

Tularemia, plague, yersiniosis, and Tyzzer's disease in wild rodents and lagomorphs in Canada: A review

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Abstract – Information related to infection of wild rodents or lagomorphs in Canada by *Francisella tularensis*, *Yersinia pestis*, other *Yersinia* spp., and *Clostridium piliforme* was searched for this study. Reports on tularemia in humans linked to these species came from diagnostic databases, literature, wildlife health specialists, and public health agencies. Tularemia has been diagnosed in 8 species of wild rodent and 2 species in the genus *Lepus* in Canada. Tularemia occurred in wild animals, or in humans associated with these species, in all jurisdictions except the Yukon and Nunavut. Tularemia was diagnosed most frequently in beaver, muskrats, and snowshoe hares, and although tularemia is closely linked to cottontail rabbits in the USA, it has not been reported in cottontails in Canada. Tularemia in humans was associated with muskrats and hares more commonly than with beaver. Plague was diagnosed in bushy-tailed woodrats in British Columbia in 1988. Based on surveys, *Y. pestis* may occur enzootically in southern Alberta, Saskatchewan, and British Columbia. Infection with *Yersinia pseudotuberculosis* and *Y. enterocolitica* has been diagnosed in beaver, muskrats, and snowshoe hares in many provinces. Tyzzer's disease has been diagnosed in muskrats in British Columbia, Saskatchewan, Ontario, and Quebec and in snowshoe hares in Ontario. Infection with these bacteria is likely much more frequent than indicated by diagnostic records.

Résumé – **Tularémie, peste, yersiniose et maladie de Tyzzer chez les rongeurs sauvages et les lagomorphes au Canada : Un compte-rendu.** Une recherche dans la documentation traitant de l'infection des rongeurs sauvages ou des lagomorphes au Canada par *Francisella tularensis*, *Yersinia pestis*, d'autres *Yersinia* spp. et *Clostridium piliforme* a été réalisée pour cette étude. Les rapports sur la tularémie chez les humains liée à ces espèces sont issus de bases de données de diagnostics, de la documentation, de spécialistes sur la santé de la faune et d'agences de santé publique. La tularémie a été diagnostiquée chez 8 espèces de rongeurs sauvages et 2 espèces du genre *Lepus* au Canada. Chez les animaux sauvages, ou chez les humains associés à ces espèces, la tularémie s'est produite dans toutes les juridictions sauf pour le Yukon et le Nunavut. La tularémie a été diagnostiquée le plus fréquemment chez les castors, les rats musqués et les lièvres d'Amérique, et, même si la tularémie est étroitement liée aux lapins à queue blanche aux États-Unis, elle n'a pas été signalée chez les lapins à queue blanche au Canada. La tularémie chez les humains a été associée aux rats musqués et aux lièvres plus communément qu'avec le castor. La peste a été diagnostiquée chez les rats à queue touffue en Colombie-Britannique en 1988. Selon les enquêtes, *Y. pestis* peut se présenter sous forme enzootique dans le Sud de l'Alberta, de la Saskatchewan et de la Colombie-Britannique. L'infection par *Yersinia pseudotuberculosis* et *Y. enterocolitica* a été diagnostiquée chez les castors, les rats musqués et les lièvres d'Amérique dans beaucoup de provinces. La maladie de Tyzzer a été diagnostiquée chez les rats musqués en Colombie-Britannique, en Saskatchewan, en Ontario et au Québec et chez les lièvres d'Amérique en Ontario. L'infection par ces bactéries est beaucoup plus fréquente que ne l'indiquent les dossiers de diagnostic.

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Introduction

Francisella tularensis, *Yersinia pestis*, *Y. pseudotuberculosis*, *Y. enterocolitica*, and *Clostridium piliforme* are pathogens that cause similar pathological lesions in wild rodents and lagomorphs (rabbits and hares). Tularemia, plague, and yersiniosis (used here to denote disease caused by *Yersinia pseudotuberculosis* and *Y. enterocolitica*) are zoonoses in which human infection often is associated with wild animal contact. Tyzzer's disease is not usually considered zoonotic but *C. piliforme* infection has been reported in an immunodeficient human (1). Our objective was to document the geographical distribution and relative frequency of diagnosis of these diseases in wild rodents and lagomorphs as baseline information for those concerned with the health of wild animals and humans.

Materials and methods

The database of the Canadian Cooperative Wildlife Health Centre (CCWHC) was the principal source searched for reports of disease in wild rodents and lagomorphs. This database contains diagnostic records beginning in 1992 from CCWHC regional centres at the Atlantic Veterinary College (AVC), University of Prince Edward Island; the Faculté de médecine vétérinaire (FMV), Université de Montréal; Ontario Veterinary College (OVC), University of Guelph; and the Western College of Veterinary Medicine (WCVM), University of Saskatchewan, and data from other laboratories, including some provincial veterinary laboratories. Records from the diagnostic laboratories at the 4 veterinary colleges prior to establishment of the CCWHC also were searched. Available records extended back to 1988 (AVC), 1979 (FMV), 1976 (OVC), and 1967 (WCVM).

Where paraffin-embedded tissue was available from cases in which tularemia had been suspected on the basis of lesions, but not confirmed by bacterial isolation, immunohistochemistry (IHC) was used to confirm the diagnosis of tularemia (2). Provincial veterinary diagnostic laboratories across Canada and wildlife disease specialists in Alberta, British Columbia, Northwest Territories, and the Yukon were contacted for information on these diseases in their jurisdiction. Literature was searched for reports of these diseases in wild animals in Canada and for reports of tularemia in humans associated with a wild rodent or lagomorph. In some reports of human tularemia, reference was to 'rabbit' without identification of the species involved. In most such instances, the species involved could be identified based on the geographic range of lagomorphs in Canada. Provincial public health officials were contacted for unpublished records of individual human cases in which an animal had been identified as the source of tularemia.

Occurrence of tularemia

The first report of tularemia in Canada was of a human case near Timmins, Ontario in 1929 linked to contact with "rabbits" (3). The only wild lagomorph in the area is the snowshoe hare (*Lepus americanus*). We found records of tularemia in wild rodents or lagomorphs, or of human cases linked to these species, in all provinces and territories except Nunavut and the Yukon (Tables 1, 2) (4–28). There were few diagnoses of tularemia in animals in the Northwest Territories. Tularemia was not reported

in animals above the treeline, but a human case, apparently as a result of insect-borne transmission, occurred in Nunavut (29). Infection in beaver (*Castor canadensis*) and muskrats (*Ondatra zibethicus*) was widespread. Most reports related to single or a few affected individuals, although a number of cases occurred in beaver across northern Ontario in 1980 and 1981. Human tularemia was associated with muskrats much more often than with beaver (Table 2). In an outbreak in the Northwest Territories (7), *F. tularensis* was isolated from beaver but the animal contact in 10 of 12 human cases had been with muskrats (23). The more frequent association of human infection with muskrats may reflect the greater number of individuals trapping muskrats and the relative number of muskrats and beaver handled by individual trappers.

Tularemia has been diagnosed in snowshoe hares in 7 provinces (Table 1) and human tularemia has been associated with snowshoe hares in 7 provinces (Table 2). A report from Quebec is notable in that 24 of 26 human cases diagnosed over a 26-year period were linked to snowshoe hares (25). This contrasts with the situation in the USA where Jellison (30) found only 5 reports of human tularemia attributable to contact with snowshoe hares. Human infection was often related to hares killed by hunters, and ticks from apparently normal snowshoe hares have been infected with *F. tularensis* (31–33), suggesting that subclinical infection occurs in hares. Eastern cottontail rabbits (*Sylvilagus floridanus*) were extirpated from an area of Michigan by tularemia while the sympatric snowshoe hare population remained viable, suggesting that the bacterium is less virulent to snowshoe hares (34). However, hares were highly susceptible to experimental infection with a "bare" strain of *F. tularensis* (32). Antibodies to *Francisella* have been detected in hares in Ontario, Alberta, and Nova Scotia, but not in Prince Edward Island (9,35,36).

Tularemia is closely linked with cottontail rabbits (*Sylvilagus* spp.) in the USA (37). Although the eastern cottontail occurs in parts of Ontario, Quebec, Manitoba, and British Columbia, and Nuttall's cottontail (*S. nuttallii*) occurs in southern Alberta and Saskatchewan, tularemia has not been diagnosed in a cottontail in Canada and no record was found of human disease associated with cottontail rabbits. The white-tailed jackrabbit (*L. townsendii*) occurs in southern British Columbia, Alberta, and Saskatchewan. A jackrabbit found dead in Alberta during a tularemia outbreak in sheep (11) was the only documentation of tularemia in this species. Brown (38) mentioned "infected jackrabbits" in the same general area but gave no details.

Francisella tularensis was isolated from Richardson's ground squirrels (*Spermophilus richardsonii*) collected in Alberta during surveys for vector-borne diseases (12,13) and from Franklin's ground squirrels (*S. franklinii*) trapped in Winnipeg, Manitoba during an outbreak of tularemia in a zoo (14). There is no record that these squirrels were abnormal when trapped. *Francisella tularensis* was isolated from ticks on a Richardson's ground squirrel found dead in Alberta (11), but the cause of death of the squirrel was not reported. A human case in Alberta was associated with skinning ground squirrels and another was associated with either ground squirrels or rabbits (28). A human case in Manitoba was associated with unidentified "squirrels" (6). About 1.5% of a sample of Richardson's ground squirrels

Table 1. Number of incidents of *Francisella tularensis* infection in wild rodents and lagomorphs in Canada. Information is from the Canadian Cooperative Wildlife Health Center (CCWHC) database or from files of Canadian veterinary colleges prior to the establishment of CCWHC in 1992, unless otherwise noted. Scientific names of species are included in the text

Species	Province/territory										
	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	NT
Beaver	5 ^{a,b}	12 ^{c,d,e}	10	1	21 ^{f,g}				1		1 ^h
Muskrat	1	2 ^{c,d}	2	1	6 ^{f,i,j}						
Snowshoe hare	1 ^k				1	1	1 ^l	1	1	1	
Richardson's ground squirrel		2 ^{m,n,o}	1								
Deer mouse		1 ^m	1 ^p	1 ^q							
House mouse	1 ⁿ			1 ^q							
White-tailed jackrabbit		1 ^m									
Franklin's ground squirrel				1 ^r							
<i>Microtus</i> spp.		1 ⁿ									
Unidentified rabbit		1 ⁿ									
Red squirrel			1								

^a Ministry of Environment, BC, unpublished data, ^b Ministry of Agriculture and Food, BC, unpublished data, ^c (4), ^d Alberta Environment and Natural Resources, unpublished data, ^e Alberta Agriculture and Rural Development, unpublished data, ^f (5), ^g (6), ^h (7), ⁱ (8), ^j (9), ^k (10), ^{l,m} (11), ⁿ (12), ^o (13), ^p (2), ^q Public Health Agency of Canada, unpublished data, ^r (14).

Table 2. Reported number of incidents of tularemia in humans in which an association was noted with a wild rodent or lagomorph

Species	Province/territory										
	BC	AB	SK	MB	ON	QC	NB	NS	NL	NT	
Beaver			2 ^a		1 ^b					1 ^c	
Muskrat		1 ^d	7 ^{a,e,f}	4 ^g	5 ^{h,i,j}	4 ^{k,l}				1 ^m	
Snowshoe hare	1 ⁿ			1 ^e	1 ^o	24 ^p	1 ^q	1 ^r	1 ^s		
Groundhog ^t						1 ^o					
Deer mouse			1 ^a								
Red squirrel										1 ^u	
Unidentified vole					1 ^v						
Ground squirrel		2 ^w									
Unidentified rodents			1 ^a								
Unidentified rabbits	1 ⁿ				2 ^b						
Unidentified squirrel	1 ^x			1 ^g							
Unidentified mouse	1 ^x										

^a Saskatchewan Health, unpublished data, ^b Infectious Diseases Branch, Ministry of Health and Long-term Care, Ontario, unpublished data, ^c (7), ^d (15), ^e (16), ^f (17), ^g (7), ^h (18), ⁱ (19), ^j (20), ^k (21), ^l (22), ^m (23), ⁿ (24), ^o (3), ^p (25), ^q J. Goltz (personal communication, 2007), ^r (26), ^s H. Whitney (personal communication, 2007), ^t *Marmota monax*, ^u (27), ^v L. Karstad (personal communication, 2007), ^w (28), ^x L. Hoang, British Columbia Centre for Disease Control (personal communication, 2007, 2008).

trapped in Alberta had a significant antibody titer to *F. tularensis* (39). Tularemia was diagnosed in a red squirrel (*Tamiasciurus hudsonicus*) found sick in Saskatchewan and human infection has been linked to this species on one occasion (27).

Reports of *F. tularensis* infection in smaller rodents are rare in Canada. The bacterium was isolated from apparently normal animals trapped during surveys, including a house mouse (*Mus musculus*) in British Columbia, a vole (*Microtus* spp.) and a deer mouse (*Peromyscus maniculatus*) in southern Alberta (12), and a house mouse and a deer mouse in Manitoba (Public Health Agency of Canada, unpublished data). A veterinarian developed tularemia after the necropsy of an unidentified vole found dead in Ontario (Karstad L., personal communication 2007). Epizootic tularemia occurred in deer mice over a large area of Saskatchewan (2).

Molecular sub-typing is used to differentiate subspecies of *F. tularensis* (40). *Francisella t.* subsp. *holarctica* occurs

throughout the northern hemisphere with little genetic diversity, although North American and Eurasian isolates appear distinct (41). In North America, this subspecies has been associated primarily with voles (*Microtus* spp.), beaver and muskrats (40). Two distinct clades, designated types A.I (A-east) and A.II (A-west) (42,43), have been identified within *F. t.* subsp. *tularensis*. Type A.I. occurs generally east of the 100th meridian in the USA, spatially correlated with the distribution of *Amblyoma americanum* and *Dermacentor variabilis*, and the eastern cottontail rabbit. Type A.II occurs in the western USA in association with *Dermacentor andersoni*, the deer fly *Chrysops discalis*, and Nuttall's cottontail (42,43). Human infection with *F. t.* subsp. *tularensis* A.II appears to be less severe than that with either *F. t.* subsp. *tularensis* A.I. or *F. t.* subsp. *holarctica* (43).

Very few isolates of *F. tularensis* from wild animals in Canada have been identified to subspecies. Based on experience elsewhere

(40), muskrats and beaver are probably infected by *F. t.* subsp. *holarctica*, and that subspecies was isolated from deer mice in Saskatchewan (2) and a deer mouse and house mouse from Manitoba (Public Health Agency of Canada, unpublished data). *Francisella tularensis* from ticks on snowshoe hares in Ontario was identified as B type (*F. t.* subsp. *holarctica*) (9) but organisms from ticks on snowshoe hares, and from hares, in Alaska were *F. t.* subsp. *tularensis* (31,32). Two isolates from humans from Alaska (where cottontail rabbits do not occur) were *F. t.* subsp. *tularensis* type A.I. (42). An isolate from a human at Kamloops, British Columbia in 1935 was identified as *F. t.* subsp. *tularensis* type A.I. and a human isolate from Muskoka, Ontario (undated) was *F. t.* subsp. *tularensis* type A.II (42).

Most diagnoses of tularemia in wild animals were based on isolation of *F. tularensis*. This method underestimates the actual rate of infection because *F. tularensis* is difficult to recover from field specimens (44). We used IHC to re-examine 45 cases diagnosed as suspicious for tularemia, based on lesions compatible with the disease. Bacteriologic culture of *F. tularensis* had been attempted in most of these cases with negative results. *Francisella tularensis* antigen was identified in lesions from 1 of 10 muskrats, 24 of 32 beaver, and 1 of 3 snowshoe hares tested by IHC, including the only record of tularemia in a muskrat in British Columbia and a snowshoe hare in Prince Edward Island.

Associations between human tularemia and wild animals were determined from history recounted by patients and may be subject to recall bias and unrecognized methods of transmission may have occurred in individuals who recalled exposure to wild animals.

“Few, if any zoonotic diseases have a broader or more complex host distribution and epizootiology” than tularemia (45). The true reservoir(s) of *F. tularensis* remain to be elucidated (46) and there “is no proof that mammals constitute the reservoir of *F. tularensis*” (47). It is likely that overlapping cycles of transmission, involving different animal species, vectors, and subspecies and clades of *F. tularensis* occur in Canada.

Occurrence of plague

Yersinia pestis emerged 1500–20 000 years ago as a clone of *Y. pseudotuberculosis* (48). Only biovar Orientalis, which caused the 3rd pandemic that began in China in the late 1800's, has been found in North America (49). Most authors believe plague was introduced to North America in the late 19th or early 20th century via ship rats (*Rattus* spp.) and their fleas. Plague is common in many locations in the USA west of the 100th meridian (49) and is spreading slowly eastward (50). The only confirmed case of disease caused by *Y. pestis* in a wild animal in Canada occurred near Lillooet, British Columbia where plague was identified in 1988 in 2 bushy-tailed woodrats (*Neotoma cinerea*) that had been found dead (51). A low prevalence (2% to 4%) of antibody to *Y. pestis* was found in mink (*Mustela vison*), bobcats (*Lynx rufus*), marten (*Martes americana*), lynx (*Lynx canadensis*), and weasels (*Mustela* spp.) from southern and central British Columbia during a survey of wild carnivores between 1985 and 1991 (Ministry of Environment, British Columbia, unpublished data).

In 1937, a mink rancher near Hanna, Alberta, who collected and prepared ground squirrels for mink food (13), died “of what

in retrospect appears to have been ...sylvatic plague” (12). This stimulated surveys for plague, tularemia, and Rocky Mountain spotted fever in western Canada between 1938 and 1946. One major survey begun in 1938 concentrated on southern Alberta and British Columbia, but was extended into southwestern Saskatchewan (12). A separate survey was conducted in 1943 by the Royal Canadian Medical Corps “in areas immediately surrounding military establishments, situated between Winnipeg and the Rocky Mountains” (13). No evidence of plague was found among > 4100 ground squirrels, (*S. richardsoni*, *S. franklinii*, *S. columbianus*, and *S. tridecemlineatus*), or from > 2000 ticks (mainly *D. andersoni*), collected during the military survey. In a general report of surveys (12), (that may have included animals tested during the military survey), results were described for 28 346 ground squirrels (species not reported). *Yersinia pestis* was identified in 6 of 817 pools of tissue from ground squirrels, in 32 of 939 pools of fleas collected from ground squirrels in southeastern Alberta, and in 2 pools of fleas from 61 Richardson's ground squirrels collected in Saskatchewan “adjacent to the infected area of Alberta.” It was concluded that “plague is well established in ground squirrels in southeastern Alberta and that the infection has at least gained a foothold in the adjoining territory of Saskatchewan” (12). Approximately 50 years later, 9.6% of rural dogs and 5.4% of rural cats from 4 sites in the same general area of Alberta and Saskatchewan had specific antibodies to *Y. pestis*, also leading to the conclusion that plague is enzootic in this region of Canada (52). How plague is maintained in this part of Canada is unknown, but rodents infected enzootically with *Y. pestis* and in which plague-associated mortality is low are likely involved. Plague may be less apparent in Canada than in the USA because colonial rodents, such as prairie dogs (*Cynomys* spp.), that have low resistance to plague and suffer very high mortality (49,53), are confined to a small focus in Grasslands National Park, Saskatchewan.

Occurrence of yersiniosis

Yersinia pseudotuberculosis and *Y. enterocolitica* are considered a heterogenous group of bacterial strains, with animal and environmental reservoirs, that may survive and replicate in soil and aquatic environments (50). Infection has been described in many animal species and is thought to occur through ingestion of contaminated food or water. Yersiniosis is an important infectious disease of the European brown hare (*Lepus europaeus*) in western Europe (54).

Yersiniosis has been diagnosed in beaver, snowshoe hares, and muskrats in many parts of Canada (Table 3) (55). Infection with *Y. pseudotuberculosis* has been more common than infection with *Y. enterocolitica*. Because these bacteria are ubiquitous, human infections are seldom linked to a specific source.

Occurrence of Tyzzer's disease

Tyzzer (56) described a fatal disease of laboratory mice in which intracellular bacteria were associated with foci of hepatic necrosis. The causative agent has been assigned to the genus *Clostridium*, as *C. piliforme*, on the basis of 16S RNA analysis. Tyzzer's disease has been described in a variety of domestic and wild species (57). An epizootic disease of muskrats, originally

Table 3. Number of incidents of yersiniosis in wild rodents and lagomorphs in Canada. The numbers refer to infection by *Yersinia pseudotuberculosis*, except for instances marked (*Y.e*) which refer to infection caused by *Y. enterocolitica*. Information is from the Canadian Cooperative Wildlife Health Center (CCWHC) database or from files of Canadian veterinary colleges prior to the establishment of CCWHC in 1992, unless otherwise noted

Species	Province/territory								
	BC	AB	SK	ON	QC	NB	PEI	NL	NT
Beaver	3	1 ^a	5	5 2 (<i>Y.e</i>)		1	1		
Muskrat		1 ^a	3 (<i>Y.e</i>)	1					
Snowshoe hare		1 ^a		2	1 (<i>Y.e</i>)	1		2	
Vancouver Island marmot ^b	1 ^c (<i>Y.e</i>)								
Brown lemming ^d									1 ^e

^a (55), ^b *Marmota vancouverensis*, ^c Ministry of Agriculture and Food, British Columbia, unpublished data, ^d *Lemmus trimucronatus*, ^e J. Blake (personal communication, 2007).

called “hemorrhagic disease” (58), is synonymous with Tyzzer’s disease (59,60). Tyzzer’s disease has been diagnosed in muskrats in Saskatchewan ($n = 6$), Ontario ($n = 10$), and Quebec ($n = 1$), and in snowshoe hares in Ontario ($n = 2$). The latter is the first record of the disease in snowshoe hares. Tyzzer’s disease has been diagnosed in wild-caught muskrats shortly after capture in Ontario (59), British Columbia (61) and Saskatchewan (Wobeser, unpublished data). Tyzzer’s disease occurs among animals stressed by poor environmental conditions (57) and the occurrence of disease in muskrats after capture may result from activation of a latent infection.

Discussion

Based on records available, tularemia, yersiniosis, and Tyzzer’s disease occur sporadically in wild rodents and lagomorphs across Canada, and plague may be enzootic in an area of Alberta and Saskatchewan and also may occur in parts of British Columbia. These diseases probably occur much more commonly than is indicated by the few wild animals that reach a diagnostic laboratory. Disease detection is difficult in wild animals, particularly in inconspicuous, solitary animals. Most rodents are cryptic and few are valued by the public, so that sick or dead rodents are seldom a cause for concern. Even a major epizootic in rodents may pass unnoticed, for instance, only 1 dead mouse was submitted for laboratory examination during a tularemia epizootic among deer mice in Saskatchewan (2). The covert nature of disease in these species is exemplified by the history of plague in Canada. An enzootic focus of *Y. pestis* infection was identified in southern Alberta and Saskatchewan about 70 years ago (12), and a recent serological survey confirmed presence of the agent in the same area (52), but plague has not been recognized in any species in the area. Beaver and muskrats comprise the majority of the rodents in which tularemia and yersiniosis have been diagnosed, likely because these furbearers are handled regularly by trappers. Rabbits and hares are relatively inconspicuous, but are hunted in most areas of Canada and are consumed by humans. Use of wild lagomorphs as food is likely less common than in the past and this may be reflected in the occurrence of tularemia in humans. Human cases of tularemia related to ‘rabbits’ were documented

primarily in the 1930’s and 1940’s, while muskrats were the predominant source of infection thereafter (17).

None of the diseases seems to have had a lasting effect on wild populations in Canada, although plague extirpated prairie dogs from areas of the USA (53). The major importance of *F. tularensis* and *Y. pestis* is the risk of human infection. Tularemia is an emerging and re-emerging disease of humans (45), but this is not apparent in Canada. Targeted surveillance, large samples, and sensitive detection methods would be needed to assess the actual extent of these diseases in Canada. This review may provide a baseline for assessing changes in distribution and occurrence of the diseases that might occur in association with environmental changes and shifting dynamics among humans, domestic animals, and wildlife.

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