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REVIEW ARTICLE

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Echinococcus multilocularis in North America: the great unknown

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Abstract – Over the last decade, studies have begun to shed light on the distribution and genetic characterization of *Echinococcus multilocularis*, the causative agent of alveolar echinococcosis (AE), in North America. Recent findings indicate that the parasite is likely expanding its range in the central region of the United States and Canada and that invasions of European strains might have occurred. In our review, we present the available data on *E. multilocularis* infections in wild and domestic animals and humans in North America and emphasize the lack of knowledge on the distribution of the parasite in wild and domestic hosts. Furthermore, we stress the need to better understand the complexity of host communities and their roles in shaping the transmission and distribution of the parasite. We hypothesize that a lack of knowledge about AE by North American physicians might result in the misdiagnosis of cases and an underestimation of disease incidence. The endemic presence of the parasite in urban areas and a recent human case in Alberta, Canada, suggest that the scientific community may need to reconsider the local public health risks, re-assess past cases that might have been overlooked and increase surveillance efforts to identify new cases of human AE.

Key words: *Echinococcus multilocularis*, North America, Alveolar Echinococcosis, Domestic hosts, Wild hosts.

Résumé – *Echinococcus multilocularis* en Amérique du Nord : le grand inconnu. Au cours des dernières décennies, un certain nombre d'études a commencé à apporter quelques éclaircissements sur la distribution et la caractérisation génétique d'*Echinococcus multilocularis*, l'agent causal de l'échinococcose alvéolaire (EA), en Amérique du Nord. D'après les résultats les plus récents, le parasite est en train d'étendre son territoire au sein des régions centrales des États-Unis et du Canada, et il semble que l'on assiste à une invasion par des souches européennes. Dans cette revue générale, nous présentons les données actuellement disponibles sur l'infection par *E. multilocularis* chez les hôtes sauvages et domestiques en Amérique du Nord, et soulignons notre manque de connaissance concernant la distribution du parasite entre ces hôtes sauvages et domestiques. De plus, nous insistons sur la nécessité de mieux comprendre la complexité des communautés d'hôtes et leur rôle respectif dans la transmission et la distribution du parasite. Nous faisons l'hypothèse que l'absence de connaissance de l'EA par les médecins nord-américains est à l'origine de diagnostics erronés et donc d'une sous-estimation de l'incidence de la maladie. La présence endémique du parasite dans les zones urbaines, et un cas humain récent dans l'Alberta, au Canada, suggèrent que la communauté scientifique aurait peut-être intérêt à reconsidérer les risques locaux pour la santé publique, à reprendre l'évaluation diagnostique de cas qui auraient pu être négligés par le passé, et à renforcer la surveillance pour identifier de nouveaux cas humains d'EA.

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Innovation for the Management of Echinococcosis.

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Introduction

Alveolar Echinococcosis (AE), a zoonosis caused by the tapeworm *Echinococcus multilocularis*, is recognized as an important emerging parasitic disease in the northern hemisphere [21, 88], and recently ranked as the third most relevant food-borne parasitic zoonosis [23]. The disease is estimated to affect more than 18,000 people per year globally, with most cases located in Europe and Asia [84]. China is believed to have the largest number of AE cases, with one study estimating that Chinese cases comprise approximately 91% of the global burden [88]. A recent study on the genetic characterization of *E. multilocularis* mitochondrial DNA [62] identified three strains corresponding to the geographical regions of Asia, Europe, and North America [18]. In North America, two sub-strains have been reported (N1 in the tundra zone and N2 in the central region) [62], supporting previous reports that parasites from Alaska and the north-central states of Montana and North Dakota differed in the development of their larval stages [5, 72].

Locally acquired human AE in North America has always been considered very rare, most cases historically reported being due to extra-continental infections (i.e. patients with travel history outside North America), with the important exception of a historical hotspot of the Asian strain that was discovered in St. Lawrence Island, Alaska, in the 1940s [78, 92]. To date, only three human cases are believed to have been caused by the central region strain of *E. multilocularis*, the first one in 1928 (Manitoba, Canada; [38]), the second in 1977 (Minnesota, USA; [26]), and the most recent in 2013 (Alberta, Canada; personal communication, Kinga T. Kowalewska-Grochowska). Despite an increased awareness of echinococcosis and other neglected tropical diseases, it is still unknown if AE is truly a rare disease in North America or if cases are being misdiagnosed due to a lack of physician knowledge about the disease [9, 92].

This review focuses on the available data on the presence of *E. multilocularis* in wild and domestic hosts and humans in North America, with the specific objectives of (1) identifying knowledge gaps in the parasite's spatial distribution in wild and domestic host species, (2) providing a summary of available data on human infections, (3) illustrating the genetic characterization of *E. multilocularis* in North America, and (4) discussing possible emerging public health risks.

Echinococcus multilocularis in wild hosts

Since the 1950s, several studies have been carried out to establish the primary wildlife hosts of *E. multilocularis* in North America, focusing on the Alaskan peninsula, Minnesota, and North Dakota, USA (e.g. [52, 53, 58, 70]) as well as Alberta, Canada [35]. However, despite the relevance of the parasite worldwide, and the groundbreaking initial work conducted by Rausch and Leiby [24, 26, 42, 50–54, 67, 68, 70–73, 79], the distribution, ecology, and epidemiology of *E. multilocularis* in North America is still largely unknown. In North America, *E. multilocularis* has been reported in the

northern tundra zone (NTZ) of Alaska and Canada, and in the north central region (NCR), including four Canadian Provinces (Alberta, Saskatchewan, Manitoba, and British Columbia) and 13 US states (North Dakota, South Dakota, Iowa, Minnesota, Montana, Wyoming, Nebraska, Illinois, Wisconsin, Indiana, Ohio, and Missouri, and more recently central and southwestern Michigan) [18, 40, 84, 85] (Table 1).

The parasite is typically maintained in a sylvatic life cycle [22], with regional hosts determined by local predator-prey communities. In the NTZ, the parasite's life cycle is sustained by the arctic fox (*Vulpes lagopus*) and its arvicoline rodent prey species such as the northern vole (*Microtus oeconomus*), the brown lemming (*Lemmus sibiricus*), and the northern red-backed vole (*Myodes rutilus*) [22]. Other carnivore species such as wolves (*Canis lupus*) may also harbor *E. multilocularis*, however, their role in parasite transmission has not been fully evaluated [80]. In the NCR, which is mostly characterized by prairie and boreal forests, the red fox (*Vulpes vulpes*) and the coyote (*Canis latrans*) are the primary definitive hosts, which prey on intermediate host species such as the deer mouse (*Peromyscus maniculatus*) and the meadow vole (*Microtus pennsylvanicus*) [35, 53]. The house mouse (*Mus musculus*) [51], the bushy tailed woodrat (*Neotoma cinerea*) [51, 53, 54], and the southern red-backed vole (*Myodes gapperi*) are other intermediate hosts of possible local importance [56].

Despite having a predominantly sylvatic life cycle, domestic animals can contribute to parasite transmission, resulting in the development of semi-synanthropic foci [22]. The most notable example of this, in North America, occurred in Native American communities on St. Lawrence Island, Alaska where domestic dogs were becoming infected by ingesting infected small mammals [77]. Another possible example is the case of two infected cats and an infected house mouse from a farm in North Dakota [54]. Although the authors speculated on the existence of a synanthropic cycle (cat – house mouse) of *E. multilocularis*, the alternative hypothesis that these latter cases were simply a spill-over from a sylvatic life cycle cannot be ruled out as no sampling from sylvatic hosts on the same farm was attempted, and the parasite was found in wild hosts no more than 13 km away from the farm. When a semi-synanthropic cycle is present, zoonotic transmission is probably more likely to occur given the close association of humans and domestic animals. Therefore, pet ownership can ultimately represent a risk factor for AE infection in certain circumstances [82]. Unfortunately, there has been a lack of consistency in the collection of data on *E. multilocularis* in North America. This lack of consistency is partially due to (1) variation in sampling designs, (2) the use of different diagnostic techniques with differing sensitivities and specificities, (3) spatial and temporal differences in data sources, and (4) regional differences in definitive and intermediate host species communities.

Sampling design

Recent data from an urban area in North America indicate that the distribution of *E. multilocularis* is spatially and

Table 1. *Echinococcus multilocularis* infections in wild hosts in North America. Strains and haplotype as described in Nakao et al. [62].

Reference	Location	Definitive host				Intermediate host		
		Species (prevalence; n)	Method	Strain	Haplotype	Species (prevalence; n)	Strain	Haplotype
Chalmers and Barrett 1974 [14]	Lethbridge, AB, Canada					<i>Peromyscus maniculatus</i> (n/a)		
Catalano et al. 2012 [13]	Calgary, AB, Canada	<i>Canis latrans</i> (20.5%; 83)	Intestine	n/a				
Liccioli et al. 2012, 2013 [55, 56]	Calgary, AB, Canada	<i>Canis latrans</i> (29.5%; 61)	Intestine					
		<i>Canis latrans</i> (21.4%; 385)	Feces			<i>Peromyscus maniculatus</i> (0.7%; 305) <i>Microtus pennsylvanicus</i> (0.7%; 267) <i>Mus musculus</i> (0%; 2) <i>Myodes gapperi</i> (1.4%; 71) <i>Sorex</i> sp. (0%; 296) <i>Zapus princeps</i> (0%; 32) <i>Spermophilus tridecemlineatus</i> (0%; 6) <i>Tamias minimus</i> (0%; 4) <i>Thomomys talpoides</i> (0%; 3) <i>Peromyscus maniculatus</i> (27.7%; 216)		
Holmes et al. 1971 [35]	Edmonton, AB, Canada					<i>Myodes gapperi</i> (0%; 122) <i>Microtus pennsylvanicus</i> (0%; 1)		
Catalano et al. 2012 [13]	Edmonton, AB, Canada	<i>Canis latrans</i> (62.5%; 8)	Intestine	n/a				
Gesy et al. 2014 [28]	Edmonton, AB, Canada	<i>Canis latrans</i> (n/a)	Intestine		E, F			
Gesy et al. 2013 [27]	Quesnel, BC, Canada	<i>Canis latrans</i> (37%; 27)	Intestine	E		<i>Peromyscus maniculatus</i> (0%; 72)		
Gesy et al. 2014 [28]	100 Mile House, BC, Canada	<i>Vulpes vulpes</i> (17%; 6)	Intestine	E		<i>Microtus pennsylvanicus</i> (0%; 59) <i>Microtus pennsylvanicus</i> (0%; 59)	E	
						<i>Zapus hudsonius</i> (0%; 16) <i>Sorex</i> spp. (0%; 7)		
Gesy et al. 2014 [28]	Quesnel, BC, Canada	<i>Canis latrans</i> (37%; 27) <i>Vulpes vulpes</i> (17%; 6)	Intestine Intestine		D, E, L, M			
Gesy et al. 2014 [28]	Sathu, NT, Canada	<i>Canis lupus</i> (8%; 73)	Intestine		A, G, H			
Gesy et al. 2014 [28]	SK, Canada	<i>Canis lupus</i> (24%; 17)	Intestine		A, I	<i>Peromyscus maniculatus</i> (5%; 783)		A, I, J, K
Gesy et al. 2014 [28]	Riding Mtn, MB, Canada	<i>Canis lupus</i> (67%; 3)	Intestine		A, E			
Gesy et al. 2014 [28]	Karrak Lake, NU, Canada	<i>Vulpes lagopus</i> (4.8%; 354)	Feces			<i>Myodes rutilus</i> (0%; 8)		
						<i>Lemmus trimucronatus</i> (0%; 37) <i>Dicrostonyx groenlandicus</i> (0%; 72)		
Gesy et al. 2014 [28]	Bylot Island, NU, Canada	<i>Vulpes lagopus</i> (22%; 50)	Feces		A, E, N, O, P, Q			

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Table 1. (continued)

Reference	Location	Definitive host			Intermediate host		
		Species (prevalence; n)	Method	Strain	Haplotype	Species (prevalence; n)	Strain
Schurer et al. 2014 [80]	NT, Canada	<i>Canis lupus</i> (8.2%; 73)	Intestine	E			
Schurer et al. 2014 [80]	SK, Canada	<i>Canis lupus</i> (23.5%; 17)	Intestine	E			
Schurer et al. 2014 [80]	MB, Canada	<i>Canis lupus</i> (67%; 3)	Intestine	E			
Rausch et al. 1990 [70]	AK, USA	<i>Vulpes lagopus</i> (80%; 1579)	Intestine				
Kirk 2011 [44]	AK, USA	<i>Vulpes lagopus</i> (27%; 26)	Intestine	A2, A4			
Holt et al. 2005 [37]	Barrow, AK, USA					<i>Lemmus trimucronatus</i> (0.9%; 467) <i>Dicrostonyx rubricatus</i> (0%; 17) voles (n/a; 11)	N1
Nakao et al. 2009 [62]	AK, USA						
Nakao et al. 2009 [62]	Indiana, USA	<i>Vulpes vulpes</i> (n/a)	Intestine	N2			
Storandt et al. 2002 [85]	NE, USA	<i>Vulpes vulpes</i> (37.5%; 72)	Intestine				
		<i>Canis latrans</i> (0%; 31)	Intestine				
Storandt et al. 2002 [85]	KS, USA	<i>Vulpes vulpes</i> (0%; 22)	Intestine				
		<i>Canis latrans</i> (0%; 89)	Intestine				
Kritsky et al. 1977 [51]	WY, USA		Intestine			<i>Neotoma cinerea rupicola</i>	
Storandt et al. 2002 [85]	WY, USA	<i>Vulpes vulpes</i> (0%; 31)	Intestine				
Storandt and Kazacos 1993 [83]	IN, USA	<i>Vulpes vulpes</i> (22%; 71)	Intestine				
		<i>Canis latrans</i> (18.6%; 70)	Intestine				
Storandt and Kazacos 1993 [83]	IL, USA	<i>Canis latrans</i> (35%; 17)	Intestine				
Storandt and Kazacos 2012 [84]	MI, USA	<i>Vulpes vulpes</i> (4.1%; 97)	Intestine				
Ballard 1984 [2]	WI, USA	<i>Vulpes vulpes</i> (8.3%; 72)	Intestine				
		<i>Urocyon cinereoargenteus</i> (0%; 31)					
Carney and Leiby 1968 [12]	MN, USA	<i>Vulpes vulpes</i>	Intestine			<i>Peromyscus maniculatus</i>	
Leiby et al. 1970, 1972 [53, 54]	MN, USA	<i>Vulpes vulpes</i> (5%; 277)	Intestine			<i>Peromyscus maniculatus</i> (1.9%; 53)	
						<i>Microtus pennsylvanicus</i> (0%; 326)	
						<i>Mus musculus</i> (0%; 24)	
Ballard and Vande Vusse 1983 [3]	NE, IL, USA	<i>Vulpes vulpes</i> (NE: 27%, 36; IL: 10%, 40)	Intestine				
Leiby et al. 1970 [53]	SD, USA	<i>Vulpes vulpes</i> (0.4%; 222)	Intestine			<i>Peromyscus maniculatus</i> (1.3%; 234)	
		<i>Canis latrans</i> (0%; 29)	Intestine			<i>Microtus pennsylvanicus</i> (0%; 67)	
						<i>Mus musculus</i> (0%; 4)	
Schantz et al. 1995 [77]	SD, USA	<i>Vulpes vulpes</i> (0.45%; 222)	Intestine				
Hildreth et al. 2000 [34]	SD, USA	<i>Canis latrans</i> (44.4%; 9)	Intestine				
		<i>Vulpes vulpes</i> (74.5%; 137)	Intestine				
Leiby et al. 1970 [53]	ND, USA	<i>Vulpes vulpes</i> (13.9%; 830)	Intestine			<i>Peromyscus maniculatus</i> (6%; 3335)	
		<i>Canis latrans</i> (6.3%; 111)	Intestine			<i>Microtus pennsylvanicus</i> (3.2%; 565)	
						<i>Mus musculus</i> (2.1%; 47)	
Rausch and Richards 1971 [72]	ND, USA	<i>Vulpes vulpes</i> (70%; 96)	Intestine			<i>Peromyscus maniculatus</i> (3%; 1080)	
Hildreth et al. 1991 [33]	ND, USA	<i>Vulpes vulpes</i> (90%; 45)	Intestine				

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Table 1. (continued)

Reference	Location	Definitive host			Intermediate host			
		Species (prevalence; n)	Method	Strain	Haplotype	Species (prevalence; n)	Strain	Haplotype
Leiby et al. 1970 [53]	IA, USA	<i>Vulpes vulpes</i> (0.5%; 200) <i>Canis latrans</i> (0%; 1)	Intestine Intestine			<i>Microtus pennsylvanicus</i> (6%; 467) <i>Sorex cinereus</i> (0%; 41) <i>Blarina brevicauda</i> (0%; 70) <i>Zapus hudsonius</i> (0%; 202) <i>Reithrodontomys megalotis</i> (0%; 5) <i>Mus musculus</i> (0%; 15) <i>Myodes gapperi</i> (0%; 1) <i>Citellus tridecemlineatus</i> (0%; 17) <i>Citellus richardsoni</i> (0%; 1) <i>Peromyscus maniculatus</i> (0.6%; 151) <i>Microtus pennsylvanicus</i> (5.5%; 36) <i>Mus musculus</i> (0%; 4) <i>Peromyscus maniculatus</i> (0.5%, 436) <i>Microtus pennsylvanicus</i> (0%; 39) <i>Mus musculus</i> (0%; 12)		
Leiby et al. 1970 [53]	MT, USA	<i>Vulpes vulpes</i> (0%; 11) <i>Canis latrans</i> (0%; 30)	Intestine Intestine					

seasonally heterogeneous [57]. The frequent lack of an appropriate sampling design, which takes into account this spatio-temporal variability, makes longitudinal analyses unreliable. Moreover, while research conducted in Europe and Asia has indicated that interannual fluctuations of intermediate hosts are major drivers of *E. multilocularis* transmission [29, 30, 74], long-term studies in North America have mainly focused on density-dependent processes regulating rodent populations (e.g. [6, 47–49]). The available cross-sectional studies have estimated local prevalence in definitive and intermediate hosts (e.g. [13, 27, 35, 70]) in not well-defined host community systems. Therefore, trends in parasite transmission intensity and distribution over time are not well understood.

When studies are conducted over a short period of time (e.g. few months), it is not possible to take into account seasonal variations or the age structure of the host populations (e.g. [10]). Since it has been shown that significant variations in prevalence can be detected across different seasons (e.g. [10, 57]), surveys carried out over short periods of time and over small spatial scales cannot be compared to longer term studies carried out over large geographic areas. For example, *E. multilocularis* infection in intermediate hosts is believed to be highly clustered, resulting in prevalence as high as 10% in areas of only a few square meters, and less than 0.01% if calculated over larger areas in the same region [31]. For the above-mentioned reasons, it is necessary to consider different spatial and temporal scales to provide an adequate picture of the distribution of infections in a region, and be able to compare it with other regions or other time points. Finally, the origin of the samples can be a source of bias. For example, the use of hunted [36], trapped [85], or road-killed [13] animals may lead to prevalence estimates that are not representative of the overall population and will, therefore, not be comparable across studies.

Diagnostic techniques

Even when the same study designs have been used (e.g. multiannual sampling of fox carcasses or feces), different diagnostic techniques with different sensitivities and specificities were often applied to detect *E. multilocularis* infections in definitive hosts. This is possibly related to the fact that studies reporting *E. multilocularis* prevalence are, in most cases, broad gastrointestinal parasite surveys (e.g. [36]) that use techniques that may not specifically target *E. multilocularis* infection. While there are methods available specifically for the detection of adult *Echinococcus* spp. [18], caution should still be used when comparing data obtained with different methodologies that have different sensitivity and different precision in counting worms per host.

The choice of diagnostic technique is important when examining definitive host feces [55]. Fecal examination and isolation of parasite eggs, for later molecular analysis, can be conducted using sugar flotation [28, 55] or centrifugation and sedimentation [57]. Although sugar flotation is commonly used for surveying gastrointestinal parasites in dogs and wild canids [75, 90], its sensitivity in detecting *E. multilocularis* in coyote feces was shown to be considerably lower than that reported for

the ZnCl₂ centrifugation and sedimentation technique (0.46 vs. 0.75) [57]. This latter protocol was specifically developed to detect *E. multilocularis* in fox feces [60], and is currently recommended for large-scale screening of canid hosts [17, 57].

Without data obtained with standardized techniques of known sensitivity, or without correcting for the differences in sensitivity, comparisons of prevalence between regions and across time intervals are likely to be misleading or uninformative. The technique adopted can also affect estimates of parasite intensity (sensu [11]). Diagnostic challenges may also occur when investigating prevalence in intermediate hosts. The investigation of macroscopic liver lesions in small mammals can result in an underestimation of prevalence [1], particularly when compared to histological and/or molecular tools which are better for the detection of early larval stage infections [10, 57].

Temporal distribution of studies

The majority of the studies carried out in the NTZ are now relatively old [67, 68, 70], with research focusing on the epidemiology and risk factors associated with AE in highly endemic Native American communities in Alaska [77, 82, 93]. Although pioneer studies conducted in the NCR during the 1960s and 1970s [35, 36, 72, 76] were followed by some research effort in the 1990s and 2000s [34, 83, 85], large temporal gaps between studies make evaluation of trends very difficult, if not impossible. Moreover, the adoption of molecular diagnostic techniques in the 1990s [1, 20, 61] makes comparisons with older studies challenging [28, 57].

Ecological communities

Differences in host communities and predator-prey relationships can affect *E. multilocularis* transmission. In the NTZ, the reliance of the arctic fox on arvicoline intermediate hosts as a food source [25] may be responsible for the high parasite prevalence observed in these definitive hosts [70], with surveys finding up to 100% of tested animals infected during a given season [24]. While coyotes and red foxes also rely on small mammals as a food source, their broader diet and more pronounced opportunism [16, 59] may partially explain why prevalence values tend to be lower in the central region, where these canid species act as the main definitive hosts. However, differences in temperature and humidity also likely affect parasite egg survival in the environment [91], and therefore, parasite transmission in the different regions [29]. Moreover, differences in host susceptibility to infection and the pathogenicity of different *E. multilocularis* strains [5] may also impact parasite transmission across eco-regions.

In summary, data available from North America are quite heterogeneous, making it difficult to identify trends in parasite distribution and abundance. While the hypothesis that the parasite's range is expanding across North America fits with available information [39], further supportive data are required. Therefore, additional studies using comparable sampling designs and diagnostic techniques are needed.

Echinococcus multilocularis in domestic hosts

Dogs as definitive hosts

Both domestic dogs and cats can serve as definitive hosts for *E. multilocularis*, albeit cats seem to play an insignificant role in maintaining the life cycle [43]. However, unlike cats, dogs have also been reported to become infected with the larval stage of the parasite [41]. Limited information is available on the extent to which dogs act as definite hosts of *E. multilocularis* in North America since very few systematic studies have been carried out addressing this question. One notable exception is the north-western region of Alaska, in particular St. Lawrence Island, where *E. multilocularis* was found in the local dog population [22, 82, 93]. Here, on postmortem examination, the infection prevalence in dogs residing in specific Native American communities was up to 12% [77]. Consequently, owning a dog and living in close proximity to dogs was identified as a risk factor for human AE [82, 93].

To control AE on St. Lawrence Island, a control program focusing on the monthly administration of praziquantel to dogs was initiated. The prevalence of infection in intermediate hosts was used as a measure of success, with an 83% reduction in the prevalence in voles achieved over a 10-year period [69]. This decrease in intermediate host prevalence helped confirm the hypothesis that domestic dogs were contributing to the maintenance of the parasite life cycle. To the best of our knowledge, to date no other studies in North America on the prevalence in domestic dogs harboring adult *E. multilocularis* have been published, except for the ones from St. Lawrence Island, although the latter was a unique situation and not really comparable to the situation in the continent obtained within our laboratory. Based on the screening of 218 dog fecal samples from Calgary, Canada, using a modified centrifugation and sedimentation protocol followed by molecular confirmation [57], we estimated an *E. multilocularis* prevalence of approximately 0.46% (1/218). The positive dog was regularly walked in a known high endemic area in the city of Calgary (Alberta, Canada; [57]) and had a history of preying upon rodents (Massolo, Klein et al. unpublished data).

Cats as definitive hosts

In North America, only a few studies have investigated the presence of *E. multilocularis* in cats. A study in Saskatchewan, Canada reported three positives out of 131 (2.29%) sampled free roaming cats [94]. The infected cats all had low intensity infections (30–50 adult worms). Around the same time, additional three cats were found to harbor adult *E. multilocularis* infections [54]. After finding an infected house mouse, in the same area, the existence of a possible domestic life cycle was hypothesized, but the alternative hypothesis that these domestic hosts were just spill-over cases was considered. However, although it is still controversial, it should be noted that cats are not optimal hosts for *E. multilocularis* and they are not believed to play a significant role in the parasite's life cycle [43].

Dogs as aberrant intermediate hosts

Rarely, dogs can develop AE with severe hepatic lesions. Recently, three dogs with AE were identified in Canada. One dog was identified in British Columbia [65], a second in Southern Ontario [64], and the third was found in Saskatoon (Audrey Tataryn, personal communication). The occurrence of these cases can either be an indicator of the spread of the disease or as a consequence of a heightened awareness of the disease following the first case report in 2012.

Human infections with *Echinococcus multilocularis* in North America

While *E. multilocularis* is known to be endemic in northern regions of North America, there have been few human cases reported in the literature. The most widely documented cases, in this region, occurred on St. Lawrence Island, Alaska, USA starting in the 1940s [69]. In this endemic focus, working dogs were found to be eating infected small mammals and, subsequently, infecting humans. Concentrated control efforts aimed at dog deworming were able to eventually control this outbreak [93].

Besides the more than 70 cases reported on St. Lawrence Island, there have only been two locally acquired human AE cases from North America described in the literature. The first reported case was a 54-year-old fisherman from Winnipeg, Manitoba, Canada who presented with an abdominal mass in 1928 [38]. The patient was operated on in 1928, but succumbed to his disease in 1935. While this case was believed to be due to AE based on lesion morphology, no molecular confirmation was ever performed. The second reported case was a 56-year-old female from Minnesota, USA who presented for abdominal pain in 1977 [26]. In a 2008 publication, molecular evaluation of the cyst material obtained from the Minnesota case was shown to be almost identical to other isolates collected from intermediate hosts in South Dakota, USA [95]. A recent comparison of the mitochondrial gene *cox1* sequence from an isolate from the Minnesota case with sequence data from adult worms collected from red fox in Indiana, USA [45] confirmed that the Minnesota case was infected with the North American N2 strain as described by Nakao and colleagues [62].

In May 2013, AE was reported in an immunosuppressed patient from Edmonton, Alberta, Canada, who had no history of travel (personal communication, Kinga T. Kowalewska-Grochowska). This case requires special consideration since immunosuppressed patients can be considered sentinels for locally emerging diseases. In a recent publication from France, a statistically significant increase in the number of immunosuppressed AE cases was described over the period 2002–2012 [15]. This report also indicated that the presence of immunosuppression may make AE cases more difficult to diagnose and treat.

A recent search of Canadian hospital discharge data, provided by the Canadian Institute for Health Information (CIHI) for the years 2001–2014, identified 242 hospital discharges with International Classification of Diseases-version

9 (ICD-9) codes for cystic echinococcosis ($n = 39$), alveolar echinococcosis ($n = 12$), or unspecified echinococcosis ($n = 191$) (Table 2, Fig. 1). These data indicate that Canadian healthcare providers have been treating cases of echinococcosis for many years. However, from this type of data, it is not possible to differentiate cases that were acquired locally from those that were acquired outside of North America. Large population centers, with considerable immigrant populations from known endemic regions, are likely to be areas with the highest numbers of identified cases. Considering the high level of immigration in North America, most of these cases are likely to have been acquired on other continents, and not represent autochthonous infections (e.g. [66]). This is not uncommon for countries characterized by high immigration rates. For example, in a study conducted in Germany, only nine out of 65 cystic echinococcosis cases were of German origin [63]. In another German study, AE was diagnosed in a refugee from an endemic area (e.g. [86]).

Based on ICD-9 data alone, it is not possible to assess how many individuals the 242 hospital discharges actually represent, or to confirm the provided diagnosis. In addition, the infecting species was recorded for only a small proportion of the hospital discharges. That said, for the last decade, there has been an average of 19 discharges per year at hospitals located in all Canadian provinces except for Quebec, with no obvious upward or downward trend in case numbers. When the number of hospital discharges coded for unspecified liver disease was evaluated, for the same time period, there also did not appear to be an upward or downward trend in these case numbers.

A review of the available human data from North America indicates that there continues to be little known about the impact of human AE on this region. A lack of official reporting mechanisms means that, if cases are occurring, they are not being centrally recorded. In addition, it is possible that physicians in Canada and the USA may be misdiagnosing cases due to lack of training about the disease and its presentation. Therefore, a retrospective study evaluating banked liver tissue samples available from health service agencies (e.g., the Alberta Provincial Laboratory for Public Health in Alberta, Canada) would be helpful in assessing if cases of hepatic AE are being misdiagnosed [81]. Establishment of multidisciplinary teams composed of public health personnel, physicians, veterinarians, wildlife biologists, laboratory personnel, molecular biologists, epidemiologists, and ecologists is needed to develop a current picture of *E. multilocularis* transmission and the human health impact of AE on North America.

Distribution of strains: the effect of globalization?

Information on the distribution of different *E. multilocularis* genotypes is needed to assess possible introductions that might have occurred in the last decades [18], as well as to evaluate the public health risks associated with different genotypes. Since the 1990s, isolates obtained from definitive and intermediate hosts originating from distinct geographical regions have been analyzed with respect to genetic differences. Analyzing a

Table 2. Canadian hospital discharge data on Cystic Echinococcosis (CE), Alveolar Echinococcosis (AE), unspecified Echinococcosis and unspecified liver diseases for the period 2001–2014 by year and province. Data from Quebec were not available.

Year	CE	AE	Unspecified Echinococcosis	Unspecified Liver disease
2001–2002	1	0	4	64
2002–2003	0	1	11	199
2003–2004	3	0	10	150
2004–2005	7	0	7	164
2005–2006	3	4	16	152
2006–2007	4	3	19	179
2007–2008	3	0	18	181
2008–2009	1	0	18	143
2009–2010	3	2	10	150
2010–2011	7	1	24	136
2011–2012	3	0	21	153
2012–2013	2	1	17	160
2013–2014	2	0	16	118
*Canadian Province				
AB	11	5	37	163
BC	3	2	40	568
MB	4	0	14	138
NB	0	0	1	103
NL	1	0	3	58
NS	0	0	4	119
NT	0	0	0	5
NU	0	0	0	1
ON	17	4	79	644
PE	0	0	0	37
SK	3	1	13	105
YT	0	0	0	8
Total	39	12	191	1949

*AB-Alberta, BC-British Columbia, MB-Manitoba, NB-New Brunswick, NL-Newfoundland and Labrador, NS-Nova Scotia, NT-Northwest Territories, NU-Nunavut, ON-Ontario, PE-Prince Edward Island, SK-Saskatchewan, YT-Yukon. Data not available for Quebec.

471 base pair region of NADH dehydrogenase 1, Bowles and McManus [7] identified two genotypes (M1 and M2). M1 was identified in specimens from China, Alaska, and central North America, while M2 was found in a single European isolate. Based on polymorphism of microsatellites in the U1 snRNA gene of 41 isolates, Bretagne and co-workers described three distinct profiles of which profile A was found in all isolates from Europe, profile B was found in isolates from Alaska and Japan, and profile C was associated with isolates from Alaska and Montana [8]. Haag and co-workers analyzed the variance of two coding and two non-coding regions of the *E. multilocularis* genome [32] in 33 isolates and found minor differences in the intron of a homeobox-containing gene. Genotype A was found worldwide, whereas genotype B was restricted to St. Lawrence Island, Alaska.

The tandem repeat multilocus microsatellite EmsB exhibits a high genetic polymorphism, resulting in this genetic marker having a higher discriminatory power compared to others. Twenty-nine distinct genotypes have been identified [4, 46]. Nakao et al. described the division of 76 isolates into three distinct branches based on their geographical origin (Europe, Asia, or North America). Within the European, Asian, and North American clusters, 5, 10, and 2 haplotypes were identified, respectively [62]. To our knowledge, no isolates from autochthonous North American AE cases have been genotyped.

In 2009, a new haplotype was discovered which has similarities to previously described European haplotypes [27]. This new haplotype was found in foxes and coyotes from rural sites in three different Canadian Provinces (British Columbia, Alberta, and Saskatchewan). Thus far, this new haplotype has not been found in intermediate hosts. More recently, Massolo, Klein, and colleagues (unpublished data) found that this newly identified European strain was circulating in both urban (Calgary and Edmonton, Alberta, Canada) and rural environments. This poses interesting questions on the spread of this European strain into an area of known endemicity for the N2 strain and the possible public health risks.

The presence of this European strain in western Canada might be explained by two hypotheses. The first hypothesis is that the appearance of this new strain occurred as a consequence of introducing foxes from Europe for commercial use [18, 19]. The second hypothesis is that the parasite was introduced with dogs imported from Europe. Canada does not require treatment of dogs with praziquantel before entering the country. A recent risk assessment on importation of dogs infected with *E. multilocularis* into the United Kingdom pointed out that without the required treatment of dogs with praziquantel, it would be impossible to prevent the introduction of this parasite [87, 89]. The proposed hypotheses are not necessarily mutually exclusive, as they both could have occurred at different times and in different areas. At present, there is

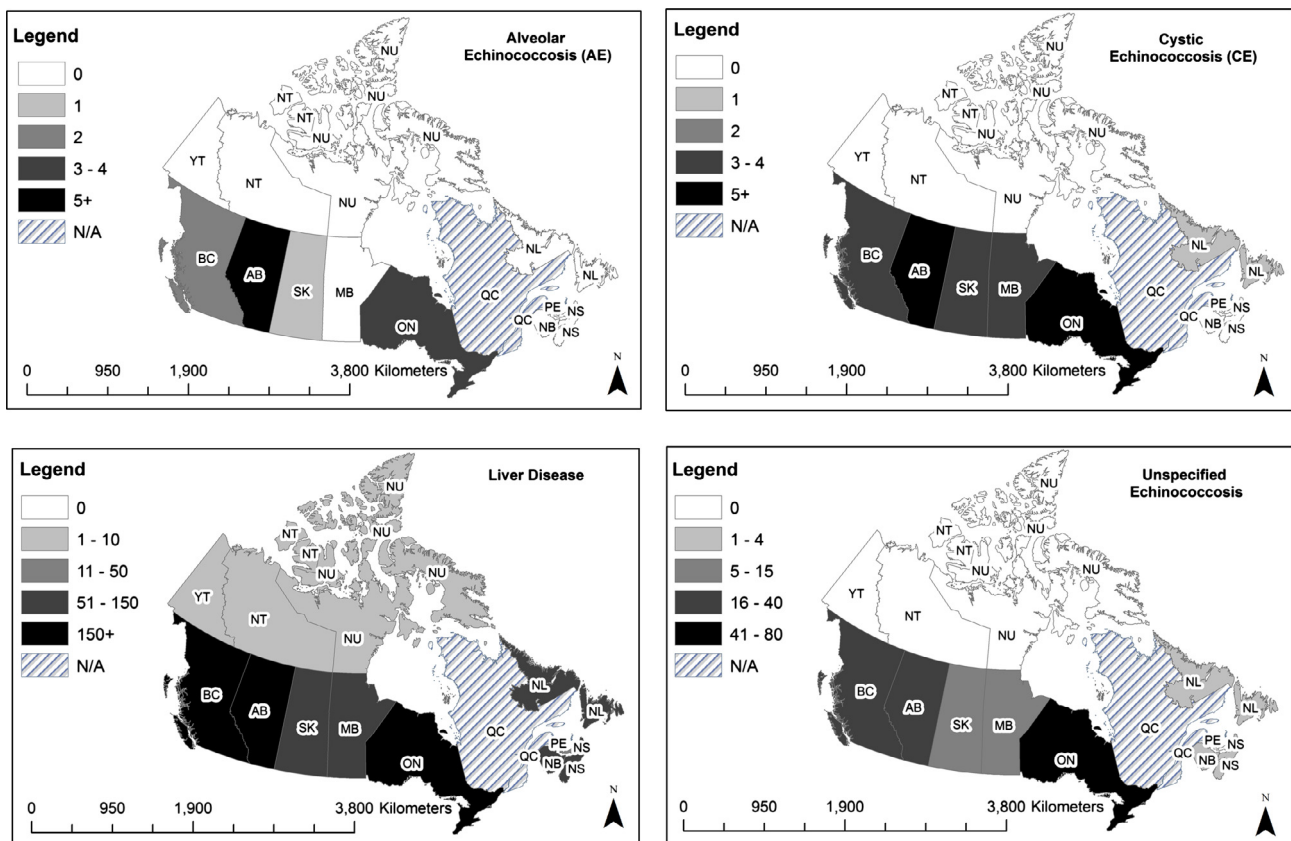


Figure 1. Distribution map by Province of Canadian hospital discharge data of Cystic Echinococcosis (CE), Alveolar Echinococcosis (AE), unspecified Echinococcosis and general liver diseases in Canada for the period 2001–2014. Data for Quebec were not available. Map by K. Berger, 2014.

not enough information to support either hypothesis. However, the implementation of a praziquantel treatment policy for dogs being imported into North America would reduce the risk of introducing additional European strains.

Conclusions and perspectives

Considering what is available in the literature on *E. multilocularis* ecology and epidemiology in North America, it is clear that there are substantial knowledge gaps. Available data are not spatially and temporally homogenous and differences in diagnostic methods and sampling design make comparisons difficult. Current hypotheses on parasite spread and the invasion of new strains are not yet sufficiently supported by data. In most cases, the presence of *E. multilocularis* in domestic animals is not monitored and its prevalence is not known even in settings where zoonotic transmission is more likely to occur (e.g., urban landscapes). The aggregation of thousands of pets in city parks and the presence of potentially infected coyotes, foxes, and small mammals should induce city managers and health authorities to assess the risk of transmission to dogs and humans. Despite their poor suitability as hosts for *E. multilocularis*, the role of cats as a potential route of infection to people should also be assessed. Reports of dogs acting as aberrant intermediate hosts have recently received increased

attention in Canada, with these cases possibly representing a change in the relevance of *E. multilocularis* from an animal health standpoint.

The presence of a European strain of *E. multilocularis* in Canada, the discovery of a highly endemic area in Calgary, and the recent diagnosis of AE in an immunosuppressed patient in Edmonton suggest that we might expect to see an increase in the number of human cases in North America, similar to what has been seen in Central Europe [18]. Additional data are needed to help decide whether to develop new policies on wildlife management in urban settings and/or importation of dogs from areas where highly pathogenic strains of *E. multilocularis* are endemic. We feel that it is a priority to implement the following actions: (1) to assess the prevalence of *E. multilocularis* in wild and domestic hosts, in well-defined ecosystems, through long term studies with comparable sampling designs and diagnostic protocols, (2) to assess whether cases of human AE have been misdiagnosed through a retrospective analysis of biological samples available in the biobanks of health service agencies, and finally (3) to develop a surveillance plan for human AE in North America. This would require the efforts of a multidisciplinary working group engaging parasitologists, ecologists, public health officers, pathologists, surgeons, veterinarians, epidemiologists, and others to increase preparedness and develop possible control and disease management strategies.

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