Fascinating Life Sciences

Charles E. Rupprecht *Editor*

History of Rabies in the Americas: From the Pre-Columbian to the Present, Volume II

Historical Introductions and Disease Status To Date

Springer

Fascinating Life Sciences

This interdisciplinary series brings together the most essential and captivating topics in the life sciences. They range from the plant sciences to zoology, from the microbiome to macrobiome, and from basic biology to biotechnology. The series not only highlights fascinating research; it also discusses major challenges associated with the life sciences and related disciplines and outlines future research directions. Individual volumes provide in-depth information, are richly illustrated with photographs, illustrations, and maps, and feature suggestions for further reading or glossaries where appropriate.

Interested researchers in all areas of the life sciences, as well as biology enthusiasts, will find the series' interdisciplinary focus and highly readable volumes especially appealing.

Charles E. Rupprecht
Editor

History of Rabies in the Americas: From the Pre-Columbian to the Present, Volume II

Historical Introductions and Disease Status To Date

Springer

Editor
Charles E. Rupprecht
Auburn University
College of Forestry Wildlife, and Environment
Auburn, AL, USA

ISSN 2509-6745 ISSN 2509-6753 (electronic)
Fascinating Life Sciences
ISBN 978-3-031-25404-8 ISBN 978-3-031-25405-5 (eBook)
https://doi.org/10.1007/978-3-031-25405-5

This Springer imprint is published by the. registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Paper in this product is recyclable.

Among the many representations of animals in pre-Columbian cultures, the dog and vampire bat stand out for their symbolic relationship with death. Both animals have deep roots in the different Mesoamerican cultures, represented with figures such as the xoloitzcuintle and camazotz. They are also associated with culture, education, and public health efforts to control rabies in Mexico. Xoloitzcuintle was respected for being a gift from the god Xólotl to guide the souls of the deceased who traveled to Mictlán or the underworld [1]. The cult of Camazotz in Mesoamerica began among the Zapotecs around the year 100 BC, as a character from Mesoamerican mythology, considered by some as a bat god of the Aztecs and Mayans. The Camazotz myth may have been spread due to the historical appreciation of vampire bats reaching Mesoamerica and Brazil [2]. This combined image is an iconographic representation made by the graphic designer Ma. Luisa L. Sierra, in which she presents both animals in their most characteristic ceremonial forms, as a framework of their presence in ancient cultures and current traditions in Mexico. Thanks to Dr. Luis Leucona and to the artist for their contribution in this context.

References

1. Solis-Guadarrama R. Xoloitzcuintle: historia del perro Y joya Azteca campus, Creatividad. 28 De Noviembre DE 2018. https://capitel.humanitas.edu.mx/xoloitzcuintle-historia-del-perro-y-joya-azteca/
2. Cazador de leyendas. Vampiros prehispánicos: CAMAZOTS. arreint.blogspot.com. 30 DE JULIO DE 2013. Cazador de leyendas: Vampiros prehispánicos: CAMAZOTS (arreint.blogspot.com)

Foreword

Due credit for this book, the *History of Rabies in the Americas: From the Pre-Columbian to the Present, Volume II*, is to the iconoclastic Professor Charles Rupprecht, for having the insight and vision to assimilate this edition to preserve our historical knowledge of rabies before it is lost for entirety. Tragically, the tacit knowledge and experience of many world-renowned rabies researchers is lost when those individuals leave this sublunary abode for pastures new. The preservation of their achievements and their contributions towards the elimination of sylvatic and dog-mediated human rabies should therefore be safeguarded for posterity. In this fashion, the failures will not be repeated, and the lessons learnt from them will be understood and managed successfully by the next generation of international rabies researchers. In a similar way, great successes and showcases will be celebrated globally. This sentiment seems more relevant than ever, as we move ever closer to the 'Rabies-by-2030' goal for the elimination of dog-mediated human rabies. The historical events leading to this vision in providing the tools and knowledge necessary have included the following: surveillance of rabies in wildlife and companion animals, epidemiology, the laboratory-based diagnosis of rabies to international standards, immunity to rabies, intervention strategies through the control of rabies in wildlife using oral vaccination, the control of rabies in dogs using parenteral vaccination and the public health management of humans at risk, clinical activities, pathogenesis, and the prophylaxis and therapy of human rabies.

The 'Zero Rabies-by-2030' (ZBT) goal for the elimination of dog-mediated human rabies appears unachievable on a global scale. However, the ambitions of the international rabies community to operate in a collegial manner towards this goal will still mean that the burden of rabies in many countries will be reduced, which is a success. The Pan American Health Organization has paved the way in showing how by working together in an operational manner, underpinned by a clear strategy, dog-mediated rabies can be eliminated with the concomitant reduction of human rabies. Interestingly, the innovators of oral rabies vaccination of wildlife faced a similar challenge when it was first attempted. History has proved them right in demonstrating how logistical management strategies will be successful if considered

within well-thought-out research and development programs supported with empirical data.

Rabies is a disease of antiquity and remains one of the oldest infectious diseases known to mankind. The history of medicine cannot be communicated without discussing the advances in rabies vaccination made by Louis Pasteur and his European colleagues, and their influence on the many seminal discoveries of others made throughout the world in following years. Early accounts of rabies from different parts of the Old World are available in multitude; the first text describing aggression in dogs and the fatal outcome in men when bitten is the pre-Mosaic Eshnunna Code of Babylon in the twenty-third century BC. For many diseases, there is minimal disagreement that they were emphatically introduced into the New World from the Old World. In the sixteenth century, dog rabies was widespread across Europe and especially in Spain, and the conquistadors and early explorers would have been familiar with rabies in dogs and humans.

How, when, and where rabies originated in the New World is unclear, and it remains unknown if rabies already occurred in the Americas during pre-Columbian times. With the colonization of the New World, Europeans also introduced Old World diseases, including smallpox, measles, and typhus. However, the first written reports on rabies cases in the Americas did not appear until the first decade of the eighteenth century from Mexico. There is no direct evidence that rabies was known in pre-Columbian Central America, but researchers are convinced that (bat) rabies was already present in these early times, especially as there was an abundance of potential wildlife reservoirs among bats and mesocarnivores. Rabies virus may have been circulating undetected in American bat populations long before the virus was identified. Few surviving records from indigenous peoples relate to infectious diseases and appreciation of their manifestations may have been attributed to supernatural forces. However, the genetic makeup of the native domestic dogs was unique, and these canine populations were much smaller and more fragmented than in the Old World. Whatever its appearance, the face of this disease began to change dramatically after the sixteenth century. The Columbian Exchange provided substantive environmental alterations and the importation of domestic animals, notably European dogs and livestock. Therefore, the spread of rabies in the New World was predominantly a result of the importation of rabies virus-infected animals from the Old World and subsequent sustained transmission in local dog and wild carnivore populations. Within two centuries of European colonization, reports of rabies appeared. British, Dutch, French, Portuguese, Russian, Spanish, and other colonial powers all contributed to the introduction and exacerbation of rabies. By the nineteenth century, nearly all parts of the Americas reported cases of rabies in dogs, humans, and wildlife. The broader appreciation of rabies in vampires and other bats only occurred during the twentieth century. Beyond epidemiological occurrence, the history of rabies in this region is important, based upon the fundamental scientific contributions in viral diagnosis, pathogenesis, and management. Moreover, the global goal of the elimination of human rabies mediated via dogs by 2030 has been met throughout the New World, not only in North America, but increasingly by low- and middle-income countries in Central and South America and the Caribbean.

There are three major issues that set rabies apart from other infectious diseases. Firstly, rabies remains the exemplar of One Health with the need to bring together the disparate groups of veterinary and human medicine with ecologists and environmentalists to develop successful intervention strategies. Secondly, rabies remains one of the few authentic zoonoses for which control of the disease must be undertaken by veterinary and animal health practitioners in the animal reservoirs at the source. Finally, with a small number of debatable exceptions, rabies is the only disease that has a 100% fatality rate once clinical symptoms in humans are observed.

Discussing the historical events of rabies with those experts that have worked in this field for longer than myself provides new and innovative insights into the disease. In mapping the history of rabies, as achieved by Professor Rupprecht and his colleagues, it means that we can have a better understanding of how we go forward in developing the future roadmap for rabies prevention and control in animal reservoirs and in humans. This volume recounts the personal history of individuals involved in the study of rabies during the twentieth century, within the context of its introduction over hundreds of years. Continued progress in the prevention, control, and elimination of this zoonosis in humans, domestic animals, and wildlife serves as a practical testament to enzootic countries in Africa and Asia that there is much to be learned and emulated from the New World towards meeting the 'ZBT' goal. The history lessons should always recap the inspiring stories that will influence the creative thinking of the next generation of rabies scholars. In reflecting further on this volume, optimism remains that the elimination of dog-mediated human rabies will follow the global successes of smallpox and rinderpest and will be included in the history books as the first zoonotic disease that has been eliminated from the human population as an exemplar to the international public health community. Sustainable national and regional programs remain the pivotal strategy for rabies management underpinned with political will and advocacy. In this context, there are additional fundamental questions that need to be answered to further our understanding and resolve the 'black boxes' in our medical and veterinary knowledge of this intriguing disease. In furthering Pasteur's legacy, Professor Rupprecht and his colleagues are to be congratulated for reminding all of us that history is critical as a dual teacher regarding both fancy and folly, and importantly what may be accomplished by working together on a fundamental disease of nature in a united One Health context.

Anthony R. Fooks
Animal and Plant Health Agency
Weybridge, UK
October 2023

Preface

> "*…At the close of day, the vampires leave the hollow of the trees, whither they had fled at the morning's dawn, and scour along the river's banks in quest of prey. On waking from sleep, the astonished traveler finds his hammock all stained with blood. It is the vampire that hath sucked him. Not man alone, but every unprotected animal, is exposed to his depredations; and so gently does this nocturnal surgeon draw the blood, that instead of being roused, the patient is lulled into a still profounder sleep…*"

Charles Waterton
Wanderings in South America, the north-west of the United States, and the Antilles, in the years 1812, 1816, 1820, and 1824: with original instructions for the perfect preservation of birds &c. for Cabinets of Natural History, 1825, London

This second volume of "History of Rabies in the Americas" transits naturally from the first volume's topical nature and focuses explicitly upon time and space and things, critical epidemiological facets that are intrinsic to a basic understanding of this ancient zoonosis in the Western Hemisphere. In retrospect, it is almost unimaginable to ponder a period when this landmass was uninhabited. Regardless, a plethora of other mammals (e.g., bats, coati, coyotes, foxes, raccoons, skunks, etc.) presided as basic raw materials for a cornucopia of pathogens. Was rabies present as well? Heretically, some of us believe so, as a quintessential disease of nature, but differing significantly to later extent and complexion! The rise of the Isthmus of Panama and formation of Beringia were two notable events supporting the peopling of a vast, united continent. With waves of *Homo sapiens* also came along unique lines of dogs. For tens of thousands of years, humans, a few domesticated animals, and diverse wildlife intermingled, but any potential appreciation of this acute, progressive, viral encephalitis was scant, likely imbued if at all within a religious perception of the world's maladies. Things forever changed during the Age of Discovery in the fifteenth century and the accidental discovery of the "Mundus Novus." Many European powers engaged prominently for their claim to the New World, including the British, Danish, Dutch, French, Spanish, and Portuguese. The aftermath of first contact with indigenous peoples and places resulted

in an anthropological multiplicity of exploration, conquest, exploitation, colonization, enslavement, genocide, terraforming, revolution, decolonization, enculturation, gradual geopolitical reconciliations, and evolving partial reparations. Besides Europeans themselves, three other translocated species had substantive impacts in the New World, as regards rabies (Figs. 1, 2, and 3). European dogs replaced indigenous breeds and introduced a cosmopolitan rabies virus, with significant public health repercussions to date. Mongoose were thought to be a solution for snakes in sugarcane plantations, but instead had disastrous consequences for native fauna and served as eventual reservoirs in the Caribbean. Old World livestock became an ecological substitute of extinct, large-bodied grazers of the Pleistocene and resourceful fodder for hematophagous vampire bats, in fact and fiction. Several hundred years passed after the colonization die were cast before rabies was recognized inarguably in the Neo-colonies. The disease has been present ever since, as has substantive scientific progress in understanding,

Fig. 1 Las resultas, etching by Goya. (Los Desastres de la Guerra, Madrid, 1863)

Fig. 2 Hydrophobia as skeleton led by a mad dog. (Homer Davenport, 1867–1912)

Fig. 3 The Mongoose. (Oliver Herford, 1863–1935)

surveillance, prevention, and control. I do hope that this collective piece will please the many thoughtful contributors that reflected upon their relatively recent past in their own words, so influenced by the Columbian exchange to date, and may prove interesting to those infectious disease connoisseurs the world over, that what happened yesterday impacts today, and influences a bonanza of tomorrows.

EX AUXILIO FAMILIAE MEAE

Lawrenceville, GA, USA
30 June 2023

Charles E. Rupprecht

Contents

From Invasion to Innovation – A History of Rabies and Its Management in Canada 1
Rowland R. Tinline, Joanne Tataryn, and Christine Fehlner-Gardiner

History of Rabies in the United States 27
April D. Davis, Sharon Messenger, and Susan M. Moore

History of Rabies in Mexico 79
Verónica Gutierrez-Cedillo, Fernando Vargas-Pino, Ignacio Antonio Chavez-Flores, and Luis Lecuona

A History of Paralytic Bovine Rabies Transmitted by Vampire Bats in Mexico 99
Elizabeth Loza-Rubio and Juan Antonio Montaño-Hirose

Rabies in Central America: An Historical Review 113
Bernal León and David Moran

Origins and Contemporary Epidemiology of Rabies in the Insular Caribbean 133
Janine F. R. Seetahal, Max Francois Millien, Are Berentsen, Sonia Cheetham, Miguel S. Núñez-Novas, Kirk Douglas, Jusayma Gonzales, and Charles E. Rupprecht

History of Rabies in Colombia 173
N. M. Cediel-Becerra, D. Angulo-Mora, A. M. Olaya-Medellín, I. Rodríguez, M. C. Pardo, L. J. Polo-Terán, and L. C. Villamil-Jiménez

History of Rabies in Ecuador 195
Andrés Flores, María Gabriela Dávila, Cecilia Paredes, and Natalia Romero-Sandoval

The History of Rabies in Peru 215
Sergio E. Recuenco

Historical Review of Rabies in Chile: A Canine Rabies Virus-Free Country 229
P. Verónica Yung

The History of Rabies in Venezuela 241
Mercedes Pérez Sarrameda and Sergio E. Recuenco

Rabies in the Guiana Shield 257
A. Picaut-Plat, F. Djossou, L. Epelboin, D. Hartley, A. A. Kpangon, B. Roman-Laverdure, J. Seetahal, B. de Thoisy, A. Vansauers, and A. Lavergne

The History of Rabies in Bolivia 271
F. A. Villegas Anze

History of Rabies in Paraguay 303
Maria C. San Miguel de Vera and Lara Lujan Vera San Miguel

Rabies in Uruguay: An Historical Review 321
Helena Guarino and Leticia Luengo

Rabies in Brazil 341
Jane Megid, Ivanete Kotait, Camila Michele Appolinário, and Maria Luiza Carrieri

History of Rabies in Argentina and the First Human Vaccination in Latin America 367
Carlos Adolfo Palacios, Fernando J. Beltran, Oscar Perez, Horacio A. Delpietro, Natalia Casas, and Daniel M. Cisterna

Index 417

From Invasion to Innovation – A History of Rabies and Its Management in Canada

Rowland R. Tinline, Joanne Tataryn, and Christine Fehlner-Gardiner

Introduction – The Country

Canada is the northernmost country in the Americas, and with a territory of almost 10 million square kilometers, also the largest. Consisting of ten provinces and three northern territories, Canada is bordered to the west, north and east by oceans and to the south and northwest by the United States (Fig. 1).

As this chapter will describe, the spatial distribution of the primary rabies virus vectors and related viral variants in Canada reflects the seven major physiographic regions, based on topography and geology, that form the country [1]. As shown in Fig. 1, six of those regions lie in north-south bands from the west to the east coast, whereas the seventh region, the Arctic Lands, covers most of the islands north of the Canadian mainland. For convenience, in this chapter, we use the term "arctic" to refer to the three northern territories, northern Quebec, Labrador and the Arctic Lands. Superimposed on this pattern are climate zones grading from south to north which, in combination with physiography, result in vegetative zones that range from cropland in the south through mixed forest, boreal forest to tundra in the arctic. The exception is the Cordillera region, where vegetative regions follow the south-north orientation of the Coastal and Rocky Mountain ranges.

R. R. Tinline
Queen's University, Kingston, ON, Canada

J. Tataryn
Public Health Agency of Canada, Saskatoon, SK, Canada

C. Fehlner-Gardiner (✉)
Canadian Food Inspection Agency, Ottawa, ON, Canada
e-mail: Christine.Fehlner-Gardiner@inspection.gc.ca

C. E. Rupprecht (ed.), *History of Rabies in the Americas: From the Pre-Columbian to the Present, Volume II*, Fascinating Life Sciences,
https://doi.org/10.1007/978-3-031-25405-5_1

Fig. 1 Physiographic zones in Canada, overlaid with provincial and territorial borders

Given the distribution of cropland and the severe climate in the north, the majority of Canada's population of over 35 million is concentrated along its southern boundary and over 80% of the land area is uninhabited [2]. This has presented both challenges and advantages for the surveillance and management of rabies.

Pre-colonial and Colonial Times

It is unknown if rabies was present in Canada before written records were kept, though phylogenetic and historical studies demonstrate that cosmopolitan dog rabies virus variants were probably not present in the Americas prior to the arrival of European colonists [3]. The Norse were the first Europeans to land in what is now known as Canada, establishing a settlement that only lasted a few years on the northwestern tip of what is now Newfoundland circa 1000 AD. Although Norse settlements persisted in Greenland over the next 500 years and those settlers had occasional contact with indigenous peoples in Canada's eastern arctic, we have no reports of anything like rabies during this period [4]. There were no other European visitors until 1497 when the English explored the Atlantic coast, followed by the

French during 1534, and the establishment by the Basque of seasonal whaling and fishing outposts along the Atlantic coast in the intervening time. The first permanent European settlements were founded during the early 1600s in "New France", the area now known as the province of Quebec. During this time, rabies in dogs was rampant in France [5]. It is likely that dogs incubating rabies virus found their way onto ships sailing for New France, though the long transatlantic voyage may have limited the introduction of dog rabies cases. The small dog populations in these early settlements may have also precluded rabies from becoming enzootic after a possible introduction. Nevertheless, it has been stated that the arrival of the fur trade brought "madness" to the animal populations of the Mohawk Peoples of Akwesasne [6].

Laboratory-confirmed cases of rabies in wild canids in Canada were not documented until the mid-twentieth century, though suggestion of its prior existence can be found in descriptions of disease consistent with rabies in northern wildlife and native dogs dating back to the late eighteenth century. However, confusion with other diseases such as canine distemper, may have occurred. Molecular clock analyses suggest that the Arctic rabies viruses emerged in the nineteenth century. It is speculated that one or more host shifts from dog to fox occurred, resulting, over time, in the enzootic of rabies in northern fox populations [4].

Though rabies virus in bats was first detected in Canada only during 1957, it is likely that bat rabies virus variants were present much earlier. As an example, a molecular clock analysis of virus isolates associated with big brown bats in Canada identified five distinct lineages estimated to have emerged from a common ancestor that existed over 400 years ago [7]. Similarly, a study of isolates from numerous American bat-associated virus lineages suggested a time to the most recent common ancestor of 732 years with 95% HPD 436–1107 years, pre-dating European colonization [8].

Post-confederation Legislative Framework for Rabies Management

Canada is a parliamentary democracy. As a federation, the country divides the responsibilities of governing between the federal government and the provinces and territories. At the federal level, the Department of Agriculture was established during 1868. A year later the *Animal Contagious Diseases Act* was enacted [9]. A revision to this Act during 1903, followed by a 1905 Order in Council naming rabies as a reportable disease, allowed for implementation and enforcement of regulations to control rabies [10, 11]. These included the requirement to report any known or suspected rabies cases in animals to the national veterinary authority. During 1977 and 1990, this act was updated and is now known as the *Health of Animals Act* [9]. Until the establishment of the Department of Health during 1919, federal responsibilities for public health fell under the mandate of the Department of Agriculture. National

reporting on selected communicable diseases in humans was established during 1924. Rabies was officially included during 1927 [12]. Similarly, all provinces and territories have legislation for reporting rabies cases in humans and animals. Licensing of veterinary and human biologics is regulated at the federal level by the Canadian Food Inspection Agency (CFIA) and Health Canada, respectively.

Roles and Responsibilities of Key Entities

Rabies management in Canada is a shared responsibility amongst many levels of government (Table 1). While the main responsibilities for health have always rested with the provincial governments, animal health responsibilities have varied and shifted over time. Historically, the federal Department of Agriculture's network of district offices staffed by veterinary inspectors coupled with a small number of federal laboratories yielded a harmonized approach to disease detection. These efforts were supported by the contributions of numerous groups, including university researchers, police, indigenous communities, private practice veterinarians and veterinary medical associations, trappers, lay vaccinators, and private industry (Table 1). Rabies management continues to rely on co-operation and collaboration amongst many sectors, public and private. A significant change in the federal roles during 2014 led to increased responsibility of provincial and territorial governments for disease investigation, sample submission, and management of exposed animals [13]. Diagnostic testing, import controls, and licensing of biologics remain under federal responsibility.

Laboratories and Diagnostic Testing

The federal system has generally followed a passive rabies surveillance model. Suspect animals are tested only if they have potentially exposed a person or a domestic animal [14]. Diagnostic testing has been carried out by the federal Department of Agriculture (now CFIA) in the National Capital Region (Ottawa, Ontario/Hull, Quebec) since 1903 [15]. Federal animal health laboratories established in other cities also conducted rabies testing during various periods: Sackville, New Brunswick (1949–1985); Vancouver, British Columbia (1957–1972); and Lethbridge, Alberta (1952-present) [9].

Rabies diagnosis was based on clinical signs and animal inoculation until 1905, after which time staining for detection of Negri bodies in brain tissue was the primary method employed [15]. A mouse inoculation test (MIT) was also performed if the suspect animal had exposed a person and Negri bodies were not detected. During 1965, the fluorescent antibody test (FAT) replaced histopathology as the primary

Table 1 Current and historical roles of key entities involved in rabies surveillance, prevention and control in Canada

Entity	Organization(s)	Key roles
Federal Government		
Agriculture	CFIA, and antecedents (AAFC, Department of Agriculture)	National surveillance for animal rabies; diagnostic testing (animal and human); research; international reference laboratory activities; animal vaccine licensing; animal import controls; public education. Pre-2014: Disease investigation in animals; risk assessments; submission of samples for testing; post-exposure management of domestic animals; liaison with provincial agriculture and health authorities; indemnity payments to producers. 1950s–60s: Mass dog vaccination clinics
Health	HC, PHAC, ISC and antecedents	National surveillance for human rabies; case definitions; national immunization guidelines; human biologics licensing and safety monitoring; human biologics procurement; research; international relations; human rabies management in First Nations and Inuit communities; diagnostic testing (human); public education.
Environment	PC	Wildlife rabies management in National Parks
	ECCC	International engagement (United States, Mexico) via the Trilateral Committee for Wildlife Ecosystem Conservation and Management
Federal Police	NWMP, RCMP	Dog control (muzzling, restraining strays, destruction) in territories during outbreaks; enforced quarantines; disseminated information on rabies; sample collection and transportation to federal laboratories; mass dog vaccination during the 1950s in some communities. RCMP withdrew from regular rabies management activities during 1995, but still provide services occasionally when there are no other options in the community.
Provincial/Territorial Governments		Post-2014: Disease investigation in animals; risk assessments; submission of samples for testing; post-exposure management of domestic animals (responsibilities are divided amongst various ministries, depending on the province/territory).
Agriculture	Numerous	Rabies management in domestic animals; in some jurisdictions, indemnity payments to livestock producers; public education; research.
Health	Numerous	Human rabies management, including procurement of biologics, animal bite investigations and post-exposure prophylaxis; decisions to test samples for rabies; public education; research.

(continued)

Table 1 (continued)

Entity	Organization(s)	Key roles
Natural Resources	Numerous	Wildlife rabies management (including enhanced surveillance and testing, wildlife rabies control programs, research); public education.
Municipal Governments	Numerous	Bylaws for animal control; in some jurisdictions, set criteria regarding mandatory pet vaccination; provide/assist with dog vaccination clinics, spay/neuter clinics; enforce licensing of pets; in some provinces, PHU are managed at the municipal level but work in concert with the ministry of health; public education.
Indigenous groups	e.g., Band councils, Health Centres, Katimavik Regional Government	Enact local laws concerning dog control, wildlife conservation, wildlife rabies control; dog vaccination programs; public education; in some areas, contributing to research and wildlife vaccination programs.
Universities/ Veterinary Colleges	Numerous	Research; diagnostic testing (wildlife surveillance); remote veterinary advice services; vaccination programs in underserviced areas.
Multi-component collaborative groups	e.g., CWHC, GREZOSP	
Veterinary Medical Associations; Associations of Veterinary Technologists	CVMA, provincial associations	Promoting rabies awareness (to public and to association members); in ON, OAVT manages sample collection and submission for human contact cases.
Private practice veterinarians	Numerous	Vaccination of pets and livestock; advising clients on rabies prevention; in some provinces, collection and submission of samples for rabies testing.
Fur harvesters/ trappers	Numerous	In some provinces, contribute to lay vaccination programs; wildlife rabies research; and wildlife rabies control programs (e.g., depopulation, enhanced surveillance, TVR, hand baiting, post-baiting serology).
Industry	Numerous	Vaccine and bait development and manufacture; collaborative research with university and government scientists; baiting machines, software.
International collaboration	e.g., USDA-APHIS WS, US-CDC, NARMP, WHO/ PAHO, WOAH	Co-ordinated ORV programming; collaborative research; sharing of epidemiological data and technical expertise.

Abbreviations: *AAFC* Agriculture and Agri-Food Canada, *CFIA* Canadian Food Inspection Agency, *CVMA* Canadian Veterinary Medical Association, *CWHC* Canadian Wildlife Health Co-operative, *ECCC* Environment and Climate Change Canada, *GREZOSP* Groupe de recherche en épidémiologie des zoonoses et santé publique, *HC* Health Canada, *ISC* Indigenous Services Canada, *NARMP* North American Rabies Management Plan, *NRBHSS* Nunavik Regional Board of Health and Social Services, *NWMP* Northwest Mounted Police, *OAVT* Ontario Association of Veterinary Technologist), *ORV* oral vaccination of wildlife, *PC* Parks Canada, *PHAC* Public Health Agency of Canada, *PHU* public health units, *RCMP* Royal Canadian Mounted Police, *TVR* trap-vaccinate-release, *USDA-APHIS WS* United States Department of Agriculture-Animal and Plant Health Inspection Service – Wildlife Services, *US-CDC* United States Centers for Disease Control and Prevention, *WHO/PAHO* World Health Organization/Pan American Health Organization, *WOAH* World Organisation for Animal Health

test, greatly increasing diagnostic sensitivity [16]. During 1976, a modification to the MIT, using a sequential kill approach, significantly shortened the time to detect positive cases [17]. During 1987, the MIT was replaced entirely by the rabies tissue culture inoculation test (RTCIT), which decreased the expense of testing for human-contact cases, the time required to obtain a negative result, and the use of animals [18]. During 2011, RTCIT was discontinued as a routine test, after 14 years without a positive result obtained on FAT-negative samples [15]. An immunohistochemistry test (IHC) for formalin-fixed samples was introduced during 1987 and modified during 1994 to increase sensitivity, however the submission of fixed samples is discouraged [15].

During the 1980s and 1990s, innovative approaches were developed for characterization of rabies virus variants. With the advent of monoclonal antibody (mAb) technology, antigenic variant typing using discriminatory mAb panels was introduced at the Ottawa laboratory during the 1980s. Initially, typing was carried out using mAbs and protocols received from collaborators in the United States [19]. This was followed by in-house development of a large collection of mAbs raised against different lyssaviruses. Thereafter, mAb panels were produced for the identification of the predominant rabies virus variants circulating in eastern and western Canada [20, 21]. In parallel with advances in antigenic typing was the evolution of molecular methods for virus detection and characterization, including diagnostic RT-PCR (conventional and real-time), variant typing by restriction fragment length polymorphism analysis, *in situ* hybridization, discriminatory RT-PCR, genomic sequencing (Sanger and next-generation methods), and phylogenetic analyses [22]. These methods have been applied extensively for studies exploring the evolution of rabies virus variants and understanding the origin and spread of the rabies outbreaks, in Canada and abroad [23].

The development of alternative test platforms, including IHC, the direct rapid immunohistochemical test for rabies (DRIT) and RT-PCR on fresh and formalin-fixed tissues, has greatly increased capacity for decentralized wildlife surveillance testing, where there has been no human or animal contact involved [24–27]. Whereas previous surveys were carried out almost exclusively under contract with one of the federal rabies laboratories, many provinces, universities and organizations, such as the Canadian Wildlife Health Co-operative, now conduct independent surveillance testing. Positive results are reported to the CFIA, and if requested, confirmatory testing and variant typing are performed.

Human case diagnosis using direct detection methods was performed in hospital laboratories and has been available at the Hull/Ottawa federal agriculture laboratory since 1959 [28]. Since 2000, molecular methods have also been used routinely for ante-mortem testing of various sample types from human suspect cases in the CFIA Ottawa laboratory [22]. Indirect tests for the detection of rabies virus neutralizing antibody were conducted by some provincial laboratories, but are now carried out at the National Microbiology Laboratory (Public Health Agency of Canada [PHAC]).

Human Rabies Epidemiology

Although not officially recorded, the earliest documented human rabies deaths date back to the early 1800s and continued sporadically through the century and into the next, often coinciding with localized dog rabies outbreaks. There were two notable outbreaks in dogs starting during 1907 and then again during 1926, which resulted in at least 20 deaths (Fig. 2). Before 1910, exposed persons were forced to travel to New York City for post-exposure prophylaxis (PEP). During 1910, two Ontario hospitals began offering vaccine procured from New York, making PEP more accessible to those who could not afford the travel [29]. By 1913, Canada began producing its own vaccine in Ontario and by 1920, rabies vaccine was available in all provinces and free to the public, which has continued to date through formally established universal medical care [30]. The last domestically acquired, dog-related death was reported during 1944. After 1944, the epidemiology of human cases shifted, reflecting the disappearance of dog rabies and the changing epizootiology. Despite large outbreaks in wild carnivores, there have been very few associated human deaths, presumably due to a combination of education efforts, an easily identifiable risk exposure, and ready access across the country to PEP. No cases have ever been reported from northern Canada, despite longstanding circulation in arctic fox populations. Since 1970, bats have accounted for all 7 deaths from domestically acquired rabies. Although 6 of 7 cases (86%) reported having direct contact with a bat, none of the cases sought care or received PEP. The most recent death of a young man during 2019 [31] emphasized the need for sustained efforts to improve education regarding recognition of bat exposures, including those that are subtle. Since national reporting on communicable diseases was established during 1924, there have been 27 cases reported across Canada (Table 2). With only 9 deaths in over 50 years, Canada's efforts to prevent human rabies deaths have proved largely successful.

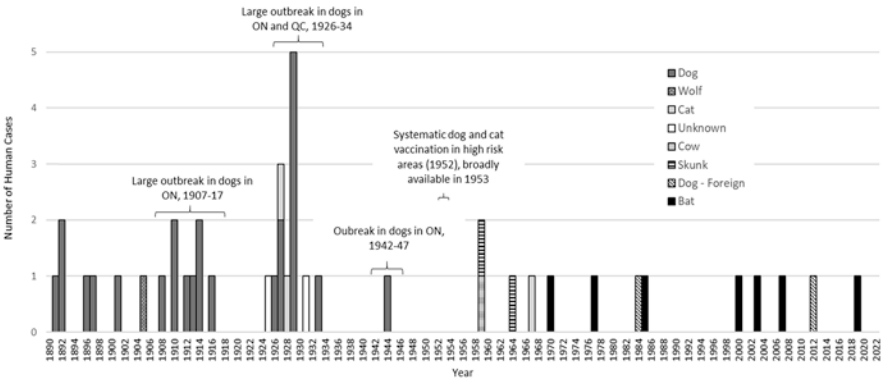

Fig. 2 Human rabies cases in Canada by animal exposure, 1890–2022

Table 2 Human rabies cases in Canada, 1924–2020

Case #	Year	Prov	Sex	Age (YR)	Animal source	Type of exposure	Body part exposed	PEP (Y/N)	References
1	1925	SK	M	12	No history of contact with dog	No history of bite or scratch	…	N	[32, 33]
2	1926	QC	M	6	Dog	Bite	Face	…	[33–35]
3	1927	QC	M	Adult	Dog	Bite	…	…	[33, 36, 37]
4	1927	QC	F	Adult	Dog	Bite	…	…	[33, 38]
5	1927	QC	M	11	Cat	Bite	Hand	Y	[33, 39]
6	1928	ON	F	4	Cat	Bite	Face	…	[40]
7	1929	QC	F	8	Dog	Bite	Face	N	[33]
8	1929	QC	F	8	Dog	Bite	Hand, Shoulder, Torso	…	[33]
9	1929	QC	F	7	Dog	Bite	Wrist	N	[33, 41]
10	1929	QC	M	Adult	Dog	Bite	…	…	[33, 42]
11	1929	ON	M	5	Dog	Bite	Face	Y	[33, 43]
12	1931	ON	M	3	Dog	Bite	Face	N	[33, 44]
13	1933	QC	M	9	Dog	Bite	…	Y	[33, 45]
14	1944	ON	M	11	Dog	Bite	Leg	N	[33, 46, 47]
15	1959	ON	M	7	Skunk	Bite	Hand	N	[48–50]
16	1959	ON	M	30	Cow	Saliva contamination	Hand	…	[48]
17	1964	QC	F	14	Skunk	Bite	Face	N	[49, 51]
18	1967	ON	F	4	Cat	Bite	Face	Y	[48, 49, 52]
19	1970	SK	M	15	Bat	Bite	Face	N	[53, 54]
20	1977	NS	M	63	Bat	Bite	Hand	N	[55]
21	1984	QC	M	43	Dog	Bite	Hand	Y	[56, 57]
22	1985	AB	M	25	Bat	Direct contact – Bite or scratch	Face	N	[49]
23	2000	QC	M	9	Bat	Bite	Arm	N	[58, 59]
24	2003	BC	M	52	Bat	No history of bite or scratch but was around bats	…	N	[60]
25	2007	AB	M	73	Bat	Bite	Shoulder	N	[61, 62]
26	2012	ON	M	41	Dog	No history of exposure	…	N	[63, 64]
27	2019	BC	M	21	Bat	Scratch	Hand	N	[31]

Abbreviations: *AB* Alberta, *BC* British Columbia, *F* Female, *M* Male, *NS* Nova Scotia, *ON* Ontario, *PEP* post-exposure prophylaxis, *Prov* province, *QC* Quebec, *SK* Saskatchewan, *YR* year

Epizootiology

Rabies has been present in Canada for over two hundred years. Unfortunately, prior to 1926 no systematic records of animal rabies cases were kept. There are, however, accounts of disease dating back to the eighteenth century, including descriptions of illness affecting northern dogs, foxes, wolves and caribou, with names like "crazy fox disease" and "arctic dog disease" [65, 66]. Local newspaper reports back to 1816 from across southern Canada describe attacks on humans, most often by dogs. More detailed annual reports from the Veterinary Director General for the Dominion of Canada from 1902 to 1942 confirm that outbreaks of rabies were typically canine in origin [67]. Since 1926, however, the federal Agriculture Department has collected and disseminated rabies data in all species for all Canada. Despite the passive surveillance approach, the result was a country-wide consistent reporting system that has demonstrated utility in monitoring rabies cases in both domestic and wildlife species.

Those records illustrate a significant change by 1950. From 1926 to 1949, 488 (74%) of the reported 660 cases were in dogs and there were only 6 reported cases in wildlife (wolf, fox). Other cases in livestock (23%) and cats (3%) were linked to dogs. From 1950 to 2022, 75,368 rabies cases were detected, approximately 1058 cases annually, compared to only 28 cases annually between 1926 and 1949. Table 3a illustrates the spatial distribution of reported cases from provinces and territories between 1950 and 2022. The prairie provinces (Alberta, Saskatchewan, Manitoba) together with central Canada (Ontario, Quebec) accounted for over 97% of reported cases. Reports from the west coast (British Columbia) and the north (Yukon, Northwest Territories, Nunavut) averaged about 8 cases per year and 12 cases per year, respectively. Reports from the maritime provinces (New Brunswick, Nova Scotia, Prince Edward Island) were low and linked to an invasion of fox rabies from Quebec during the late 1960s and then to incursions of raccoon rabies into New Brunswick from Maine since 2000.

Since 1950, wildlife were the primary vector(s) in all provinces and the species involved varied by region. Bats comprised 95% of all reported cases in British Columbia; skunks accounted for 76% of cases in the prairies; and the red fox/arctic fox accounted for over 40% of cases in the central provinces and the Maritimes and over 70% in Newfoundland and Labrador and the northern territories (Table 3b). Since 1999, however, the raccoon has become an important species in eastern Canada due to incursions from bordering States. Approximately 60% of all raccoon cases reported in Table 3 stem from those incursions.

The patterns shown in Table 3 reflect three major invasions of rabies into southern Canada. As Nadin-Davis (2020) demonstrated, the patterns are also associated with three rabies virus variants: AFXV – the variant in arctic and red foxes; WSKV – the variant in skunks on the prairies; and RACV – the variant in raccoons, now predominant in eastern Canada [23].

Figure 3 illustrates the origins and probable routes of spread of those invasions associated with arctic/red foxes, skunks, and raccoons. The first was the spread of

Table 3 Diagnosed rabies cases in Canada 1950–2022

	BC	AB-SK-MB	ON-QC	NB-NS-PE	NL	YK-NT-NU	ALL
(a)	Number of rabies cases by province and species class						
FOX	5	112	28,570	202	126	632	29,597
SKUNK	3	7793	11,877	28	0	0	19,699
LIVESTOCK	2	999	12,794	84	3	0	13,880
DOG/CAT	7	573	6211	32	12	194	7022
BAT	553	669	1906	39	1	0	2632
RACCOON	4	10	985	90	0	0	1085
OTHER	6	133	648	4	11	37	833
TOTAL	580	10,302	62,991	479	153	863	74,806
(b)	Relative distribution (%) of rabies cases by province and species class						
FOX	0.9	1.1	45.4	42.2	82.4	73.2	39.6
SKUNK	0.5	75.6	18.9	5.8	0.0	0.0	26.3
LIVESTOCK	0.3	9.7	20.3	17.5	2.0	0.0	18.6
DOG/CAT	1.2	5.6	9.9	6.7	7.8	22.5	9.4
BAT	95.3	6.5	3.0	8.1	0.7	0.0	3.5
RACCOON	0.7	0.1	1.6	18.8	0.0	0.0	1.5
OTHER	1.0	1.3	1.0	0.8	7.2	4.3	1.1

The upper table (a) lists cases by province and species class and the lower table (b) shows the relative (%) distribution of those cases by province and species class. The OTHER category is primarily coyote and wolf (75%) although it includes a wide variety of other mammals (e.g., bear, deer, etc.). Abbreviations: *BC* British Columbia, *AB* Alberta, *SK* Saskatchewan, *MB* Manitoba, *ON* Ontario, *QC* Quebec, *NB* New Brunswick, *NS* Nova Scotia, *PE* Prince Edward Island, *NL* Newfoundland and Labrador, *YK* Yukon, *NT* Northwest Territories, *NU* Nunavut. Figure 3 shows the locations of the provinces and territories. Data source: CFIA

rabies (AFXV) during the late 1940s and early 1950s from northern into southern Canada and subsequently into neighbouring New York. Despite persistent reports of "arctic dog disease" from the 1920s to 1940s, rabies was officially diagnosed in the Northwest Territories during 1947, and then near the northern borders of Alberta, Manitoba, and Quebec by 1951 [68]. Rabies spread rapidly south in two major streams: the first through the Interior Plains into Alberta and then into Saskatchewan and Manitoba; and the second through the Hudson Bay Lowland and Canadian Shield into Ontario, Quebec, and Labrador. The primary vectors were the coyote and fox in Alberta and the arctic and red fox in the other provinces. The epizootic was controlled in Alberta by 1956 and there were only a few cases reported in Saskatchewan, Manitoba, and Labrador [69]. The experience in Ontario and Quebec was quite different. Cases surged as the disease moved south into the Great Lakes-St. Lawrence Lowlands, peaking at 326 cases during 1957 in Quebec and 2493 cases in Ontario during 1958. From this core, rabies spread eastwards through the Appalachian Uplands into the Maritime Provinces during the mid-1960s, where it then disappeared by the mid-1970s.

Rabies persisted in wildlife populations in southern Ontario and Quebec. Until recently, the red fox (with AFXV) was the primary reservoir with over 45% of

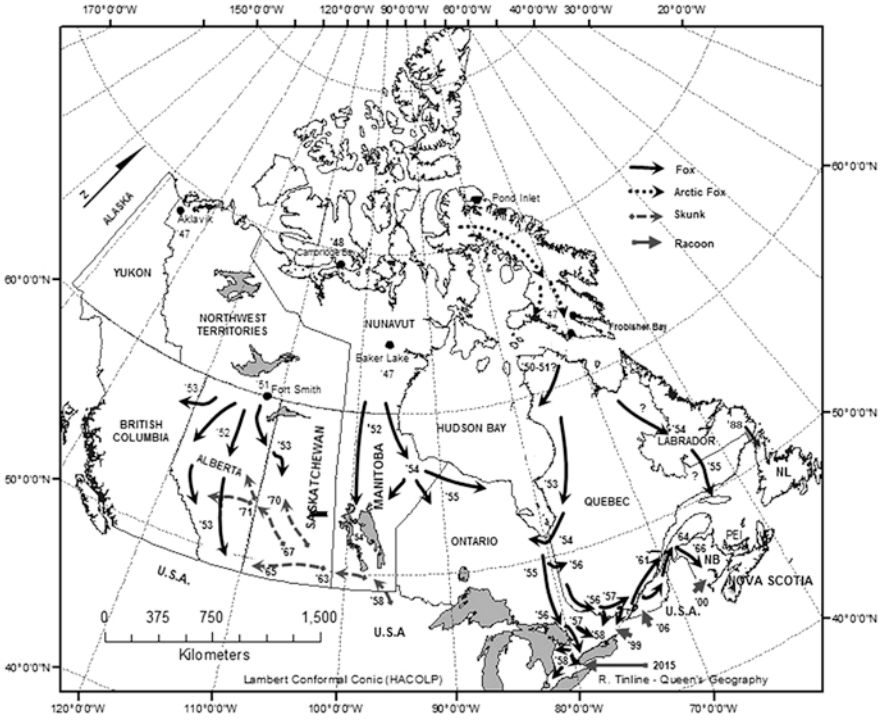

Fig. 3 Invasion paths of rabies into southern Canada 1947–2015. This figure is based on a map drawn by Tabel et al. [64] and subsequently updated by one of us (Tinline). The arrows showing fox movements represent both arctic and red foxes, since early reports did not distinguish species. (Data source: CFIA)

diagnosed cases, though in Ontario and Quebec skunks accounted for almost 19% of cases (Table 3). As cases in wildlife in southern Canada increased, so did cases in dogs/cats and livestock. In relative terms, however, occurrence in dogs/cats dropped dramatically, from 77% before 1950 to 10% afterwards, while the relative proportion of reported cases in livestock remained about the same (20–25%).

Unlike central Canada there was no appreciable spillover of the AFXV virus into the skunk populations on the prairies during the coyote/fox invasion during the early 1950s. However, rabies in skunks entered southeastern Manitoba, spreading from the bordering states of Minnesota and North Dakota during 1958 [68]. The disease spread west across the southern agricultural areas of the prairies infecting southern Saskatchewan during the 1960s and Alberta during the early 1970s (Fig. 3). Rabies disappeared in Alberta by 1994 after a sustained population reduction management program but persists in Saskatchewan and Manitoba to the present [70]. Almost 76% of all cases are in skunks (Table 3) and most are associated with the WSKV virus.

In eastern Canada, the prevalence of rabies in raccoons was low and associated with AFXV. This changed with the first incursions of RACV during July 1999 in

eastern Ontario [71]. Since then, there have been additional incursions in eastern Canada from the United States: two in New Brunswick (2000–2002, 2014–present) from neighbouring Maine; two in Quebec (2005–2009, and a single case detected during 2015) from neighbouring New York; and another in the Hamilton area in southern Ontario during December 2015 [72]. While the incursions before 2015 were related to sub-variants of the RACV circulating immediately across the border, the 2015 Ontario incursion was likely the result of a long-distance transport of an infected animal from southeastern New York [73].

Bats are the other important wildlife species involved in rabies. During June 1957, the first case of rabies in a bat in Canada was confirmed in a big brown bat from British Columbia [74]. Since then, rabies in bats has been reported in all regions except the northern territories. Cases have been reported in 15 of the 19 species of bats known to inhabit Canada, with big brown bats most reported as rabid. Overall occurrence in bats has been low, typically 40–60 cases per year or about 3.5% of all reported rabies cases in Canada from 1950 to 2022 (Table 3) [75]. Approximately half of those cases were reported in Ontario and most of the remainder were reported in the western provinces, particularly British Columbia. Generally, the number of bat cases has remained steady but as control programs reduced cases in other species, the relative prevalence in bats has increased since 2000 and in the last decade accounted an average of 40% of annual cases in Canada.

The role of bats in rabies remains to be better understood. Of interest, most recent human cases of rabies in Canada have been linked to virus variants in silver-haired bats [76]. Bat rabies virus variants have also been found in other domestic and wildlife species in scattered locations across Canada [23]. Hence, bats are a rabies virus reservoir and a source for re-introduction in other animals.

Rabies Management and Control in Canada

The patterns noted above have also been shaped by the three methods of rabies prevention and control employed in Canada: quarantine/muzzling/culling of domestic dogs; population reduction (PR) of wildlife; and vaccination of domestic and wild animals.

Quarantine/Muzzling/Culling of Domestic Dogs

During the first half of the twentieth century, sporadic outbreaks associated with dogs were effectively controlled by a combination of muzzling, quarantine and culling which involved, in many cases, widespread killing of local strays [77]. Most outbreaks were attributed to importation of dogs from the United States and, given that rabies was not enzootic in the dog populations in Canada, these methods worked [68].

Vaccination of Domestic Animals

In the United States, however, rabies in dogs was enzootic in many states [78]. Dog rabies vaccines were developed during the 1920s and employed widely during the 1940s, but those vaccines were not licenced in Canada [77]. There was little inclination to develop mass immunization programs for dogs or livestock in Canada given the success with previous measures. The growing awareness of wildlife rabies in the north during the later 1940s and the severity of the outbreak in Alberta during 1952–1953, prompted the federal government to allow private veterinarians to vaccinate dogs against rabies during 1953 [77]. Increasing pressure from the dramatic upswing of cases in Ontario during the late 1950s led to free immunization clinics in that province for dogs and cats and the development of similar vaccination programs in the other provinces [77, 79].

Population Reduction

The first strategy used in Canada for wildlife rabies control was PR. Alberta was successful in the application of PR to eliminate fox rabies during the 1950s and again during the 1970s and 1980s to eliminate skunk rabies that had entered from neighboring jurisdictions [69, 70, 80]. In addition, PR was used to eliminate an introduction of AFXV into the northwestern peninsula of Newfoundland during 1988 by establishing elimination zones around index cases, limiting the outbreak to five fox cases [81].

More recently, PR has been used in combination with other strategies, such as in Ontario and Quebec in combination with trap-vaccinate-release (TVR) and oral rabies vaccination (ORV) [82, 83]. The combination of methods was developed originally in Ontario as a means of point infection control (PIC) against RACV and has also been applied in Newfoundland and Labrador in response to a 2002 outbreak of AFXV [84, 85]. The combination of PR and TVR was sufficient to control the 2000–2002 RACV outbreak in New Brunswick [72].

Vaccination for Wildlife

Success in vaccinating dogs, cats and livestock, and the continuing presence of wildlife rabies in southern Ontario, led to consideration of methods to immunize wildlife. By 1968, this challenge was undertaken by Ontario and overseen by a committee with members from the provincial Ministries of Health and Natural Resources (OMNR) and Agriculture Canada. Two factors were paramount: developing a safe, efficacious vaccine and finding method(s) to vaccinate animals in the wild. Pioneering work at Connaught Laboratories demonstrated that vaccination of foxes by the oral route was possible with an attenuated Evelyn-Rokitnicki-Abelseth