RESEARCH ARTICLE

Widespread exposure to *Francisella tularensis* in *Rangifer tarandus* in Canada and Alaska

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Abstract

The range of tularemia, a disease caused by the bacterium *Francisella tularensis,* may expand alongside climate change in the North. Transmission occurs via biting arthropods, contaminated water sources, infected animal tissues and fluids and even aerosolized bacteria. Little research has been published on *F. tularensis* in northern Canada. We investigated whether *Rangifer* (caribou and reindeer) in Canada and Alaska are exposed to *F. tularensis,* as they provide significant cultural and subsistence value. From 2016 to 2020, 336 serum samples were collected from *Rangifer* across 17 herds, including captive reindeer in Alaska (n = 30) and wild caribou across Canada (n = 306) during collaring or harvesting efforts. Using a microagglutination test, we detected antibodies against *F. tularensis* in 7% of captive reindeer (CI_{95} 2–21), 6% of migratory tundra caribou (CI_{95} 4–11) and 10% of mountain woodland caribou (CI_{95} 6–17), with the highest seroprevalence observed in animals from Nunavut (17%) and British Columbia, Canada (18%). Ten of the herds (n = 10/17; 59%) had at least one positive animal. Evidence of exposure to *F. tularensis* indicates that further studies are needed to characterize sources of transmission for *Rangifer* species and any potential health effects following infection.

Keywords
Caribou; reindeer; tularemia; climate change; Arctic; zoonoses

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Abbreviations
ANOVA: analysis of variance
BC: British Columbia
cELISA: competitive enzyme linked immunosorbent assay
CI_{95}: 95% confidence level
MAT: microagglutination test

Introduction

Tularemia is a zoonotic disease caused by *Francisella tularensis*, a highly infectious Gram-negative coccobacillus that is found throughout the Northern Hemisphere (Petersen et al. 2009). Since it was first described, *F. tularensis* has been isolated in over 300 species, including mammals, birds, amphibians and invertebrates (Keim et al. 2007). Two subspecies have been identified in Canada and the US. Type A (subsp. *tularensis*) is the most virulent, generally associated with a terrestrial cycle of transmission and is found throughout North America (Sjostedt 2007). Alternatively, Type B (subsp. *holarctica*) is usually associated with aquatic environments and found in North America and other parts of the world, such as Australia, Japan and Europe (Jackson et al. 2012; Hansen & Dresvyannikova 2022; Fig. 1). In humans, manifestations of disease depend on the route of entry, with the most common presentation being ulceroglandular tularemia following the introduction of bacteria into the skin via an arthropod bite or while handling infected carcasses (Snowden & Simonsen 2022). This form is rarely fatal, whereas pneumonic tularemia, resulting from inhalation of aerosolized bacteria, can cause mortality in 30% of human cases if left untreated (Sjostedt 2007). Waterborne transmission is also possible, with most humans developing oropharyngeal tularemia following ingestion of contaminated water (Petersen et al. 2009; Hennebique et al. 2019). The bacteria are highly transmissible, with as little as 10 organisms causing disease in humans (Snowden & Simonsen 2022). Once inside the body, the organism rapidly multiplies and has an intracellular lifecycle, which enables it to evade a host's immune response (Sjostedt 2007).

Rodents and lagomorphs are maintenance hosts for *F. tularensis* and large mortality events occur in these animals during outbreaks (Kaysser et al. 2008; Gürcan 2014). In general, predators that scavenge or prey on

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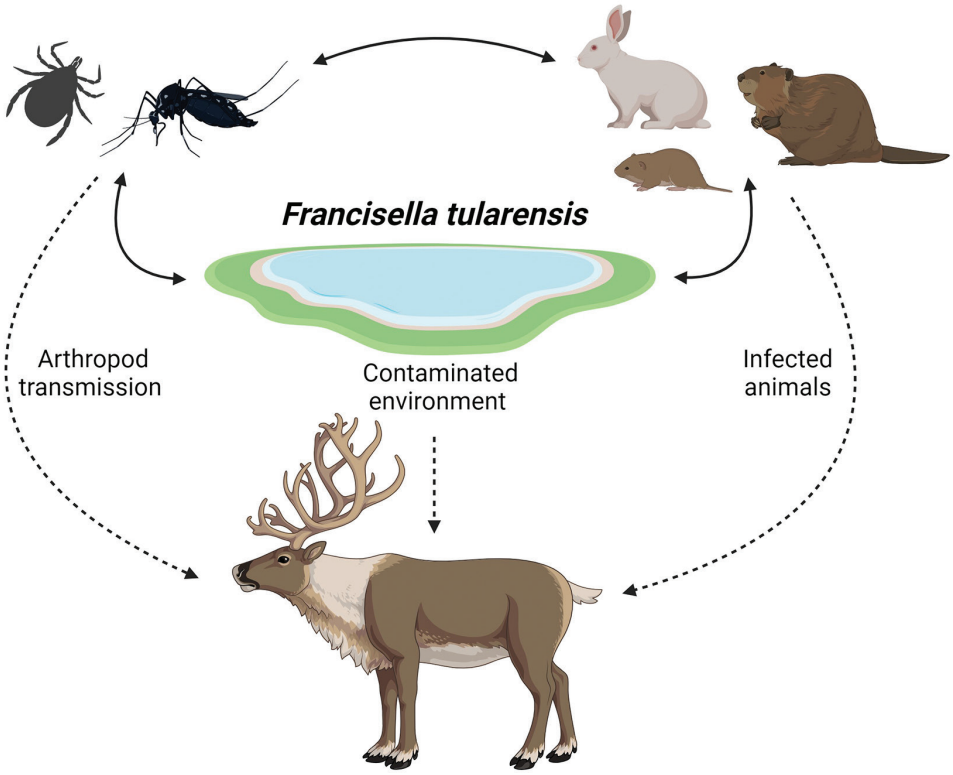

Fig. 1 Potential sources of *F. tularensis* transmission for *Rangifer* species. (Figure created with BioRender.)

these animals appear to be effective sentinels for *F. tularensis* (Hansen et al. 2011; Buhler et al. 2022). For example, two studies by Zarnke et al. (1987, 2004) found that higher exposure in wolves followed peaks in snowshoe hare (*Lepus americanus*) populations. Canids are thought to be relatively resistant to tularemia, though illness has been documented in hunting dogs with recent exposure to lagomorphs and lemmings that were *F. tularensis* positive (Foley & Nieto 2010; Nordstoga et al. 2014).

On rare occasions, cases of tularemia in humans have been traced back to deer carcasses (Emmons et al. 1976), highlighting that there is potential for exposure to this zoonotic pathogen while hunting and skinning cervid carcasses. However, most reports in northern wildlife are limited to rodents, lagomorphs, large predators or birds (Hansen et al. 2011). The handful of studies in northern ungulates report antibodies against *F. tularensis* in moose (*Alces alces*; 7%; n = 208; Quebec, Canada; Bourque & Higgins 1984), caribou (*Rangifer tarandus*; 6.5%; n = 46; east-central Brooks Range, Alaska; Smith et al. 2022), and red deer (*Cervus elaphus*; 12%; n = 60; Fennoscandia; Omland et al. 1977). Thus far, no reindeer from Fennoscandia have tested positive for antibodies against *F. tularensis* (Omland et al. 1977; Åsbakk et al. 1999).

Caribou and reindeer (*Rangifer tarandus*) are an abundant large herbivore in the circumpolar north and play a key role in northern ecosystems via their grazing effects on plant communities and the food resource that they provide (Mallory & Boyce 2018). Understanding the effects of emerging infectious diseases on the health and fecundity of this iconic northern species is of utmost importance, as some herds are declining (Vors & Boyce 2009; Hanke et al. 2021). Aggressive climate variability may contribute to range shifts and population fluctuations, which shines a spotlight on the need for further studies to characterize the relationship between *Rangifer* and climate sensitive diseases (Mallory & Boyce 2018). In this study, we determine if caribou and reindeer across Canada and Alaska have been exposed to *F. tularensis* and identify associations between exposure, ecotype and year to determine if differences in their habitat use influence transmission risk.

Methods

Sample collection

This study uses convenience sampling of sera collected from harvested animals and animals live-captured for collaring in BC (n = 56), Yukon (n = 147), Northwest

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Territories (n = 50) and Nunavut (n = 53; Fig. 2). In addition, sera were collected from a herd of 30 reindeer housed at the Large Animal Research Station (University of Alaska Fairbanks) for the purpose of a separate study (Buhler et al. n.d.). Samples were kept frozen until they were sent to the Western College of Veterinary Medicine (University of Saskatchewan, Canada) for testing. The number of animals sampled from each herd is listed in Table 1. It is important to observe that tundra caribou are seasonally migratory and the region/location of sample collection does not represent the full range of these herds (Fig. 2).

MAT assay to detect antibodies for F. tularensis

A MAT assay was used to detect IgM and IgG antibodies for *F. tularensis* in *Rangifer* serum samples (Sato et al. 1990). Arctic fox sera previously tested with the MAT were used as controls in each run, including a high positive control (1:1024), low positive control (1:128) and negative control. Briefly, 25 µl of microagglutination buffer (phosphate buffered saline with 1% normal rabbit serum and 0.4% formalin) was added to the wells of flat-bottom plates. Serum samples were serially diluted across each row by mixing 10 times and transferring 25 µl to the following well with a multichannel pipettor (including serial dilutions equivalent to 1:64, 1:128, 1:256, 1:512, 1:1024 and 1:2048). The remaining 25 µl from the final row was discarded. Next, 25 µl of antigen (formalin-killed *F. tularensis* cells) was added to the wells. Each plate was then covered with plastic wrap and incubated for 24 hours at room temperature in a sealed container. Titres ≥ 1:128 were considered positive.

Statistical analysis

The effects of year and ecotype for *F. tularensis* exposure in caribou were tested with generalized mixed-effect models with binomial distributions, incorporating herd as a random grouping factor. The year of sampling was included as fixed effects because we hypothesized that

Table 1 Results for antibodies against *Francisella tularensis* in *Rangifer* herds in Canada and Alaska.

Ecotype	Province or state	Herd name	Year	Seroprevalence (positive/tested)	CI_{95}[a]
Captive	Alaska	Large Animal Research Station	2020	7 (2/30)	2–21
Mountain	BC	Columbia North	2017	100 (1/1)	
woodland		Hart Ranges	2017	50 (1/2)	
			2020	22 (2/9)	6–55
		Little Rancheria	Unknown	0 (0/3)	
		North Cariboo	2020	25 (1/4)	
		Swan Lake	2020	18 (4/22)	7–39
		Tsenaglode	2020	7 (1/15)	1–30
	Yukon	Clear Creek	2018	3 (1/40)	0–13
		Heart River	2017	0 (0/5)	
			2018	8 (1/12)	2–35
			2019	17 (1/6)	3–56
		Ibex	2019	0 (0/8)	0–32
		Laberge	2019	0 (0/1)	
	Total			10 (13/128)	6–17
Migratory	Yukon	Forty Mile	2018	20 (1/5)	
tundra		Porcupine	2017	0 (0/29)	0–12
			2018	0 (0/21)	0–16
			2019	0 (0/20)	0–16
	Northwest Territories	Bluenose East	2018	7 (1/15)	1–30
		Beverly	2017	0 (0/4)	
			2018	0 (0/8)	0–32
		Bathurst	2017	0 (0/2)	
			2018	0 (0/11)	0–26
		Unassigned[b]	2017	0 (0/3)	
			2018	0 (0/7)	0–35
	Nunavut	Dolphin and Union	2018	20 (9/44)	11–35
			2019	0 (0/9)	0–30
	Total			6 (11/178)	4–11

[a]95% confidence level is indicated for >5 animals; [b]Unassigned animals are those for which the herd is not known.

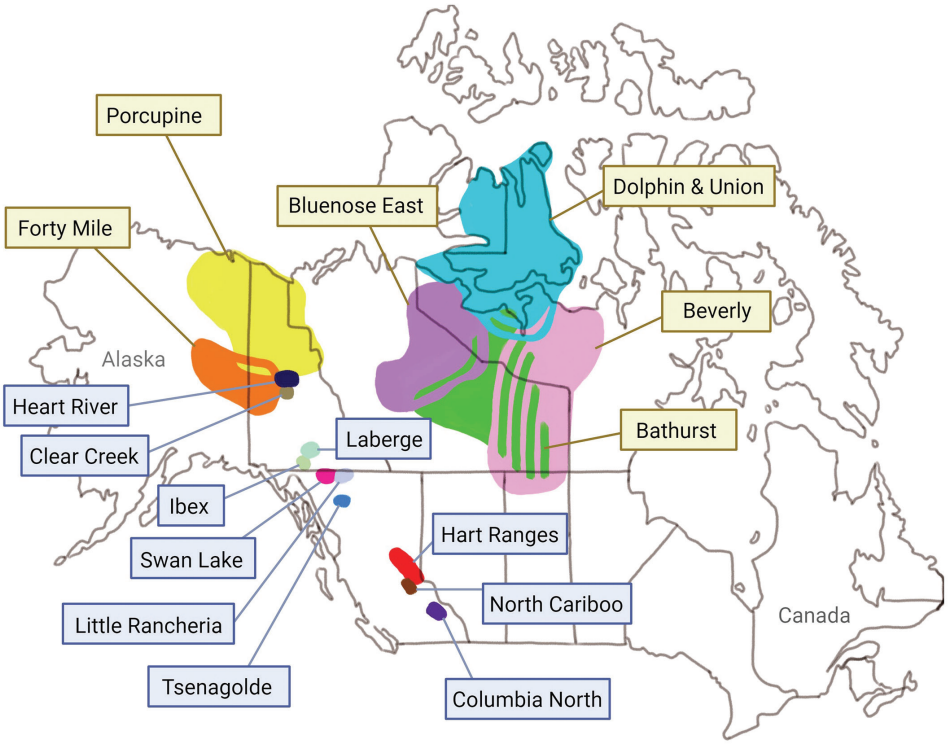

Fig. 2 Ranges of the caribou herds included in this study. Brown labels are herds that fall within the migratory tundra ecotype and blue labels are herds that fall within the mountain woodland ecotype. Overlapping ranges are indicated by stripped lines.

important annual fluctuations of *F. tularensis* exposure may occur (Kaysser et al. 2008) and we were interested in assessing this annual variability. No information on individual factors (sex and age) was available to assess them as predictors. Nested models were compared with each other and with a null model using ANOVA and likelihood ratio tests. To complement these analyses, we subsequently assessed differences in seropositivity rates between herds with a Fisher's exact test. Statistical analyses were performed with R software (R Core Team 2021, Vienna, Austria), and linear mixed models were fitted with the R lme4 package (Bates et al. 2016). The seroprevalence of *F. tularensis* antibodies in caribou and captive reindeer, along with 95% confidence intervals for a population proportion (CI_{95}), were calculated using EpiTools epidemiological calculators (Sergeant 2019).

Results

The highest overall seroprevalence of *F. tularensis* antibodies was found in caribou from BC (18%; CI_{95} 10–30) and Nunavut (17%; CI_{95} 9–29). Seroprevalence in other animals from Yukon and Northwest Territories ranged between 1 and 4% (Table 1). In addition, two animals in the captive reindeer herd at the University of Alaska Fairbanks had antibodies for *F. tularensis* (7%; CI_{95} 2–21). Within their ecotypes, 10% of the mountain woodland ecotype were exposed (CI_{95} 6–17) compared to 6% of the migratory tundra ecotype (CI_{95} 4–11). However, none of the variables tested in the mixed-effect models, including year and ecotype, showed statistical significance in the fitted models. In fact, none of the models incorporating year and ecotype as predictors demonstrated greater parsimony than the null model, suggesting that the explanatory power of these variables, at least in the context of this study, did not justify their inclusion as predictors. The differences in seropositivity rates across herds were found to be statistically significant using the Fisher's exact test ($p < 0.01$).

Discussion

This study documents widespread exposure to *F. tularensis* in caribou and captive reindeer across Canada and Alaska. When *Rangifer* were combined by ecotypes, seroprevalence was relatively similar across herds, ranging from 6 to 10% (Table 1, Fig. 2). This is consistent with other cervids that have been tested from more southern locations (Omland et al. 1977; Bourque & Higgins 1984) and a recent study identifying antibodies in 6.5% of caribou

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from the east-central Brooks Range, Alaska (Smith et al. 2022).

Seroprevalence in our study animals varied between herds. The Dolphin and Union Herd from Nunavut had the largest number of animals that were seropositive during our study. Interestingly, eight of the nine positive animals were sampled in 2018 (Table 1) and most of the positive animals identified in the Yukon and Northwest Territories were also sampled in 2018. This may be consistent with an outbreak documented in Arctic foxes on the mainland of Nunavut in 2018, where 44% of pups born in the spring developed antibodies for *F. tularensis* (Buhler et al. 2022). The Dolphin and Union Herd ranges on Victoria Island during the summer and the adjacent mainland during the winter (Hanke et al. 2021). Their wintering grounds are located north-west of Karrak Lake (Nunavut, Canada), where this tularemia outbreak was first documented (Buhler et al. 2022). Exposure in foxes from this region was associated with climate factors and rodent abundance, indicating that climate change will likely impact the distribution of this bacteria in northern Canada and that rodents (especially those associated with wetter habitats, such as voles) play an important role in transmission beyond the treeline. Indeed, across the circumpolar Arctic, rodents and lagomorphs exhibit cyclical population irruptions (Keith 1983). Mechanisms behind these cycles are thought to include predation, social interactions and dispersal, and effects of climate variability, which create ideal scenarios for tularemia outbreaks that might explain annual variations observed in our samples (Krebs et al. 2002). However, none of our explanatory variables (including year) were significantly associated with exposure. This may be due to convenience and unbalanced sampling, along with the limited sample size that was available for each herd during this study.

It is unclear how transmission may have occurred for caribou, though ingestion of contaminated water sources or grazing in areas contaminated with rodent/lagomorph carcasses may be a likely source (Fig. 1). Water-borne transmission following contamination with infected carcasses has been well documented and typically involves the subspecies *holarctica* (Forsman et al. 2000; Hennebique et al. 2019). It can remain viable in cold water (8°C) for at least 70 days (Forsman et al. 2000). *Francisella tularensis* DNA has also been documented in snow surrounding infected animal carcasses, which could suggest that transmission may be possible during the winter months (Schulze et al. 2016). Mosquito-borne transmission has been suggested in other polar regions and may represent a significant source of transmission for *Rangifer* species. Years with more mosquito activity have been linked with human outbreaks of tularemia in Fennoscandia (Abdellahoum et al. 2020). Ticks are also important for environmental persistence and transmission, though the species that are commonly reported as vectors (*Amblyomma americanum, Dermacentor andersoni, D. occidentalis* and *D. variabilis*) have little or no overlap with caribou ranges at this time (Zellner & Huntley 2019).

Warming temperatures in northern ecosystems have created ideal scenarios for the transmission of arthropod-borne pathogens, especially for *Rangifer* species, which experience significant harassment by insects during summer months (Mörschel & Klein 1997). Temperature sensitive changes observed with northern mosquitoes, such as increased survival due to faster development and earlier emergence, provides longer opportunities for transmission during and after the calving season, when *Rangifer* are more vulnerable and less mobile (Culler et al. 2015). In addition, caribou have been shown to adjust the timing of their migratory and reproductive behaviour in response to climate warming, which may create even more overlap with periods of arthropod activity (Mallory et al. 2020).

It is theorized that mosquitoes may obtain *F. tularensis* via both horizontal (directly from infected animals during blood meals) and vertical (transstadial and transovarial) routes of transmission; however, the vector competence of mosquito species in North America remains poorly understood (Abdellahoum et al. 2020). Larvae may also acquire bacteria from infected water, which suggests that water contamination and mosquito-borne transmission are closely linked (Abdellahoum et al. 2020; Triebenbach et al. 2010). *Francisella tularensis* is well known for its environmental resistance and transmissibility, given that as little as 10 organisms can cause disease in humans (Forsman et al. 2000; Snowden & Simonsen 2022). Thus, any exposure to infected water, vegetation or biting vectors may play a role in transmission to *Rangifer* species in Canada and Alaska.

The highest seroprevalence observed during this study was in animals from BC (Table 1). Most positive samples were from northern BC (Swan Lake and Tseneglode herds), but positives were also identified in southern caribou herds, suggesting a wide distribution of the pathogen. Though it is unknown if there were outbreaks of tularemia in rodents or predators during the time when caribou were sampled, we suggest that there may have been a lot of bacteria present in the environment during 2020 or years prior, when most of the positive animals from this province were sampled. It is difficult to draw conclusions due to the small sample size of animals from each herd along with the lack of information available for how long antibody production lasts following infection in cervids. A previous study found high antibody titres (generally > 1:512) in Arctic fox

pups exposed during the summer of their birth year, indicating that a high titre would likely accompany an animal that had been recently exposed (Buhler et al. 2022). Most caribou had a titre of 1:128, which would not suggest recent exposure. In addition, most of the free-ranging animals included in this study are seasonally migratory and are not necessarily present year-round within the province/territory where they were captured. We cannot determine where animals were exposed to the bacteria, as *F. tularensis* may be transmitted during each season; however, more sources of exposure are likely to be present during spring and summer months (insects and stagnant water).

The results for all animals from all provinces/states must be interpreted with caution, as false-positives can occur due to antigenic cross-reactivity with *Brucella suis* (Curry et al. 2011), a bacterium that occurs throughout North America and is associated with infertility and abortions in caribou. There have been no previous reports of *Brucella* in caribou from BC or in the captive reindeer herd at the University of Alaska Fairbanks, which suggests that the results on the MAT indicate true positives (Government of British Columbia n.d.). In addition, all *F. tularensis*-positive animals from the Bluenose East and the Dolphin and Union herds were negative for *Brucella* antibodies during government surveillance (cELISA conducted by Canadian Food Inspection Agency), providing further support for the MAT results. Cross-reactions are more frequently observed for agglutination titres in the range of 1:10–40, which is why the proposed cut-off titre of ≥1:128 outlined by World Health Organization guidelines was used in this study (Syrjälä et al. 1986; Tärnvik 2007). Cross-reactivity has also been observed between anti-*Francisella* IgG antibodies and *Yersinia* outer membrane proteins (Golkocheva-Markova et al. 2011). However, to our knowledge, infection with *Yersinia* has not been diagnosed in any of the herds included in this study.

Unfortunately, we were not able to identify the subspecies of *F. tularensis* involved with infection in *Rangifer*, as the MAT only determines whether animals have been previously exposed (antibodies). Little is known about the clinical presentation of tularemia in cervids, though its severity may also depend on how the infection is acquired (as seen with humans; Sjostedt 2007). In other species, such as rodents, the bacteria cause extensive histological changes to the liver and spleen due to the replication of the bacteria, while fluids such as blood and bloody urine may also contain bacteria (Conlan et al. 2003; Schulze et al. 2016). *Francisella tularensis* has been identified in the bone marrow of a mule deer, which indicates that the bacteria may be able to cause a systemic infection in cervids (Emmons et al. 1976). However, most of the antibody-positive animals that were identified during this study had low titres, which probably suggests that they had not been exposed recently at the time of sampling (winter) and that they had survived infection (Buhler et al. 2022). No information was available for the health status of these animals (signs of disease) and it is possible that the positive animals in our study only represent those that survived infection, which leaves many questions regarding the mortality and morbidity that can be attributed to tularemia in *Rangifer* species.

Conclusion

In conclusion, we identified widespread exposure to *F. tularensis* in *Rangifer* across Canada and Alaska, with the highest seroprevalence observed in animals from BC and Nunavut. *Rangifer* species are essential for economic security, food security and indigenous culture in Arctic and Subarctic regions (Hanke et al. 2021). Future studies could focus sampling efforts during summer months, when transmission is more likely because of insect activity, exposed deceased maintenance hosts as snow diminishes, and more stagnant water sources (Buhler et al. 2022). Our findings are consistent with other reports of tularemia outbreaks in Nunavut during 2018 (Buhler et al. 2022) and highlight the need for further studies to determine sources of transmission for cervids and whether there are health effects after infection for circumpolar *Rangifer* species.

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Ethics and research approval

Reindeer samples from Alaska were collected under the University of Alaska Fairbanks Institutional Animal Care and Use Committee-approved protocols 1552224-2, 1654054-5 and 1654058-3. BC caribou samples were collected under Wildlife Act permits (FJ14-93094, FJ18-421458, FJ19-426636, FJ21-618702 and PG17-284065). Yukon caribou samples were also collected under the Wildlife Act (exemption for Yukon Government staff) and protocols were approved by the Yukon Government Wildlife Care Committee. Samples from Northwest Territories were collected under Wildlife Care Committee numbers NWT-WCC-2017-009 and NWT-WCC-2018-002. All animal use adhered to the Canadian Council on Animal Care guidelines for humane animal use (https://ccac.ca/en/standards/guidelines/).

Disclosure statement

The authors report no conflict of interest.

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