26	or/1-25
27	Sentinel Surveillance/
28	(sentinel adj4 (surveillance or network* or system*)).tw,kw,kf.
29	Sentinel*
30	or/27-29
31	26 and 30

d. Final search for additional studies when review near completion

Using a snowball strategy, additional articles used during the construction of the decision tool included:

- Animal and Plant Health Inspection Service (APHIS) (2003). Bluetongue surveillance. The 2000 serological survey of slaughter cattle for antibody against bluetongue virus. Diagnostic Virology Laboratory, National Veterinary Services Laboratories, Ames. Online: (aphis.usda.gov/vs/nahps/blue tongue/serological_survey.html. Accessed on 12 June 2022.
- European Council. (1992). Directive 92/119/EEC of 17 December 1992 introducing general Community measures for the control of certain animal diseases and specific measures relating to swine vesicular disease. *Off. J.,* L 062, 69-85.
- Hetzel MW, Pulford, J, Maraga S, Barnadas C, Reimer LJ, Tavul L, Jamea-Maiasa S, Tandrapah T, Maalsen A, Makita L, Siba PM, Mueller I. (2014). Evaluation of the Global Fund-supported National Malaria Control Program in Papua New Guinea, 2009-2014. *Papua and New Guinea medical journal*, **57**(1-4), 7–29.
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Step 3: Appraise primary studies and extract data

a. Use judgement to supplement formal critical appraisal checklists

Realist reviews support the principle of evaluating data quality, as done in systematic review, however, utilize a different position. Whilst that systematic reviews evaluate data quality based on a strict hierarchy of evidence, this model limits greatly the information which can be obtained compared to a realist review. In comparison, during the realist review, multiple methods and approaches should be assessed to evaluate complex interventions.

Thus, the use of the investigator's judgement is the realist solution to quality control. The **relevance** and **rigour** of the retained articles are evaluated during this step (1).

Relevance: Relevance within a realist review is not about whether the study covered a particular topic, but whether it addressed the theory under test.

Rigour: Whether a particular inference drawn by the original researcher has sufficient weight to make a methodologically credible contribution to the test of a particular intervention theory

b. Develop a 'bespoke' set of data extraction forms

Conversely to systematic reviews, or even scoping reviews, realist review will assimilate information more by note-taking and annotation than by extracting data as such e.g., using data extraction forms. The aim of this process is to identify theories within the retained articles, and whether the interventions (i.e., criteria using to select locations for sentinel units) have had successful outcomes (i.e., have reached surveillance objectives).

Thus, the database for note taking will contain the following headings:

Article name	Relevance	Rigor	Criteria used	Context	Theory

c. Extract different data from different studies to populate evaluative framework with evidence

The data from the different studies was collated into an Excel document.

Step 4: Synthesize evidence and draw conclusion

Step 4 can be summarized in four steps,

a. Synthesize data to achieve refinement of programme theory
b. Allow purpose of review (see Step 1b) to drive the synthesis process
c. Use 'contradictory' evidence to generate insights about the influence of context
d. Present conclusions as a series of contextualized decision points of the general format

These steps aim to determine what works for whom, how and under what circumstances, using the information obtained by step 3c). This have been done in an iterative manner in order to build a decision tool which will be presented as the final product.

Step 5: Disseminate, implement and evaluation

a. Draft and test out recommendations and conclusions

Once a 'final' decision tool, which incorporates recommendations and conclusions has been approved by the research team, it will be presented to experts and stakeholders for their opinion. The tool will be modified in consequence.

b. Work with practitioners and policy-makers to apply recommendations in particular contexts

This step is beyond the scope of the current article. However, its functionality will be illustrated though the use of a case example – for building a sentinel surveillance network in the south of Canada.

c. Evaluate

This step is beyond the scope of the current article. It will be a limit of the decision – to ensure its functionality and internal validity, sentinel surveillance programmes which develop using this tool will have to be evaluated.

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Appendix

Table 33. Summary of key steps in realist review as described by Pawson *et al.* (1)

Step 1: Clarify scope a. Identify the review question • Nature and content of the intervention • Circumstances of context for its use • Policy intentions or objectives b. Refine the purpose of the review • Theory integrity – does the intervention work as predicted? • Theory adjudication – which theories fit best? • Comparison – how does the intervention work in different setting, for different groups? • Reality testing – how does the intervention work in different setting, for different groups? c. Articulate key theories to be explored • Draw up a 'longlist' of relevant programme theories by exploratory searching (see Step 2) • Group, categorize, or synthesize theories
Step 2: search for evidence a. Exploratory background search to get a feel for the literature b. Progressive focusing to identify key programme theories, refining inclusion criteria in the light of emerging data c. Purposive sampling to test a defied subset of these theories, with additional 'snowball' sampling to explore new hypotheses as they emerge d. Final search for additional studies when review near completion
Step 3: Appraise primary studies and extract data a. Use judgement to supplement formal critical appraisal checklists, and consider 'fitness for purpose' • Relevance – does the research address the theory under test? • Rigour – does the research support the conclusions drawn from it by the researchers or the reviewers b. Develop bespoke set of data extraction form and notation devices c. Extract different data from different studies to population evaluative framework with evidence
Step 4: synthesize evidence and draw conclusions a. Synthesize data to achieve refinement of programme theory – that is, to determine what works for whom, how and under what circumstances b. Allow purpose of review (see Step 1b) to drive the synthesis process c. Use 'contradictory' evidence to generate insights about the influence of context d. Present conclusions as a series of contextualized decision points of the general format 'If A, then B' or 'in the case of C, D is unlikely to work'

Step 5: Disseminate, implement and evaluate

a. Draft and test out recommendations and conclusions with key stakeholders, focusing especially on levers that can be pulled in here-and-now policy contexts
b. Work with practitioners and policy-makers to apply recommendations in particular contexts
c. Evaluate in terms of extent to which programmes are adjusted to take account of contextual influences revealed by the review: the 'same' programme might be expanded in one setting, modified in another and abandoned in another

Appendix 3

Criteria for selecting sentinel unit locations in a surveillance system for vector-borne disease: A decision tool

Guillot Camille[*1,2,3], Bouchard Catherine[1,4], Aenishaenslin Cécile[1], Berthiaume Philippe[1,4], Milord François[2] & Leighton Patrick A[1,3]

Supplementary material

Validation for decision tool

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[3] Centre de recherche en santé publique de l'Université de Montréal et du CIUSSS du Centre-Sud-de-l'île-de-Montréal (CReSP)

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Contents

1) Contact email for participation of experts

Below is the contact email which was sent to 11 experts to ask for their participation in validating the decision tool:

Dear all,

For those of you who don't know me, I am a PhD student in Dr Patrick Leighton's lab. My thesis looks at sentinel surveillance, in the context of vector-borne diseases, and more specifically for Lyme disease.

In the process of designing a surveillance system for vector-borne diseases, selecting the best sentinel sites can be challenging. In the context of my PhD, I have created a decisional tool which aims to help users to choose relevant criteria which can be used to objectively select such sites. The output of the decisional tool is a list of criteria, which can be used to determine where in space these sentinel sites should be located e.g., used as part of a multi-criteria decision analysis.

The tool was created with information gained from conducting a literature search, and data compiled to create a logical tool. It follows on from a previous article:

> Guillot C, Bouchard C, Berthiaume P, Mascarenhas M, Sauvé C, Villeneuve CA, Leighton P. A Portrait of Sentinel Surveillance Networks for Vector-Borne Diseases: A Scoping Review Supporting Sentinel Network Design. Vector Borne Zoonotic Dis. 2021 Aug 4. doi: 10.1089/vbz.2021.0008. Epub ahead of print. PMID: 34348055.

However, **this tool needs to be validated by experts** (academic and public health) to ensure its relevance, functionality, and completeness, before its publication.

I have created a questionnaire (about 30 mins) to allow for this assessment – your contribution would be greatly appreciated! In order to carry out the tool validation, please follow this link:

NA

Furthermore, the tool is available as a pdf attachment along with a case study which illustrates how to use the tool.

If you could complete the questionnaire by the **18th of October**, I would be very grateful.

Many thanks and don't hesitate to get in touch with any questions,

Camille

2) Introduction to the questionnaire

Below is the description of the task which was provided to experts for validation of the decision tool:

Hello,

Thank you for taking the time to complete this validation step for a new decisional tool.

In the process of designing a surveillance system for vector-borne diseases, selecting the best sentinel sites can be challenging. In the context of my PhD, I have created a decisional tool which aims to help users to choose relevant criteria which can be used to objectively select such sites. The output of the decisional tool is a list of criteria, which can be used to determine where in space these sentinel sites should be located e.g., used as part of a multi-criteria decision analysis.

The tool was created with information gained from conducting a literature search, and data compiled to create a logical tool. It follows on from a previous article:

Guillot C, Bouchard C, Berthiaume P, Mascarenhas M, Sauvé C, Villeneuve CA, Leighton P. A Portrait of Sentinel Surveillance Networks for Vector-Borne Diseases: A Scoping Review Supporting Sentinel Network Design. Vector Borne Zoonotic Dis. 2021 Aug 4. doi: 10.1089/vbz.2021.0008. Epub ahead of print. PMID: 34348055.

However, this tool needs to be validated by experts (academic and public health) to ensure its relevance, functionality, and completeness, before its publication.

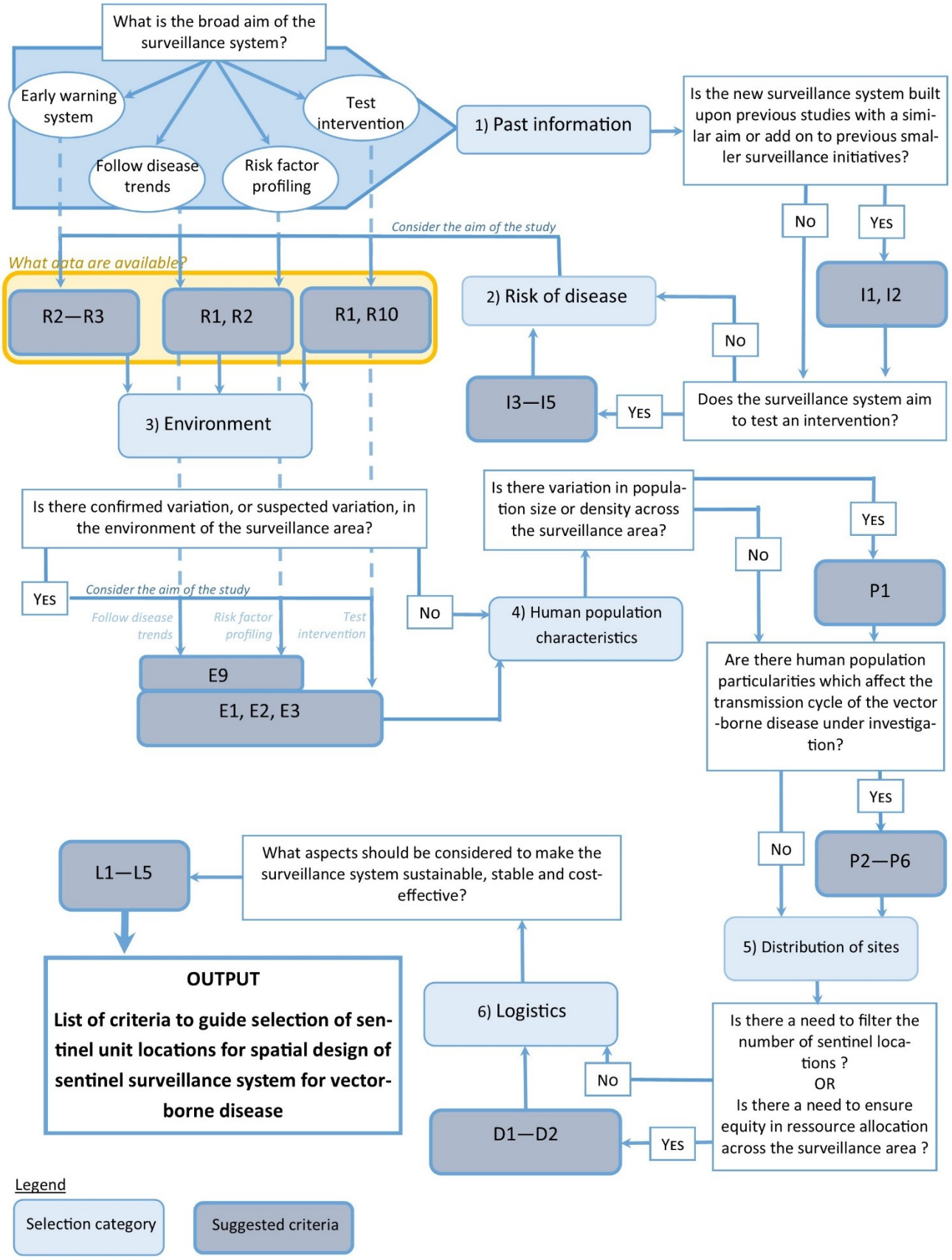
I have created a short questionnaire (20-30 mins) to allow for its assessment. Please use the pdf sent to you by email in order to answer the questions.

Once again, many thanks and don't hesitate to get in touch with any questions,

Camille

3) Original decision tool provided to experts

The following decision tool (**Figure 29**) was provided in pdf form to experts. It was used to answer the questions within the online survey.


What is the broad aim of the surveillance system?
Early warning system
Test intervention
Follow disease trends
Risk factor profiling
1) Past information
Is the new surveillance system built upon previous studies with a similar aim or add on to previous smaller surveillance initiatives?
No
Yes
I1, I2
Consider the aim of the study
What data are available?
R2—R3
R1, R2
R1, R10
2) Risk of disease
No
I3—I5
Yes
Does the surveillance system aim to test an intervention?
3) Environment
Is there confirmed variation, or suspected variation, in the environment of the surveillance area?
Yes
Consider the aim of the study
Follow disease trends
Risk factor profiling
Test intervention
No
E9
E1, E2, E3
4) Human population characteristics
Is there variation in population size or density across the surveillance area?
Yes
No
P1
Are there human population particularities which affect the transmission cycle of the vector-borne disease under investigation?
Yes
No
P2—P6
5) Distribution of sites
Is there a need to filter the number of sentinel locations ?
OR
Is there a need to ensure equity in ressource allocation across the surveillance area ?
No
Yes
D1—D2
6) Logistics
What aspects should be considered to make the surveillance system sustainable, stable and cost-effective?
L1—L5
OUTPUT
List of criteria to guide selection of sentinel unit locations for spatial design of sentinel surveillance system for vector-borne disease
Legend
Selection category
Suggested criteria

D1 Consideration of administrative boundaries
D2 Random distribution of locations within the surveillance zone
E1 Consideration of the geography
E2 Presence of appropriate ecology for the presence of the vector
E9[1] Consideration of climate
I1 Selection of locations previously used in surveillance programs
I2 Selection of locations previously used in scientific studies
I3 Previous public health interventions carried out within the sentinel unit locations
I4 No previous public health interventions carried out within the sentinel unit locations
I5 Variation in public health interventions carried out across the sentinel unit locations
L1 Consideration of logistical constraints (e.g., traveling distance, access)
L2 Voluntary enrollment of sentinel unit locations
L3 Stakeholders' preferences, suggestions, or recommendations
L4 Presence of specialists or a specialist center within or near the sentinel unit location
L5 Presence of adequate communication facilities within or nearby the sentinel unit location
P1 Selection of the sentinel unit locations to maximize the population surveyed
P2 Consideration of population demographics (e.g., age, gender, socioeconomic status)
P3 Stability of human population (no immigration / emigration)
P5 Presence of a specific type of human activity (e.g., fishing, hunting, wild mushroom picking)
P6 Consideration of the patient demographics from participating the health clinics (e.g., age, gender, socioeconomic status)
R1 Presence of documented risk of disease, based on human case data
R2 Variation in degree of risk of the disease between the sentinel unit locations
R3 Presence of documented risk of disease, based on presence of appropriate disease vectors
R10 Presence of documented risk of disease, based on the evidence of vector-human contact
[1]criteria codes were kept from previous publication to keep these constant across our work

Figure 29. Decision tool provided to experts during tool validation step

4) Case study provided to experts for demonstration of functionality of the decision tool

Case study: Lyme disease at a national level

In North America, Lyme disease (LD) has been identified a priority VBD for public health due to its ongoing emergence, accelerated by climate change. In eastern Canada, the vector tick species, *Ixodes scapularis,* was first studied in the 70s at Long Point, Ontario and its range has shown ongoing expansion since this time. With Canada's vast territory, and the heterogeneous spread of tick populations in space, sentinel surveillance could allow a cost-effective, nationwide surveillance strategy to monitor the environmental risk of LD and track the risk through time. Hence, LD surveillance at a national level will be used as a case example to illustrate the application of the criteria selection tool in the determination of sentinel unit locations.

Such a surveillance system will be constructed by the Canadian Lyme Disease Research Network (CLyDRN) in the form of the Canadian Lyme Sentinel Network (CaLSeN). The aim of this system will be to follow trends in Lyme disease risk over time across Canada by evaluating the environmental risk of LD through active field surveillance of ticks. The sentinel unit will be a sentinel region, a geographical unit of 100km diameter around a population center. There will be minimally one sentinel region per province, and thus, the criteria selection tool will be used to determine which locations would be the most appropriate to act as sentinel regions at the provincial level.

Past information

Although there has been past active surveillance done in most Canadian provinces, they are no sentinel regions established for more intensive surveillance initiatives. Currently, there are no planned public health interventions as part of the surveillance system.

Risk

The primary aim of the sentinel surveillance system will be to follow trends in LD risk exposure in the environment. In the context of LD, although it was deemed a notifiable disease in 2009 in Canada, the

human data case is owned by individual health boards and the geographic scale of the location of acquisition varies greatly between provinces. Due to these circumstances, data from passive surveillance is more easily accessible and remains the earliest signal of environmental risk of LD. Thus, for the system, the risk associated with the presence of the vectors will be used as a criterion for the selection of sentinel regional location.

Environment

Habitats vary greatly among and within provinces – from urban, barren land, wetlands, cropland, needle leaf forests, grassland, etc. (Canada Land Cover 2015). Many of these habitats will not be appropriate for the establishment of *Ixodes spp.* ticks, which require mixed or deciduous forests. Thus, this heterogenous land cover should be considered, and the presence of appropriate habitats for the establishment of vector populations should also be retained from the criteria selection tool. Furthermore, as the primary aim of the surveillance system is to follow disease trends, we can also select the criterion in which climatic features are considered, in this case temperature is the most relevant variable.

Population

Human population density varies greatly across provinces, with most of the population concentrated in urban centers. Thus, population density will be considered as a selection criterion. However, as LD remains a relatively rare disease in Canada, with an incidence of 2.7 cases / 100 000, population demographics or behaviors will not be considered.

Distribution

To ensure a minimum level of geographic representativeness, at least one sentinel region will be selected within each province, and up to three sentinel regions in the larger provinces that report higher incidences of LD, such as Ontario and Québec.

Logistics

As the system will cover a large geographical area, and that the system is intended to be maintained for many years to provide a longer temporal series, logistical aspects including costs of functioning are

important to consider. Costs will vary with travel distance between research base and the sentinel region location. Materials, communication, and laboratory test results will stay constant regardless of the sentinel region location. Thus, to minimize costs and save time, travel distance between the sentinel region and the nearest research base should be considered during the selection of sentinel region location.

To summarize this case study, the criteria which researchers should use to select sentinel region location at the provincial level include:

1) There is documented risk of disease due to the presence of appropriate vector disease within the sentinel region (use of passive surveillance data).
2) Climate: considering temperature in the form of accumulated degree days.
3) The ecology of the sentinel region is appropriate for the presence of the vector (presence of mixed or deciduous forests).
4) Selection of the sentinel region to maximize the population reached within the units of the study zone.
5) Logistical constraints (e.g., traveling distance) are considered when selecting sentinel regions.

5) Questions within the survey

The questionnaire comprised of a total of 14 questions.

1. Does category 1 (*Past information*) capture the required and relevant knowledge which should be considered initially, in order to build a surveillance system? (If not, please explain why)

2. Do you believe that use of surveillance aims / objectives to orientate which criteria should be selected from category 2 (*Risk of disease*) is relevant? (If not, please explain why)

3. Do you believe that the criteria suggested for category 2 (*Risk of disease*), according to surveillance aims, are relevant? (If not, please explain why)

4. For category 3 (*Environment*) do you think that the most relevant criteria have been included? (If not, please explain why)

5. Do you believe that the criteria suggested for category 3 (*Environment*), according to surveillance aims, are relevant? (If not, please explain why)

6. Do you believe that in building a public health surveillance system, population numbers / density should be considered? (If not, please explain)

7. For category 4 (*Population*), population particularities e.g., demographics, human activity, etc., are mentioned. The statement is broad in order to remain flexible and relevant for a variety of VBDs. Do you think this is appropriate and adequately formulated? (If not, please explain)

8. For category 5 (*Distribution of sites*), do you think there would be another reason, apart from filtering the number of sentinel locations or to ensure equity, do use this selection category? (If so, please explain why)

9. Category 6 (*Logistics*) has been included at the end of the decision tool in order to ensure that the surveillance system is sustainable. Do you agree with this step? (If not, please explain)

10. Do you think all relevant criteria, and relevant selection categories, are included within the decision tool? If not, which one(s) is(are) missing?

11. Is the decision tool clear and self-explanatory? Please write in the text box any suggestions to make the tool clearer or easier to use.

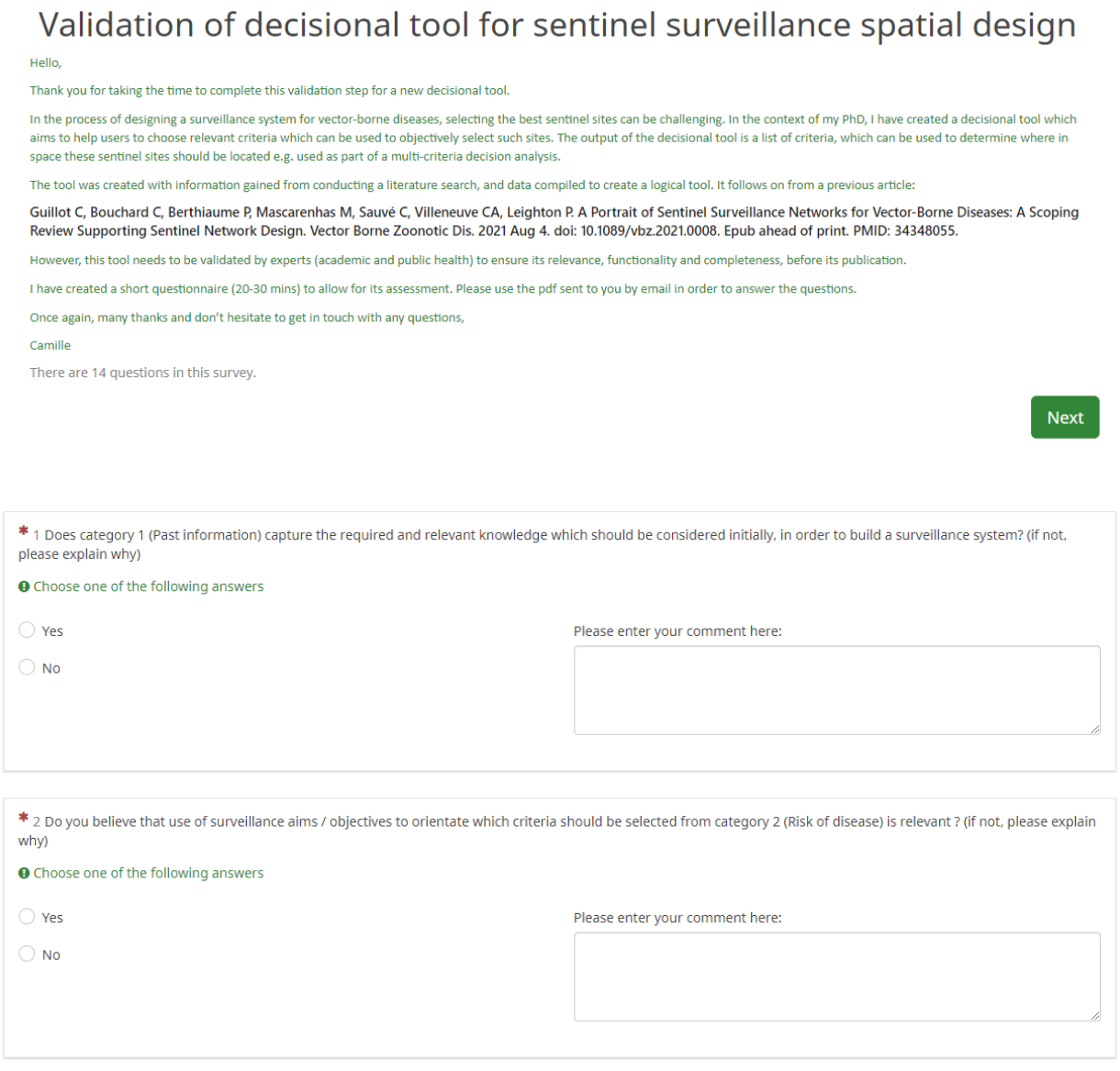
12. Is the flow of the decision tool logical? Please comment in the text box any suggestions on how to optimize the sequence of the tool.

13. Do you believe that the tool is flexible and adaptable to different vector-borne diseases in different geographical locations? (If not, please explain)

14. Please write any other comments or suggestions.

6) Copy of the survey

The online survey was carried out on LimeSurvey[16], as the principal investigator had access to a premier premium version through her Université de Sherbrooke affiliation. This version of LimeSurvey did not limit the number of respondents nor the number of questions which could be included. All questions were compulsory.



Validation of decisional tool for sentinel surveillance spatial design

Hello,

Thank you for taking the time to complete this validation step for a new decisional tool.

In the process of designing a surveillance system for vector-borne diseases, selecting the best sentinel sites can be challenging. In the context of my PhD, I have created a decisional tool which aims to help users to choose relevant criteria which can be used to objectively select such sites. The output of the decisional tool is a list of criteria, which can be used to determine where in space these sentinel sites should be located e.g. used as part of a multi-criteria decision analysis.

The tool was created with information gained from conducting a literature search, and data compiled to create a logical tool. It follows on from a previous article:

Guillot C, Bouchard C, Berthiaume P, Mascarenhas M, Sauvé C, Villeneuve CA, Leighton P. A Portrait of Sentinel Surveillance Networks for Vector-Borne Diseases: A Scoping Review Supporting Sentinel Network Design. Vector Borne Zoonotic Dis. 2021 Aug 4. doi: 10.1089/vbz.2021.0008. Epub ahead of print. PMID: 34348055.

However, this tool needs to be validated by experts (academic and public health) to ensure its relevance, functionality and completeness, before its publication.

I have created a short questionnaire (20-30 mins) to allow for its assessment. Please use the pdf sent to you by email in order to answer the questions.

Once again, many thanks and don't hesitate to get in touch with any questions,

Camille

There are 14 questions in this survey.

Next

* 1 Does category 1 (Past information) capture the required and relevant knowledge which should be considered initially, in order to build a surveillance system? (if not, please explain why)

Choose one of the following answers

Yes

No

Please enter your comment here:

* 2 Do you believe that use of surveillance aims / objectives to orientate which criteria should be selected from category 2 (Risk of disease) is relevant ? (if not, please explain why)

Choose one of the following answers

Yes

No

Please enter your comment here:

[16] https://www.med.usherbrooke.ca/limesurvey257/index2.php?r=admin

* 3 Do you believe that the criteria suggested for category 2 (Risk of disease), according to surveillance aims, are relevant ? (if not, please explain why)

Choose one of the following answers

- Yes
- No

Please enter your comment here:

* 4 For category 3 (Environment) do you think that the most relevant criteria have been included ? (if not, please explain why)

Choose one of the following answers

- Yes
- No

Please enter your comment here:

* 5 Do you believe that the criteria suggested for category 3 (Environment), according to surveillance aims, are relevant ? (if not, please explain why)

Choose one of the following answers

- Yes
- No

Please enter your comment here:

* 6 Do you believe that in building a public health surveillance system, population numbers / density should be considered ? (if not, please explain)

Choose one of the following answers

- Yes
- No

Please enter your comment here:

* 7 For category 4 (Population), population particularities e.g. demographics, human activity, etc., are mentioned. The statement is broad in order to remain flexible and relevant for a variety of VBDs. Do you think this is appropriate and adequately formulated ? (if not, please explain)

Choose one of the following answers

- Yes
- No

Please enter your comment here:

* 8 For category 5 (Distribution of sites), do you think there would be another reason, apart from filtering the number of sentinel locations or to ensure equity, do use this selection category ? (if so, please explain why)

Choose one of the following answers

- Yes
- No

Please enter your comment here:

* 9 Category 6 (Logistics) has been included at the end of the decisional tool in order to ensure that the surveillance system is sustainable. Do you agree with this step? (if not, please explain)

Choose one of the following answers

- Yes
- No

Please enter your comment here:

* 10 Do you think all relevant criteria, and relevant selection categories, are included within the decisional tool? If not, which one(s) is(are) missing?

Choose one of the following answers

- Yes
- No

Please enter your comment here:

Previous

Next

Overall assessment

* 11 Is the decisional tool clear and self-explanatory ? Please write in the text box any suggestions to make the tool clearer or easier to use.

Choose one of the following answers

- Yes
- No

Please enter your comment here:

* 12 Is the flow of the decisional tool logical ? Please comment in the text box any suggestions on how to optimise the sequence of the tool.

Choose one of the following answers

- Yes
- No

Please enter your comment here:

* 13 Do you believe that the tool is flexible and adaptable to different vector-borne diseases in different geographical locations ? (if not, please explain)

Choose one of the following answers

- Yes
- No

Please enter your comment here:

14 Please write any other comments or suggestions.

Previous

Submit

7) Survey responses

A total of 6 experts (43% response rate) responded to the questionnaire (**Table 34**). Three experts (27%) contacted the principal investigator to explain that time constraints did not permit their participation.

Table 34. Survey responses of experts for validation of preliminary decision tool

Reviewer ID	Yes / No	Comments
1.	Does category 1 (*Past information*) capture the required and relevant knowledge which should be considered initially, in order to build a surveillance system? (If not, please explain why)	
2	No	I'm not sure why this point is put first. For me, initial information would include: is the vector present here? In neighboring regions? Is there a risk of introduction? Are there cases? What is the impact? To see if it is useful or not to initiate surveillance and choose this type of surveillance. Additional, if a system already exists, it is not necessarily useful to do another one in.
3	Yes	
4	Yes	
5	Yes	
7	No	Even if selection of sites already known may seem like a good idea and could save time, their selection should not be systematic. Their selection should be dependent upon comparison with other possible options and 'pass the test' of this decisional tool, notably to validate that the selection criteria are in sync with the objectives. Instead of writing 'selection of locations in I1 and I2, I would write, 'consideration of locations'.
11	Yes	
2.	Do you believe that use of surveillance aims / objectives to orientate which criteria should be selected from category 2 (*Risk of disease*) is relevant? (If not, please explain why)	
2	Yes	No comment
3	Yes	No comment
4	Yes	No comment
5	Yes	No comment
7	Yes	No comment
11	Yes	No comment
3.	Do you believe that the criteria suggested for category 2 (*Risk of disease*), according to surveillance aims, are relevant? (If not, please explain why)	
2	Yes	Yes, however, should be more precise e.g., cases in domestic animals, wild animals or livestock, the risk of introduction of the vector / pathogen, specify the location of the risk, the abundance of the vector, host (animal or human)
3	Yes	
4	Yes	Relevant criteria included, seems thorough, I cannot identify other ones
5	Yes	

7	No	I'm not sure to understand R2 relative to the Early Warning System objective. For this same objective, we could also decide to detect the first appearance of a vector on the territory. In this case, R3 no longer applies. This depends on how early we want to be. The other criteria appear relevant with respect to the objectives
11	Yes	

4.	For category 3 (*Environment*) do you think that the most relevant criteria have been included? (If not, please explain why)	
2	No	Other criteria can be including seasonality, preferential hosts, climatic and meteorological conditions for presence, activity and reproduction, conditions for the vector but also for the pathogen
3	Yes	
4	Yes	
5	Yes	
7	Yes	The description for criterion E3 is missing
11	No	Legend is missing E3 description.

5.	Do you believe that the criteria suggested for category 3 (*Environment*), according to surveillance aims, are relevant? (If not, please explain why)	
2	Yes	The description for criterion E3 is missing
3	Yes	
4	Yes	
5	Yes	
7	Yes	I do not think it is clear if criteria E1, E2 and E3 apply to 'follow diseases trend and 'risk factor profiling'
11	No	E1 is a bit vague and should explain what geographical information is needed (for example topography, bioclimatic region, etc.).

6.	Do you believe that in building a public health surveillance system, population numbers / density should be considered? (If not, please explain)	
2	Yes	It would depend on the surveillance objective: to detect the vector/pathogen/risk area or estimate the risk of transmission to humans. It also depends on the point of view e.g., a citizen who lives or walks somewhere versus public health who wants to know where there will be more cases
3	Yes	
4	Yes	
5	Yes	
7	Yes	The influx of people in a region for work or tourism should also be considered. A region could have a low population but be very touristic and represent a risk for the population
11	Yes	

7. For category 4 (*Population*), population particularities e.g., demographics, human activity, etc., are mentioned. The statement is broad in order to remain flexible and relevant for a variety of VBDs. Do you think this is appropriate and adequately formulated? (If not, please explain)		
2	Yes	
		Appropriate: Yes
3	No	Formulation: I suggest 'under surveillance' instead of 'under investigation' for the tool to be more coherent
4	Yes	
5	Yes	
7	Yes	
		P5 should be rephrased to be specifically about human activity susceptible to influence exposure, because many types of activities would not be relevant here, such as those indoors or without a strong component performed within natural settings. Also, I would use the widely recognized example of camping instead of wild mushroom
11	No	picking.
8. For category 5 (*Distribution of sites*), do you think there would be another reason, apart from filtering the number of sentinel locations or to ensure equity, do use this selection category? (If so, please explain why)		
2	Yes	On the whole study zone (if vector is already present) or a probable zone of emergence (borders / airport)
3	No	
4	No	
5	No	
7	Yes	Preference of local public health authorities (however this is included within the logistic criterion)
11	No	
9. Category 6 (*Logistics*) has been included at the end of the decision tool in order to ensure that the surveillance system is sustainable. Do you agree with this step? (If not, please explain)		
		Cost, long-term management of the surveillance system, standardization of the protocol (data collection, laboratory analyses, data analyses, information key actors)
2	Yes	
3	Yes	
4	Yes	
5	Yes	
		Evaluation of the impact level of each of these logistical aspects on the sustainability and functionality of the system. Ideally, do not make too many comprises relating to these criteria, to prevent deviating from the initial objective, unless this has an important impact on the quality of the system and the data. Overcome these logistical
7	Yes	difficulties by finding alternative or finding measures to decrease these impacts, if possible.

11	Yes	

10. Do you think all relevant criteria, and relevant selection categories, are included within the decision tool? If not, which one(s) is(are) missing?

		Type of data collected (vector collection? Serology? Human cases?)
2	No	Is there really a need for sentinel sites within the surveillance system? yes/no
3	Yes	
4	Yes	
5	Yes	
7	No	Incidence rate or abundance of ticks high enough to be able to meet the objectives (except early warning system). For example, if the number of ticks collected or the number of human cases is low, this could prevent trends from being identified due to small numbers and statistical uncertainties.
11	Yes	

11. Is the decisional tool clear and self-explanatory? Please write in the text box any suggestions to make the tool clearer or easier to use.

2	No	Objective of the decision tool should be well explained. Difficult to understand and follow without a text that accompanies the different steps and explains the logic. Not clear what we get at the end of the algorithm.
3	Yes	
4	Yes	
5	No	
7	No	Complex to understand, especially for someone who has never done surveillance site selection. The case study helps to understand: good idea. A presentation of the tool or an explanatory document could also have helped. At the end of the process, a question remains: which criterion(s) should be prioritized if we cannot find a sentinel unit corresponding to all these criteria? What do you suggest? Does the order of the criteria reflect the weight of the criteria? Could be translated in French (reviewer was francophone)
11	No	I just have some general formatting suggestions. It would be great if you could move the legend on the same page as the schematic, as it would make it a lot easier to go around it. Also, legend items do not have to be in alphabetical order and listing them in the order they are mentioned makes more sense. Also, avoid skipping numerical labels for easier reading. For example, we have R1 to R3 but skip to R10 after, so in this case I would switch the label R10 to R4, if this makes sense.

12. Is the flow of the decision tool logical? Please comment in the text box any suggestions on how to optimize the sequence of the tool.

2	Yes	
3	Yes	

4	Yes	
5		
7	No	Work on the graph, especially the dashed arrows which make the trajectory confusing… maybe put in different colors instead?
11	Yes	

13. Do you believe that the tool is flexible and adaptable to different vector-borne diseases in different geographical locations? (If not, please explain)

2	Yes	Probably because the categories are very broad, but not sure that it fits all vector-borne diseases, the algorithm seems more oriented towards Lyme
3	Yes	
4	Yes	
5		
7	Yes	
11	Yes	

14. Please write any other comments or suggestions.

2	NA	
3	NA	Given that all the arrows (yes and no) arrive at the end of the algorithm, I wonder if an algorithm is really relevant in relation to a table that includes all the criteria to be taken into account to choose the sentinel sites
4	NA	
5	NA	
7	NA	
11	NA	Great job getting this done!

8) Responses to comments and improvement of the tool

Comments were analyzed (**Table 35**) and regrouped into large points. These were addressed, and the decision tool was modified in consequence (**Figure 30**).

Table 35. Analysis of responses from experts to the survey and consequences on decision tool

Comment from survey	Addressing the comment	Consequence on decision tool
Putting past information (from previous work) at the start of the decision tool may not be relevant	• 4/6 reviewers believe it to be relevant (potentially 5, as reviewer 7 does not question its place within the algorithm) • From authors' previous experience, we believe that it is necessary to know what is already in place prior to building a new surveillance system • However, important point it that the tool is not linear – this should be emphasized in the text • Previous work (realist-type review) supports the use of these sites	• Nil
Selection of previous surveillance sites should not be systematic	• Old sites should be considered, however, also compared with new ones to ensure that sites are optimized • Thus, this should be illustrated in the tool • Also ensure that they meet surveillance objectives	• Create decision steps – these are not obligatory, however, identify key decision points that should be considered by decision makers (DMs) • DMs must choose to accept or reject the criteria propositions

Criteria relating to risk should be more precise	• Several very relevant and specific criteria are provided e.g., cases in domestic / wild animals / livestock • However, we believe these are too specific for the decision tool in itself; due to space and for usefulness, we are aiming for simplicity. • We believe that the specificity suggested are present within broader criteria which are suggested e.g., risk in animal hosts includes domestic / wild and livestock, and experts should refer to their knowledge of the VBD when using the tool • In terms of location of the risk, this is inherent to the approach suggested by the paper – it does not seem relevant • Hosts (animal or human) are separated into two categories (risk in human versus risk in hosts); however data availability constraints are also a very important limitation to the type of data which can be accessed and subsequently used	• Nil in the decision tool itself; we aim to keep broader and more flexible so it can be applicable to a wide range of contexts • However, this is a very important point which must be highlighted in the results section, how the tool was constructed, using concrete case examples where specific risk criteria are developed
Presence of appropriate ecology for the presence of the vector relative to the Early Warning System (EWS) objective does not seem appropriate	• Very few examples of sentinel surveillance systems used as EWS for VBDs in the literature; due to few surveillance sites, it poses important logistical barriers to use this type of surveillance • On second examination of realist-type review material, authors also agreed that this criterion is less relevant than others	• Risk criteria relative ecology was removed, and more general vector and host animal risk data were retained
Criteria relating to environment should be more precise	• Reviewer has suggested some important and precise criteria which could be considered	• Nil in the decision tool itself; we aim to keep broader and more

	• However, we argue that these are included in larger criteria • We believe these are too specific for the decision tool in itself; due to space and for usefulness, we are aiming for simplicity	flexible so it can be applicable to a wide range of contexts • However, this is a very important point which has to be highlighted in the results section, how the tool was constructed, using concrete case examples where specific risk criteria are developed
Application of criterion E1-E3 to other surveillance objectives	• Structure of the decision tool means it is not clear to what surveillance objectives these criteria should apply	• Change of the structure of the tool to make it easier to follow and know which criteria apply at which point
Description of E3 is missing	• The description is absent from the Legend	• Authors believe that this legend and the criteria ID is confusing, thus these have been removed from the figure; they are written out instead for ease of understanding
Criteria E1 'consideration of the geography' is a bit vague	• We aim for simplicity and flexibility of the tool • But indeed, formulation of the criteria is confusing and is very broad • More specific example should be given	• Change of formulation: geographical features • Kept broad to allow flexibility; this requires users expertise relating to the disease under surveillance; it is an important limit which should be highlighted in the discussion Functionality will be highlighted within the results section (specific examples plus case example)
Consideration of population density depends on the surveillance objective	• Finding cases versus vectors is given as a case • However, otherwise the rest of the reviewers agree that this is a relevant consideration	• Nil

	• Less likely to identify presence of vectors in a region where there is no human population – as there is no chance of exposure to the VBD and thus no risk • Furthermore, the algorithm is for the use of public health authorities, using population-based versus individual-based approach	
Population flux relating to tourism and occupation can have an important impact on population density	• This can be very important for highly touristic areas, or for diseases where there is an occupational risk e.g., parks where park rangers are present	• Footnote added to the maximizing population criteria to account for population influx resulting from tourism / occupation
Formulation 'Are there human population particularities which affect the transmission cycle of the vector-borne disease under investigation?' is hard to understand	• Formation was deemed confusing • Be rephrased to be specifically about human activity susceptible to influence exposure	• Formulation changed and footnote added to specify activities susceptible to influence exposure
Distribution of sites	• Reviewers overall thought it was relevant • Some comments about criteria which are included elsewhere (e.g., relative to the distribution of the risk of disease, or relating to public health authority preference) • This decision criteria group was examined retrospectively, as it may not necessarily to be used for equity of resource allocations • Using the literature, it is usually used to obtain a better geographical representation	• Changed according to iterative inspection of realist-type review, as not many comments from reviewers
Evaluation of the impact level of each of these logistical aspects on the sustainability and functionality of the system	• Very important point, logistic criteria must not be used independently of other criteria • This will be limited using an MCDA approach subsequent to finalizing selection criteria	• Nil, however, this point must be considered when criteria will be used e.g., using an MCDA approach

Other relevant criteria could include: Is there a need for sentinel sites within the surveillance system?	• This decision should normally have been addressed prior to using the tool	• Nil
Other relevant criteria could include: standardization of the protocol	• Important point during planning of the surveillance system • Should not be impacted by sentinel unit location (unless protocol cannot be carried out, and this aspect must be considered by the decision makers, but is incorporated within the logistic criteria)	• Nil: however, standardization of the protocol will be discussed in the discussion
Other relevant criteria could include: minimum threshold for risk determined by incidence rate or abundance of ticks	• Very interesting idea and relevant to the surveillance context	• Although difficult to incorporate this idea with the decision tool, could include minimum threshold for each of the criteria during MCDA approach or general use of retained criteria; this should be discussed
May not be useful in all VBD contexts	• This is an aspect which was difficult to develop for the decision tool • Realist-type review covered all types of VBDs • Will remain a limitation: must be used and evaluated using different systems	• Review of all material within realist-type review • However, will likely remain a limitation; must be discussed
Overall, format of the decision tool is confusing and suboptimal	• This was pointed out by several reviewers • Case example is very important for illustrating the functionality of the decision tool	• Important effort was made to reduce complexity of the decision tool and make more user-friendly
How to use the criteria retained in the decision tool is not clear	• This was pointed out by several reviewers • This point will be discussed within the current paper, however, will be detailed further in future work	• Nil: this point will be discussed within the current paper, however, will be detailed further in future work

9) Improvement of the decision tool

Subsequently from analyzing the comments from expert reviewers and returning iteratively within the realist-type review material, an improved version of the decision tool was produced (**Figure 30**).

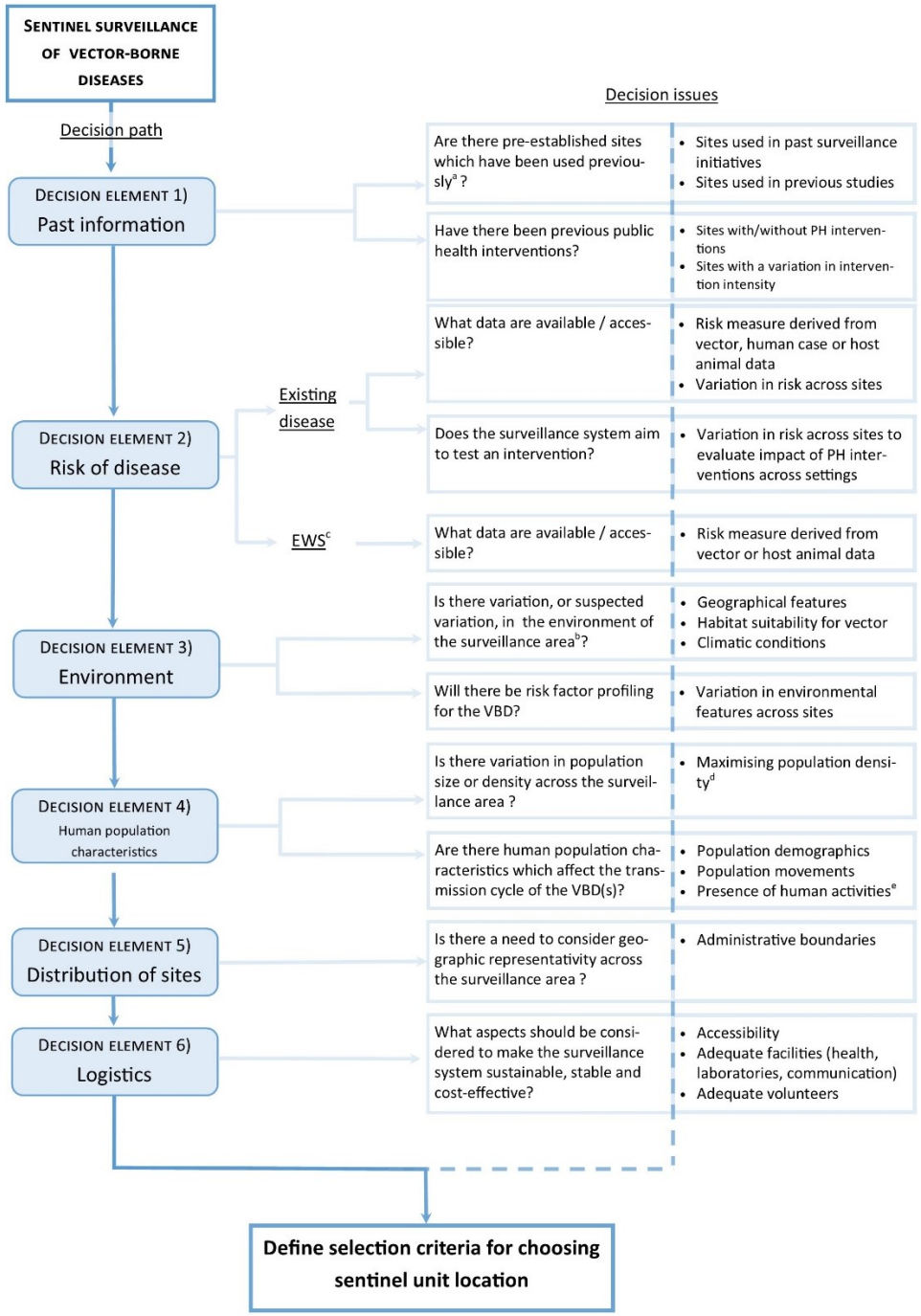


Figure 30. Decision tool for determining key criteria in developing a protocol for the selection of sentinel unit locations for vector-borne diseases

[a] Site should have been used for a similar objective

[b] The variation in the environment is judged significant by the investigators

[c] Early warning system

[d] It is also relevant to consider potential important population influx e.g., from tourism, occupational reasons

[e] Human activities which influence exposure to vectors / vector-borne diseases

Appendix 4

Spatial multi-criteria decision analysis for the selection of sentinel regions in tick-borne disease surveillance

Supplementary material: Threshold values for Lyme disease risk in provinces where passive surveillance was discontinued within some localities

The data using to represent risk of Lyme disease for the multi-criteria decision analyse was passive surveillance submissions (number of ticks submitted per logarithm of the population). For most of the provinces, a tick index was derived using these data (172) by summing the number of tick submissions over a period of ten years, from 2005 to 2015, divided by the logarithm of the population.

However, this measure was deemed inappropriate for provinces where passive surveillance was discontinued in regions of high submissions. These included Ontario, Quebec and Nova Scotia. For these provinces, a second establishment period index was developed. Koffi et al. (2012) identified a threshold of passive tick submissions associated with the presence of questing ticks in the environment during active surveillance within a given CSD. Leighton et al. (2012) then applied this threshold to identify CSDs with a high likelihood of containing an established tick population as those which exceeded the threshold for two consecutive years, since persistent observations of high tick submissions provided stronger biological evidence of a locally reproducing tick population.

We applied the approach of Leighton et al. (2012), analyzing the full passive surveillance data set to identify years from 2000-2015 in which tick submissions from each CSD exceeded a threshold of 1 tick submission per logarithm of the population and cumulating "years of establishment" following the second consecutive year in which the threshold was exceeded (203). This empirical cut-off was determined by evaluating the risk distribution across CSDs by province and selecting a threshold which was discriminatory, and which allowed within

province comparisons (**Figure 31**). The final index was thus a duration-of-establishment period, in years, which was used as a measure of risk for these provinces.

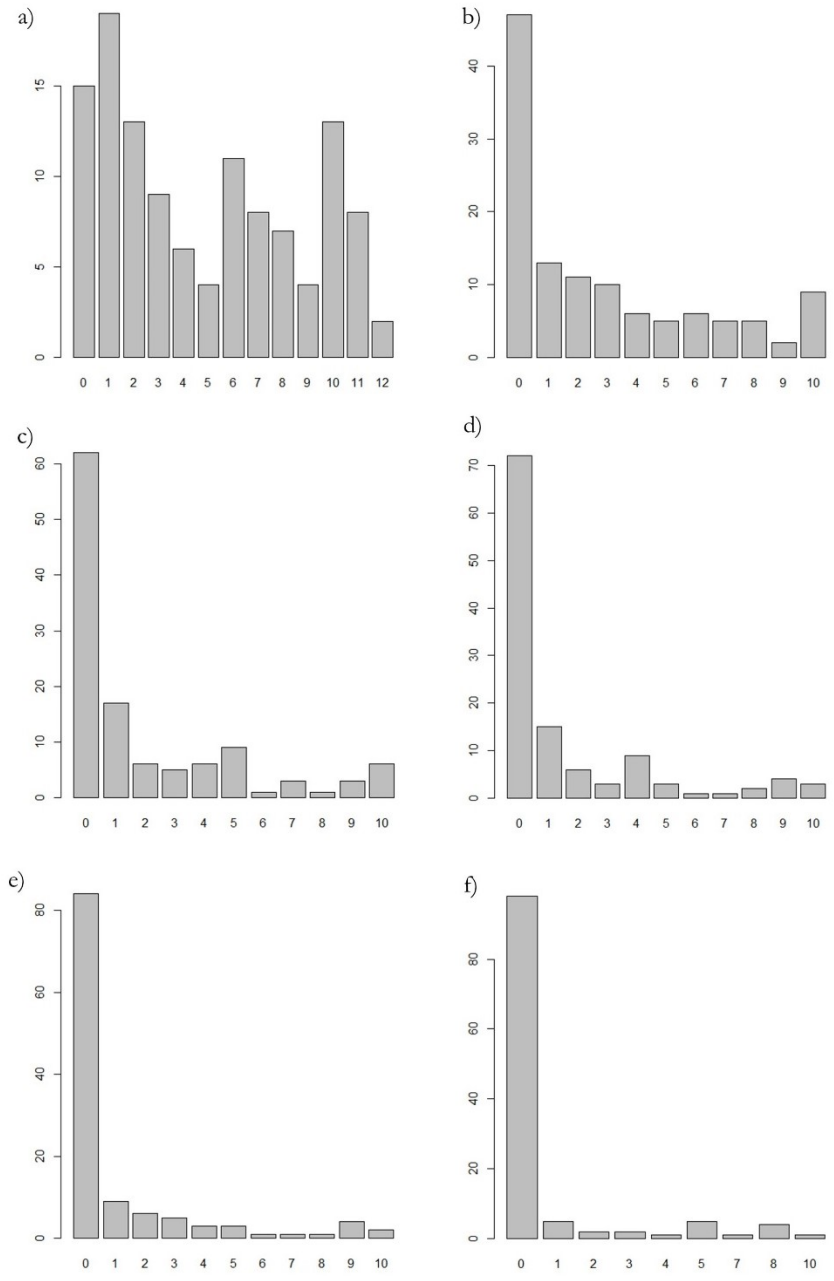


Figure 31. Distribution of Lyme disease risk, in the form of duration-of-establishment period of *Ixodes scapularis*, according to different thresholds a) 0.1 tick submission per logarithm of the population b) 0.5 tick submission per logarithm of the population c) 1 tick submission per logarithm of the

population d) 1.5 tick submission per logarithm of the population e) 2.5 tick submissions per logarithm of the population f) 5 tick submissions per logarithm of the population

Appendix 5

Sentinel surveillance of Lyme disease risk in Canada, 2019: Results from the first year of the Canadian Lyme Sentinel Network (CaLSeN)

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KEYWORDS: Lyme disease, Sentinel surveillance, *Ixodes* tick, *Borrelia*, Canadian Lyme Disease Research Network (CLyDRN)

Abstract

Background: Lyme disease is an emerging vector-borne zoonotic disease of increasing public health importance in Canada. As part of its mandate, the Canadian Lyme Disease Research Network (CLyDRN) launched a pan-Canadian sentinel surveillance initiative, the Canadian Lyme Sentinel Network (CaLSeN), in 2019.

Objectives: To create a standardized, national sentinel surveillance network providing a real-time portrait of the evolving environmental risk of Lyme disease in each province.

Methods: A multi-criteria decision analysis approach was used in the selection of sentinel regions. Within each sentinel region, a systematic drag sampling protocol was performed in selected sampling sites. Ticks collected during these active surveillance visits were identified to species, and *Ixodes* spp. ticks were tested for infection with *Borrelia burgdorferi*, *Borrelia miyamotoi*, *Anaplasma phagocytophilum*, *Babesia microti* and Powassan virus.

Results: In 2019, a total of 567 *Ixodes* spp. ticks (I. scapularis [n=550]; *I. pacificus* [n=10]; and *I. angustus* [n=7]) were collected in seven provinces: British Columbia, Manitoba, Ontario, Québec, New Brunswick, Nova Scotia, and Prince Edward Island. The highest mean tick densities (nymphs/100 m^2) were found in sentinel regions of Lunenburg (0.45), Montréal (0.43) and Granby (0.38). Overall, the Borrelia burgdorferi prevalence in ticks was 25.2% (0%–45.0%). One *I. angustus* nymph from British Columbia was positive for Babesia microti, a first for the province. The deer tick lineage of Powassan virus was detected in one adult *I. scapularis* in Nova Scotia.

Conclusion: CaLSeN provides the first coordinated national active surveillance initiative for tick-borne disease in Canada. Through multidisciplinary collaborations between experts in each province, the pilot year was successful in establishing a baseline for Lyme disease risk across the country, allowing future trends to be detected and studied.

Introduction

In Canada, Lyme disease (LD) is an emerging vector-borne zoonotic disease of increasing public health importance (1). LD is caused by the bacterium *Borrelia burgdorferi* and is primarily transmitted to humans by the blacklegged tick (*Ixodes scapularis*) in central and eastern Canada and the western blacklegged tick (*Ixodes pacificus*) in British Columbia. Since LD became a nationally notifiable disease in 2009, the annual number of confirmed cases has risen from 144 to over 2000 in 2017 (2, 3).

In response to the increasing risk of LD to the Canadian population and ongoing knowledge gaps, the Canadian Institutes of Health Research (CIHR) funded the creation of a national research network on Lyme disease (4). Launched in 2018, the Canadian Lyme Disease Research Network (CLyDRN) is a multidisciplinary initiative bringing together patients,

physicians, social scientists, veterinarians, and both academic and government researchers, with a patient-centered approach focused on improving the diagnosis, surveillance, prevention, and treatment of LD in Canada. A key objective of the network is to better understand the risk of LD across the country, and how this risk is evolving. Thus, one of the first actions of the network was to establish a pan-Canadian surveillance structure to collect comparable data about environmental risk across the country.

An important consideration in the planning of LD surveillance is that LD risk is not uniformly distributed across the country (5), largely due to important regional differences in tick species and environments (6-9) and the uneven pattern of ongoing range expansion of *I. scapularis* populations in Canada (10). Furthermore, regional differences in socio-economical status of Canadians are likely to influence how environmental risk affects regional incidence of LD cases (11).

While considerable effort has already been invested in the measurement of LD risk for Canadians, surveillance remains heterogenous throughout the country. Passive surveillance, the submission of ticks collected on humans or animals, provides valuable information on risk (12, 13) but cannot be maintained uniformly throughout the country due to resource limitations. Active surveillance, the collection of ticks from the environment by drag sampling or rodent capture, is also resource-intensive and is carried out independently in each province according to region-specific objectives, sampling protocols and funding availability.

Here we report the first results from the Canadian Lyme Sentinel Network (CaLSeN), a new pan-Canadian LD surveillance network launched by CLyDRN in 2019. In this pilot year, we carried out standardized active surveillance of ticks in the environment across Canada using a sentinel surveillance approach. Sentinel surveillance has the advantage of concentrating surveillance effort in selected sentinel regions, providing a comparable measure of environmental risk for Lyme disease and other tick-borne diseases across the country and in-depth risk information that is complementary to ongoing federal and provincial surveillance activities.

Objectives

With surveillance carried out annually in sentinel regions located in each Canadian province, CaLSeN aims to:

1. Provide the first standardized, national, real-time portrait of evolving environmental Lyme disease risk in Canada.
2. Support research on regional variation in risk and its determinants.

Methods

Sentinel region selection

Sentinel regions were selected by CLyDRN's Surveillance Working Group, a group of tick-borne disease surveillance experts from both academic and public health settings. Sentinel regions were defined geographically as the area within a 25km radius around the geographic centre of a selected focal municipality. A multi-criteria decision analysis (MCDA) approach was used to prioritize 1-4 initial sentinel regions in each province, with the objective of including additional regions over time (14). Selection criteria included evidence of LD emergence based on existing passive surveillance data (number of *Ixodes* tick submissions / 100 000 people) (10), human population covered by the network, and logistical criteria associated with field sampling and suitability of the environment for *Ixodes* ticks, such as presence of deciduous or mixed forests. Sentinel regions were not established in the Yukon, the Northwest Territories, Nunavut and Labrador due to the current absence of suitable environmental conditions for *Ixodes* spp. tick establishment at these latitudes (15).

Tick collection

Ticks were collected in each sentinel region using a standardized drag sampling protocol (16, 17). This involved dragging a 1m x 1m piece of white flannel cloth over 2000 m^2 of ground vegetation in linear transects, stopping every 25m to collect questing ticks that had clung to the passing cloth. Multiple sampling sites were selected in each sentinel region, targeting locations with suitable tick habitat, with surveillance effort increased in known LD endemic areas in order to obtain fine-scale information on the distribution of risk within these areas (**Table 36**). Each site was sampled once during the summer (May-August of 2019), targeting the regional peak in activity of nymphal *Ixodes* spp. ticks, the stage of greatest public health significance (18-20). In addition to collecting ticks, we collected data on leaf litter depth, canopy cover and soil humidity at each sampling location and noted ambient temperature and

weather conditions during collection to account for the possible effects of these variables on tick collection.

Laboratory analyses

All ticks collected by drag sampling were identified to species, but only *I. scapularis* (n=550), *I. pacificus* (n=10) and *I. angustus* (n=7) were tested for the presence of pathogens as they are known vectors for *Borrelia burgdorferi* and other pathogens. Individual ticks were tested for the presence of *Anaplasma phagocytophilum*, *Babesia microti*, *Borrelia burgdorferi*, *Borrelia miyamotoi* and Powassan virus (POWV) by real-time polymerase chain reaction (PCR) or reverse transcriptase-PCR with slight modifications to methods previously described (21). Briefly, nucleic acids were extracted from ticks using QIAGEN RNeasy 96 kits (QIAGEN Inc., Mississauga, ON, Canada). Extracts contained both RNA and DNA and were screened for all the pathogens described above. Modifications to testing algorithms included the use of an in-house triplex screening assay targeting the 18S rRNA gene of *Babesia* species, followed by the *Ba. microti*-specific CCT eta real-time assay for confirmation, as well as a duplex assay (22) to confirm the presence of *B. burgdorferi* and / or *B. miyamotoi*.

Statistical analyses

Results are presented as descriptive statistics. A paired Wilcoxon test was used to compare mean *Borrelia* prevalence in adult and nymphal ticks. Analyses were conducted using R version 3.6.2 (23).

Results

Sentinel regions and sampling sites

In total, 96 sites in 14 sentinel regions (**Figure 32**) were sampled from 22 May 2019 to 20 August 2019, with 3-15 sampling sites per region (**Table 36**).

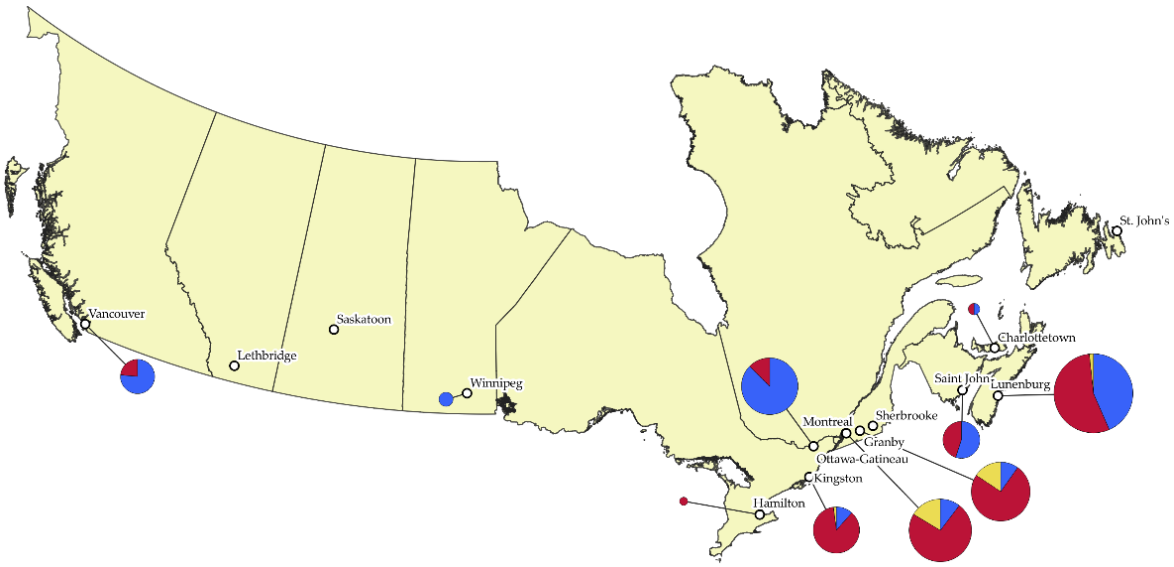


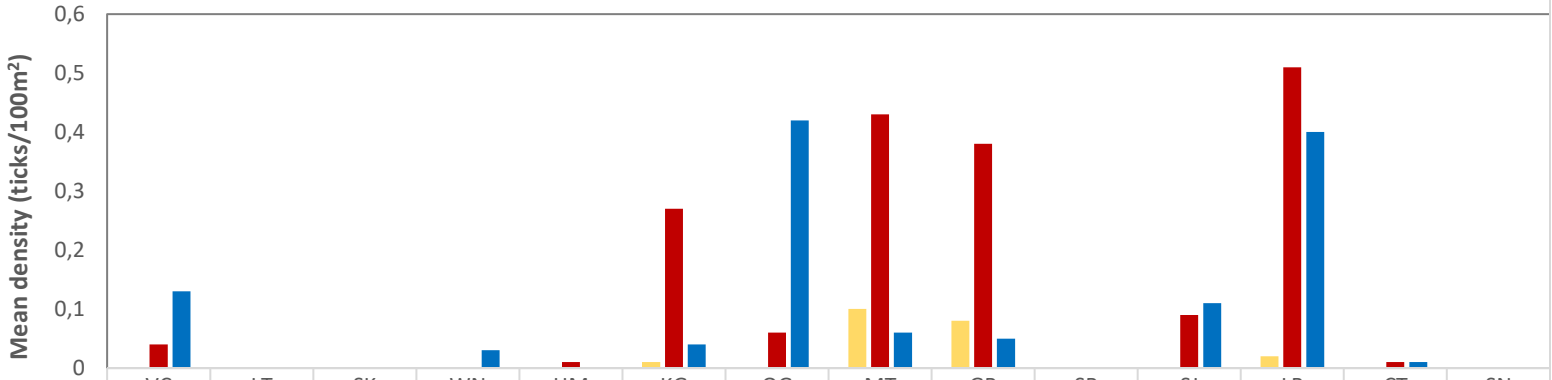
Figure 32. Location of sentinel regions in the Canadian Lyme Sentinel Network in 2019 with pie charts representing stages of *Ixodes* spp. specimens collected. Pie charts size is scaled to mean tick density (ticks / 100 m2) across all surveillance sites within the sentinel region[a, b]

[a] Pie charts area is scaled linearly with mean density of *Ixodes* spp. ticks collected in the sentinel region.
[b] Yellow (larva); red (nymphs); blue (adults)

Ixodes spp. ticks

A total of 567 *Ixodes* spp. ticks were collected in 10 sentinel regions located in 7 provinces: British Columbia, Manitoba, Ontario, Québec, New Brunswick, Nova Scotia, and Prince Edward Island. *I. pacificus* (n=10) and *I. angustus* (n=7) ticks were collected exclusively in Vancouver, BC. *I. scapularis* ticks (n=550) where collected in Manitoba, Ontario, Québec, New Brunswick, Nova Scotia, and Prince Edward Island.

Nymphs were collected in each of these provinces, except for Manitoba (Winnipeg) where only adults were collected (**Figure 33**). Mean density of nymphs (nymphs/100m^2), which pose the greatest risk of infection to humans, was highest in the sentinel regions of Lunenburg (0.45 ± 0.74 SD), Montreal (0.43 ± 0.91 SD), Granby (0.38 ± 0.48 SD), and Kingston (0.27 ± 0.38 SD) (**Table 36**). The Ottawa-Gatineau region was sampled early in the season, yielding a lower density of nymphs (0.06 ± 0.12 SD), but a high density of adults (0.42 ± 0.72 SD) which also pose a significant health risk.



	VC	LT	SK	WN	HM	KG	OG	MT	GB	SB	SJ	LB	CT	SN
Larva	0	0	0	0	0	0,01	0	0,1	0,08	0	0	0,02	0	0
Nymph	0,04	0	0	0	0,01	0,27	0,06	0,43	0,38	0	0,09	0,51	0,01	0
Adult	0,13	0	0	0,03	0	0,04	0,42	0,06	0,05	0	0,11	0,4	0,01	0

Figure 33. *Ixodes* spp. tick densities by stage (larva, nymph and adult) for each sentinel region in the Canadian Lyme Sentinel Network in 2019. Abbreviations: VC, Vancouver, British Columbia; LT, Lethbridge, Alberta; SK, Saskatoon, Saskatchewan; WN, Winnipeg, Manitoba; HM, Hamilton, Ontario; KG, Kingston, Ontario; OG, Ottawa-Gatineau, Ontario/Quebec; MT, Montreal, Quebec; GB, Granby, Quebec; SB, Sherbrooke, Quebec; SJ, Saint John, New Brunswick; LB, Lunenburg, Nova Scotia; CT, Charlottetown, Prince Edward Island; SN, St John's, Newfoundland and Labrador

Table 36. Density of *Ixodes* spp. nymphs collected across all sampling sites within each sentinel regions of the Canadian Lyme Sentinel Network, 2019

Sentinel region	No. of sites visited	Minimum density (nymphs/100m2)	Maximum density (nymphs /100m2)	Mean density (nymphs /100m2)	Standard deviation
Vancouver, BC	5	0	0.10	0.04	0.04
Lethbridge, AB	3	0	0	0	0
Saskatoon, SK	3	0	0	0	0
Winnipeg, MB	5	0	0	0	0
Hamilton, ON	5	0	0.1	0.02	0.04
Kingston, ON	15	0.05	1.15	0.27	0.38
Ottawa/Gatineau, ON/QC	10	0	0.4	0.06[a]	0.12
Montreal, QC	10	0	2.90	0.43	0.91

Granby, QC	5	0	1.15	0.38	0.48
Sherbrooke, QC	5	0	0	0	0
Saint John, NB	5	0	0.30	0.09	0.13
Charlottetown, PEI	5	0	0.05	0.01	0.02
Lunenburg, NS	10	0	2.45	0.45	0.74
St John's, NL	5	0	0	0	0

[a] Site visits in the Ottawa/Gatineau region were conducted in early June, prior to the peak in nymphal tick abundance, thus reported densities may not be representative of densities later in the summer

Laboratory analyses

B. burgdorferi infection prevalence in all *Ixodes* ticks (nymphs and adults) ranged from 0-45% (**Table 37**). Mean infection prevalence was higher in adult ticks (36.3%) than nymphal ticks (22.0%) but this difference was not statistically significant (paired Wilcoxon test; p=0.142; V=3). *B. miyamotoi* was found in 2 specimens, one from Ottawa/Gatineau and another from Montreal. *A. phagocytophilum* infection prevalence varied from 0-4.1% in sentinel regions where *I. scapularis* ticks were found. *Babesia microti* was found in one *I. angustus* tick in the Vancouver sentinel region. One adult *I. scapularis* was positive for Powassan virus in the Lunenburg sentinel region.

Table 37. *Ixodes* spp. tick abundance in sentinel regions of the Canadian Lyme Sentinel Network in 2019 and infection prevalence of tick-borne pathogens

Sentinel region	Ixodes spp. abundance				Infection prevalence (%)[a,b]						
	Larva	Nymph	Adult	Total	BbN	BbA	BbT	Bm	Ap	Bmi	PV
Vancouver, BC	0	4	13	17	0[c]	0	0	0	0	5.9[e]	0
Lethbridge, AB	0	0	0	0	NA	NA	NA	NA	NA	NA	NA
Saskatoon, SK	0	0	0	0	NA	NA	NA	NA	NA	NA	NA
Winnipeg, MB	0	0	3	3	NA	0	0	0	0	0	0
Hamilton, ON	0	2	0	2	0	0	0	0	0	0	0
Kingston, ON	2	82	11	95	28.0[f]	54.5	31.2	0	1.1[d]	0	0
Ottawa, ON	0	12	83	95	33.3	39.8	38.9	1.1	0	0	0
Montreal, QC	19	85	12	116	14.1	66.7	20.6	1.0	1.0	0	0
Granby, QC	3	37	5	45	13.5	60	19.0	0	2.4	0	0
Sherbrooke, QC	0	0	0	0	NA	NA	NA	NA	NA	NA	NA
Saint John, NB	0	9	11	20	55.6	36.4	45	0	5	0	0
Charlottetown, PEI	0	1	1	2	0	0	0	0	0	0	0
Lunenburg, NS	3	96	73	172	24.0	31.5	26.6	0	4.1	0	0.6

St. John's, NL	0	0	0	0	NA	NA	NA	NA	NA	NA	NA
Total no. of ticks	27	328	212	567	NA	NA	NA	NA	NA	NA	NA
Overall prevalence					22.0	36.3	26.6	<0.01	0.02	<0.01	<0.01

Abbreviations: Ap, *Anaplasma phagocytophilum*; BbA *Borrelia burgdorferi* infection prevalence in adult ticks; BbN *Borrelia burgdorferi* infection prevalence in nymphal ticks; BbT *Borrelia burgdorferi* infection prevalence in adult and nymphal ticks; Bm, *Borrelia miyamotoi*; Bmi, *Babesia microti*; PV, Powassan virus; spp., species.

[a] Only adult and nymphal *Ixodes* spp. ticks were tested
[b] Infection prevalence presented as tick numbers in some sentinel regions are too small to infer a prevalence rate
[c] Zero (green) no infected ticks
[d] Infection prevalence <5% (yellow)
[e] Infection prevalence 5-20% (orange)
[f] Infection prevalence >20% (red)

Discussion

In its pilot year, the Canadian Lyme Sentinel Network (CaLSeN) documented the presence of *Ixodes* tick species that are vectors of *B. burgdorferi* and four other human pathogens in 7 out of 10 Canadian provinces, with an overall infection prevalence of 25.2% (0-45.0%) for *Borrelia burgdorferi*. However, we note a great variability among regions: whilst no *Borrelia* were found in British Columbia, Prince Edward Island, and Manitoba, infection prevalence in sentinel regions in Ontario, Québec, New Brunswick and Nova Scotia ranged between 19.0-45.0%. These results are well-aligned with the results of recent studies of the distribution of *I. scapularis* ticks in Canada (22, 24-26), suggesting the sentinel approach adopted by the CaLSeN is successfully capturing regional variation in Lyme disease risk.

Surveillance results highlighted notable regional variation in density of *Ixodes scapularis* within Ontario and Quebec. Mean density of nymphs in Granby and Montreal regions were 0.38 and 0.43 ticks/100m^2, respectively, whereas no blacklegged ticks were found in Sherbrooke. In Ontario, nymph densities were high in Kingston (0.27 nymphs/100m^2) but much lower in southern Ontario, with only 0.02 nymphs/100m^2 in Hamilton. Nymph densities from Ottawa should be interpreted with caution, as sampling was undertaken earlier in the summer, prior to the summer peak in nymph activity.

The 2019 surveillance by the CaLSeN represents the first effort to detect locally reproducing populations of *I. scapularis* ticks through active surveillance in both Prince Edward Island and the island portion of Newfoundland and Labrador. Thus, the presence of *I. scapularis* confirmed by drag sampling in PEI was a novel finding. The detection of two different stages

(nymph and adult) in the environment at two separate sampling sites is early evidence that local reproduction of ticks may be occurring. However, it is possible that the two specimens were adventitious ticks carried to the island by migrating birds and further active surveillance will be important to confirm the presence of tick establishment in the province.

Laboratory analyses of collected ticks yielded two noteworthy pathogen detections. Firstly, *Babesia microti* was detected in an *I. angustus* nymph, providing the first report of a tick infected with this pathogen in British Columbia. Secondly, the deer tick lineage of Powassan virus was detected in the Lunenburg sentinel region, and this is only the second detection of this pathogen in questing ticks in the region (27).

Strengths and limitations

A major strength of our surveillance network is the establishment of collaborations between provinces, and between public health authorities and academics. These links have allowed knowledge translation between involved parties and have been crucial during the planning phases of the network. Partnership was essential during the selection of sentinel regions and in carrying out the field work. To strengthen these collaborations, the CaLSeN will continue to work closely with provincial health authorities to ensure that the activities of the network are complementary to and coordinated with provincial surveillance objectives.

An important limitation to the interpretation of results is the variable timing of the sampling in each region. This may have contributed to differences in the abundance of the tick stages collected, as adults are generally active earlier in the spring with nymphal abundance peaking slightly later in the summer (28). The absolute values of reported tick densities therefore need to be interpreted with caution. The inclusion of variables such as temperature and weather during the sampling event in further statistical analyses carried out on these data will also be important to control for variability in timing of tick sampling. Finally, pursuing yearly sampling within a timeframe more closely aligned with the peak in nymphal activity will provide better data for documenting change in regional risk over time.

Conclusion

The Canadian Lyme Sentinel Network provides the first coordinated national active surveillance initiative for tick-borne disease in Canada. To our knowledge, the sentinel

surveillance approach has not been applied to LD on the national scale elsewhere in North America or Europe, making CaLSeN a useful model for other countries affected by LD and other tick-borne illnesses. Following the establishment of baseline data on LD vectors and prevalence of *Borrelia*, an important next step will be to establish the link between the environmental risk and the regional incidence of human LD cases. Further collection of environmental, social, and human case data across sentinel regions will allow the exploration of the broader representativity of sentinel-based risk measures for tick-borne disease surveillance.

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