SCIENTIFIC SECTION

Review Article

Tularemia in Canada with a focus on Saskatchewan

TOM MARTIN,* MA
IAN H. HOLMES,† MD, FRCP[C]
GARY A. WOBESER,‡ DVM, PH D
RENE F. ANTHONY,§ MB, BS, FRCS
INEKE GREEFKES,‖ ART

Although rare among humans in Canada, tularemia is often endemic in wildlife. The inhabitants of rural areas are especially likely to be exposed to the causative bacterium, *Francisella tularensis*, through trapping or through the bites of arthropods. Muskrats have replaced rabbits as the principal source of infection, as illustrated by a familial outbreak of oropharyngeal tularemia in Saskatchewan. In humans the disease has six distinct forms and can be asymptomatic, but it generally comes to medical attention as fever, persistent ulcers and enlarged lymph nodes. Serologic tests will confirm the diagnosis.

Bien que la tularémie soit rare chez l'homme au Canada, elle existe souvent à l'état endémique parmi les animaux sauvages. Les habitants des régions rurales sont particulièrement susceptibles d'être exposés à l'agent étiologique, *Francisella tularensis*, lors du trappage ou par les morsures d'arthropodes. Le rat musqué a maintenant remplacé le lapin comme principale source d'infection, tel que l'illustre une poussée de tularémie oropharyngienne chez une famille de Saskatchewan. Chez l'humain la maladie prend six formes distinctes, et elle peut être asymptomatique, mais elle se présente généralement à l'attention du médecin comme une fièvre accompagnée d'ulcères persistants et d'une tuméfaction ganglionnaire. Les épreuves sérologiques confirment le diagnostic.

Tularemia is an infectious disease of animals that may be transmitted to humans. The etiologic agent, *Francisella tularensis* (formerly *Pasteurella tularensis*), is an aerobic gram-negative bacterium that occurs in both coccal and bacillary forms. It has been isolated from many kinds of mammals and birds, some arthropods, mud and water.[1-6] The two varieties of the species, *F. tularensis* var. *tularensis* (type A) and *F. tularensis* var. *palaearctica* (type B), both occur on this continent, and the severity of disease they produce in humans differs, type A being the more virulent.[7]

In the early part of this century Canadians usually acquired tularemia from the rabbit. Since the '50s, however, the muskrat has become the main source of the infection. Similarly, most of the recent human cases in Saskatchewan have resulted from contact with infected muskrats.

Tularemia in humans was originally classified by Francis[8] and Foshay[9] into four clinical types, and two others have since been added.[10-12] Their main characteristics are summarized in Table I. Streptomycin is now recognized as the drug of choice for treatment, as it

Table I—Characteristics of the various types of tularemia

All clinical types	
Exposure to animals, especially muskrats, rabbits, ticks or biting flies. Fever (often persistent), with or without chills, headache, malaise and myalgia	
Ulceroglandular type	**Pneumonic type**
Persistent ulcer or paronychia following cut on finger or hand Enlargement of regional lymph nodes (usually axillary) Ulcer and lymphadenitis often in groin in tick-borne disease Chronic granulomatous inflammation of lymph nodes, with occasional multinucleated giant cells	Pulmonary involvement in 50% of typhoidal tularemia and in 12% of ulceroglandular cases In chest roentgenograms: • Common: bronchopneumonia hilar adenopathy • Less common: pleural effusion consolidation apical infiltrate oval density
Glandular type	**Oculoglandular type**
Similar to ulceroglandular type but without primary lesion Usually involvement of axillary or epitrochlear lymph nodes	Primary lesion conjunctivitis, with swelling of eyelids Regional lymph nodes tender and enlarged
Typhoidal type	**Oropharyngeal type**
Presents as fever of unknown origin Should be especially considered in the following: • Hunting and trapping seasons • Aboriginal population • Persons residing or working in rural areas	Persistent fever, pharyngitis and/or tonsillitis, and cervical adenitis Cultures negative for group A streptococci and *Corynebacterium diphtheriae* Commonly grey or white diphtheritic-type tonsillar or nasal membranes, occasionally ulcers and hyperemia of pharynx, tonsil, uvula or soft palate without membranes, and sometimes earache and purulent exudate May follow the drinking of unboiled lake or stream water or eating of improperly cooked rabbit or muskrat

From the departments of *microbiology, †medicine and ‡veterinary pathology, University of Saskatchewan, Saskatoon, §the Nipawin Medical Group, Nipawin, Sask. and ‖the department of clinical microbiology, University Hospital, Saskatoon

Reprint requests to: Mr. Tom Martin, Department of clinical microbiology, University Hospital, Saskatoon, Sask. S7N 0X0

results in fewer relapses than treatment with either tetracycline or chloramphenicol.[13]

Tularemia in humans

Saskatchewan cases

From a review of the literature concerning tularemia in Saskatchewan, a search of Statistics Canada's annual reports of notifiable diseases, and communication with physicians, nurses, microbiologists and epidemiologists we learned of 7 cases of the disease reported in 1956,[14] and found records of 17 others, 1 of them fatal, that occurred from 1956 to 1981. Over half of these 17 cases were diagnosed in 1980 or early 1981.

At University Hospital in Saskatoon, tube agglutination tests had been performed and read by Snyder's method,[15] using *F. tularensis* antigen suspension (Difco Laboratories, Detroit). The tubes were incubated at 37°C overnight, and the serum was tested in parallel dilutions with *Brucella abortus* antigen. Our review of the test results for the period 1971 through 1981 and those of the provincial laboratories in Regina for 1980 led us to examine the clinical and epidemiologic findings in each of 11 patients' medical records. Their titres for *F. tularensis* agglutinins ranged from 1:80 to 1:2560.

One outbreak of oropharyngeal tularemia in a family from Cumberland House, Sask. is especially noteworthy. All four members of the family had significant levels of the agglutinins in their serum, but one of them remained free of symptoms. They had shared a meal of smoked muskrat meat after working their trap line. The three symptomatic members all had fever, headache, furry tongue and pharyngitis; other problems included right-sided cervical adenitis and a lump under the left arm in the father, a pimple-like rash in the mother, and nausea, diarrhea and weakness in the 8-year-old boy. The daughter, pregnant at the time, complained of headache and dizziness, but had no fever, pharyngitis or lymphadenitis. The first three members were treated successfully with streptomycin.

A number of other outbreaks of oropharyngeal tularemia within families have followed the ingestion of rabbit meat,[16,17] and in at least one case the organism was probably carried to the mouth on the patient's own fingers.[18] Oropharyngeal tularemia related to drinking contaminated water has been reported from Russia and North America.[11,19]

Tularemia in Canadians

The first recorded case of tularemia in a Canadian occurred in 1929,[20] and over the next 50 years there were another 290 recorded by Statistics Canada (formerly the Dominion Bureau of Statistics) in its annual reports of notifiable diseases. Although tularemia may seem rare in this country, probably a great many cases are not detected simply because they are mild. Furthermore, not all physicians are familiar with the various clinical forms of tularemia.

Of 84 Canadian cases in which the clinical form of the disease was either reported or may be deduced from the description,[7,14,20-45] only 47% were of the ulceroglandular type. In the United States, by contrast, this type accounts for some 85% of tularemia cases.[8,9] Another 30% of the Canadian cases were typhoidal or pneumonic; most of these were found by Millar[40] among the aboriginal population of northwestern Ontario. These two types of tularemia are particularly difficult to diagnose.

Greenberg and associates[46] in 1957 reported low serum levels of *F. tularensis* agglutinins in 9% of Canadian Indians in southern Saskatchewan and detectable levels in 29% in the James Bay area of Ontario. Only a few years before, Wood[38] had reported titres varying from 1:25 to 1:1600 in 11.7% of agglutination tests on 2940 serum samples from Indians in northwestern Ontario and Manitoba. North of the 53rd parallel this proportion rose to 22.6%. These titres were found in spite of the apparent absence of clinical disease. To explain this, Wood pointed to the remoteness from medical services of the areas of highest incidence and the relative mildness of the disease there. Some of the cases he studied may well have been caused by the type B strain of the bacterium.

Animal sources

Of 73 cases across Canada in which the source of the infection was known, rabbits were involved in 29 (40%) and muskrats in 22 (30%), but almost all of the disease derived from rabbits occurred in the '30s and '40s; in the last three decades the muskrat has been the principal source of infection.

The Western College of Veterinary Medicine, Saskatoon, has isolated *F. tularensis* from a small number of beavers and ground squirrels, as well as muskrats that were trapped in central Saskatchewan — an area coinciding with the distribution of human cases over the last 50 years (Fig. 1).

F. tularensis was isolated from animal tissues either by inoculation directly onto cystine–heart agar or by inoculation of guinea pigs, with subsequent isolation of the organism on a cystine-enriched medium. The bacteria were identified by their morphologic features in Gram-stained smears, their failure to grow on media lacking cystine and their agglutination with commercial antiserum.

In view of the prominence of the muskrat in this disease it is surprising that no *F. tularensis* agglutinins were found in the serum of 123 muskrats live-trapped at Pike Lake, Sask. in 1977. One of four mink caught by accident, however, did have the agglutinins.

F. tularensis has been isolated from a variety of other warm-blooded animals and arthropods.[47,48] Among those implicated in human infections in Canada have been farm and zoo animals, cats, red squirrels, coyotes, grouse, ticks and deer flies.[7,22,30,31,33-35,41,49] Bruce[50] has reported serologic evidence of tularemia in Alberta ground squirrels; the disease seems to be endemic in these animals.

In 1978 an outbreak in a monkey colony at a Winnipeg zoo killed several of the animals and resulted in ulceroglandular tularemia in a veterinarian who was bitten by the surviving monkey.[7] The discovery of *F. tularensis* in ground squirrels and their fleas around the

monkey cages suggests the probable source and route of the animals' infections.

Laboratory diagnosis

The tube agglutination test for *F. tularensis* is reliable under controlled conditions if interpreted correctly.[9,15] It should be performed whenever tularemia is suspected, even though the appearance of detectable antibody levels may be delayed for as much as one month. Serum samples should be tested weekly until a significant titre is found. Ideally, at least a fourfold rise in titre between the acute and convalescent stages should be demonstrated. Foshay,[9] however, accepted a titre of 1:80 or greater as a good diagnostic guide provided the *Brucella* agglutination test had a negative result. The serum of some patients with tularemia will show low-level cross-agglutination with suspensions of *B. abortus* or *Proteus* OX-19.

Gram-staining of clinical material is not particularly helpful, though culture of *F. tularensis* from selected specimens may be attempted in laboratories with efficient biohazard hoods. The use of experimental animals to isolate the organism is very hazardous.

Table II lists the clinical specimens that are appropriate for the isolation of *F. tularensis*. Attempts at isolation from blood rarely succeed. Cystine–glucose–blood agar is the classic medium for this organism, but chocolate blood agar enriched with cystine or cysteine-containing supplements has also been used successfully.[51] Selective media are required for specimens from body sites with normal flora. Thayer–Martin medium, as used for isolating gonococci, may prove to be useful and convenient.[52] Plate cultures are incubated aerobically at 35° to 37°C until growth appears, or for 5 days.

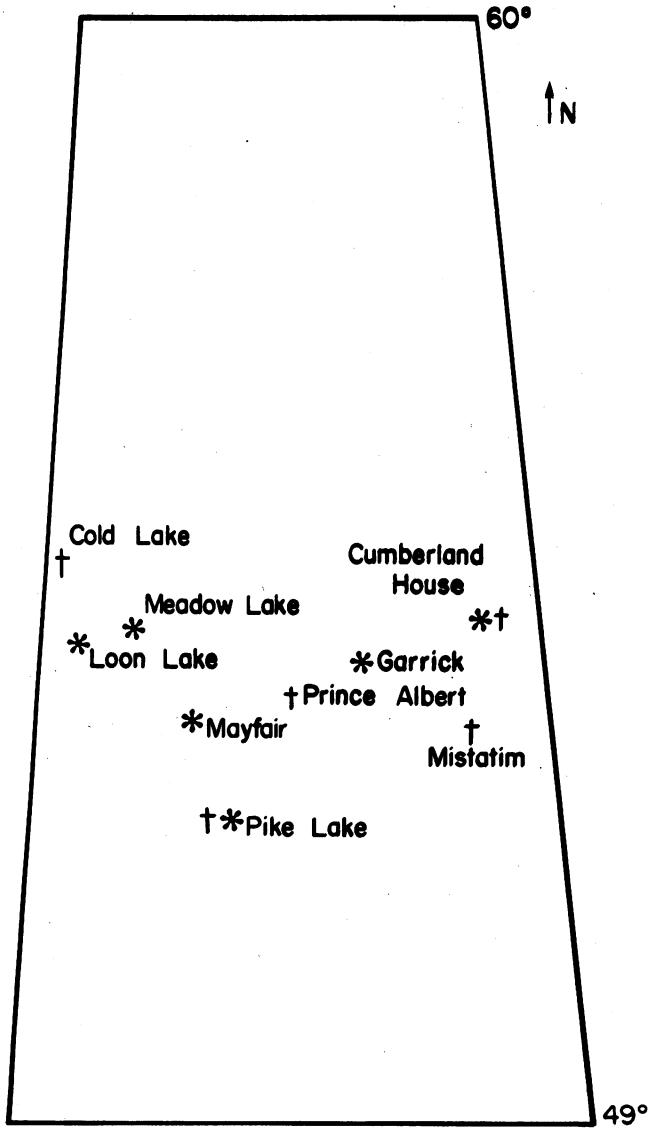

FIG. 1—Distribution of *human and †animal cases of tularemia in Saskatchewan.

Table II—Appropriate specimens for isolation of *Francisella tularensis*

Clinical type of tularemia	Specimen
Ulceroglandular/glandular	Lymph node aspirate Paronychial swab
Oculoglandular	Conjunctival scrapings
Pneumonic/typhoidal	Sputum Nasopharyngeal swab Pleural fluid
Oropharyngeal	Throat and tonsil swab Nasopharyngeal swab

Conclusion

When tularemia is suspected on clinical and epidemiologic grounds the diagnosis is readily confirmed in the laboratory by the tube agglutination test. Physicians should keep this disease in mind when faced with fever of unknown origin, atypical pneumonia, suspected tuberculosis, lymphadenitis, conjunctivitis or pharyngitis in patients, particularly those of rural or aboriginal populations, who have had recent zoonotic exposure.

Although the muskrat is now the most common source of human tularemia in Canada, the bacteria can be acquired from a variety of animals through even a slight break in the skin or by ingestion of either infected meat or contaminated water.

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