National Collaborating Centre for Environmental Health
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Surveillance for Emerging Infectious Diseases: A Canadian Perspective

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Summary

- Surveillance approaches for emerging zoonotic infectious diseases is less well developed than for traditional clearly-defined diseases.

- Zoonotic diseases with recent implications in Canada include: influenza, West Nile Virus (WNV), Lyme Disease (LD), Hantavirus Pulmonary Disease (HPS), and food-borne zoonoses, with influenza having the greatest human impact.

- Emerging zoonotic disease (EZD) surveillance focuses on detecting both range expansions of known pathogens and the emergence of new pathogens, for which the causative agents, reservoirs or vectors may remain unknown.

- Suggested EZD surveillance approaches include:
  - Syndromic or rapid response surveillance;
  - Information surveillance;
  - Sentinel surveillance;
  - Laboratory surveillance.

- Perhaps the greatest challenge in EZD surveillance is the lack of a clear case definition or identified causative agent when looking for novel disease emergence.

Target Audience

Emerging zoonotic disease surveillance is inherently interdisciplinary, requiring co-operation between public health, clinical medicine, veterinary medicine, and ecology. Each field comes with a unique knowledge base that typically focuses on either animal or human health, but rarely both. This review is targeted towards public health practitioners and policymakers, among whom it is felt that knowledge of zoonotic disease surveillance is limited. This review is also limited to zoonotic disease and zoonotic disease surveillance as it pertains to Canada.

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Introduction

Emerging Zoonotic Disease (EZD)

Zoonoses are diseases spread from animals to humans (or vice versa),[1] with the causal agent being viruses, bacteria, fungi, or prions.[2] Emerging zoonoses are newly recognized diseases or those that have increased in incidence or expanded their geographic, host or vector range.[3-5] Approximately 60% of infectious diseases in humans originate in animals,[6] while 75% of newly emerging infectious diseases are zoonoses.[7] Transmission of zoonotic diseases occur through direct human-animal contact, inhalation of blood, faeces or other body fluids (e.g., inhalation of drops, sputum, urine), arthropod vectors or through ingestion of contaminated food or water (Fig. 1).[2] Zoonoses can cause severe disease in humans and, while many zoonotic infections do not result in human-to-human transmission, some do cause epidemic transmission in human populations.[2] Examples of emerging zoonoses include West Nile Virus (WNV), Ebola, human immunodeficiency virus (HIV), severe acute respiratory disease (SARS), hantavirus, avian influenza, and the 2009 influenza pandemic.[8,9]

The rate of zoonotic disease emergence has increased significantly since the 1940s,[6] likely due to a combination of demographic changes, land-use alterations, urbanization, increased travel, agricultural practices, and encroachment into animal habitat.[10,11] Zoonoses not only affect human health but also have economic costs. Canadian outbreaks of bovine spongiform encephalopathy cost 6.3 billion,[12] food-borne zoonoses up to 1.3 billion annually,[13] and the 2004 outbreak of avian influenza in BC led to economic losses of up to 380 million dollars.[14]

Recent Emerging Zoonoses with Implication in Canada

H1N1 Pandemic Influenza and H5N1

Influenza has likely impacted more humans than any other zoonotic disease: the Spanish flu (1918) alone killed 40-100 million worldwide.[15] Influenza is believed to originate in aquatic birds, with swine often acting as *mixing vessels* in which human and bird flu strains undergo antegenic shift.[16] In the spring of 2009, a swine-based influenza virus emerged in Mexico and caused a higher proportion of illness in young children than in adults.[17] Like many influenza viruses, this particular strain evolved from a combination of an H3N2 strain circulating in pigs, a classical swine lineage, and an Eurasian *avian-like* H1N1 strain.[18] This virus adapted for efficient person-to-person transmission and, although attack rates for the 2009 H1N1 outbreak (estimated at 27%) were lower than previous pandemics,[18] the H1N1 virus caused at least 410 deaths in Canada by the end of 2009 and 18,449 deaths worldwide as of August 2010.[19] While the H1N1 pandemic was less severe than anticipated, a highly fatal avian-based influenza has been reported in humans since 2003 in southeast Asia, China, the middle east, eastern Europe, and parts of Africa,[20] with previous outbreaks reported in both Hong Kong (1997)[21] and the Netherlands (2003).[22] However, after the species jump human-to-human transmission remains rare for this strain.

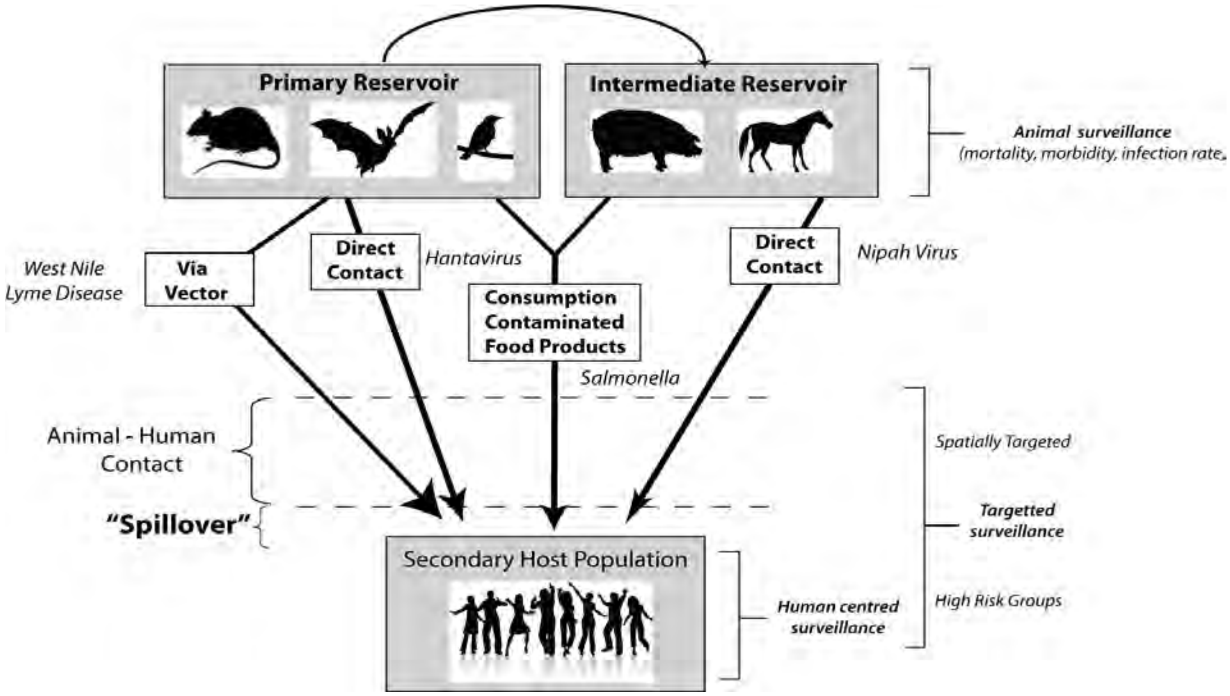

Figure 1: Transmission pathways for zoonotic disease. Modified from Childs et al. (2007).[23]

West Nile Virus

In the summer of 1999, 59 cases of severe neurological disease and seven deaths were reported in New York City. A die-off of wild crows and exotic birds in a nearby zoo occurred concurrently with the human deaths, but was not initially recognized by public health as etiologically related.[24] The cause of these human and animal deaths was identified as WNV,[25-27] a Flavivirus spread between avian reservoirs by mosquito vectors.

WNV is an ecological generalist, having been identified from 59 mosquito species and 248 bird species in North America alone.[28,29] Birds are the natural viral reservoir and likely play an important role in viral dispersal.[30,31] Birds vary in their susceptibility to infection; some dying quickly, while others show no outward symptoms.[32] WNV virus is spread from birds to humans via the bite of an infected mosquito; in North America, mosquitoes of the genus Culex are the most common disease vectors.[28,29] Most human infections cause no illness; about 20% suffer from WN fever, and less than 1% experience severe neurological disease including meningitis and encephalitis.[27,33] Since 1999, there have been over 30,000 confirmed WNV cases in the U.S.[34] and over 4,500 in Canada[35]; however, these values under-represent the true infection rates as most infected individuals remain asymptomatic or do not seek medical attention. Minimal WNV activity has been observed in Canada since 2007, with only 54 human cases reported between 2008-2010.[34]

Lyme Disease

Lyme disease (LD) was recognized as a unique condition in 1976[36] after mothers in the village of Lyme, Connecticut noticed an abnormal cluster of juvenile arthritis. The causative agent, the spirochetal bacteria *Borellia burgdorferi* (*B. burgdorferi*), was subsequently discovered in 1981.[36] *B. burgdorferi* is transmitted between rodent species, particularly white-footed mice and chipmunks, and to humans by larval and nymphal hard-bodied ticks. The primary vector in eastern North America is *Ixodes scapularis*, with *I. pacificus* being the dominant western vector.[37]

LD is the most common tick-borne disease in the U.S. with over 20,000 human cases reported annually.[38] Symptoms include skin rash, joint pain, fatigue, and potentially serious neurological disorders.[37] The incidence of Lyme disease in eastern Canada is historically less than 15 cases per year; however, disease incidence is increasing with worst-case modeling estimates of 8,000 cases annually in south-central and south-eastern Canada by 2050.[39] LD incidence in western Canada is lower than eastern Canada,[39] likely due to east-west differences in vector and reservoir infection rates.[40,41] Similar reservoir-driven differences in Lyme disease vector infection rates occur between the north-east (competent reservoir, high vector infection) and southern states (incompetent reservoir, low infection).[42]

Hantavirus

Hantavirus Pulmonary Disease (HPS) was first detected in North America in 1993, in a cluster of First Nations patients from the Four Corners regions of the southern United States.[43] By the completion of the outbreak, 59 patients had presented with acute pulmonary distress, headaches, myalgia, and hypovolemic hypotension; mortality rates reached 40-50%.[43,44] Genetic analysis revealed a novel strain of hantavirus, subsequently named Sin Nombre virus (SNV).[45]

SNV is carried by murid rodents and human infection occurs through the inhalation of aerosolized rodent excreta.[43,46,47] In North America, the disease is carried primarily by the ubiquitous deer mouse (*Peromyscus maniculatus*), a rodent distributed across the continent south of the tree line. The majority of Canadian cases become infected during farming or domestic activities in rural settings,[48] likely resulting from individuals living or working in close quarters with deer mice.

Although HPS is rare in Canada, the severity of the disease justified public health concern. No treatment exists for this disease and early recognition and pulmonary and hemodynamic support is critical.[47] Serological evidence suggests that SNV is carried by rodents in all Canadian provinces, with the exception of Prince Edward Island and Nova Scotia.[48] However, most human cases of the disease are reported in Manitoba, Saskatchewan, Alberta, and British Columbia,[48] with a single case in Quebec.[49] As of 2010, there have been over 70 confirmed cases in Canada.[49]

Food-borne Zoonoses

Zoonotic infections can also be spread by food or by water that is contaminated by bacteria, protists, parasites or viruses originally found in animals. Thirty-five million cases of gastroenteritis are estimated to occur in Canada each year and many of the most common causes of food-related illness have a zoonotic origin,[50-52] examples include: Camplylobacter, Salmonella, *Toxoplasma gondii*, and *Esherichia coli O157:H7*.[53] Furthermore, approximately two new food-borne pathogens are identified every year, the majority of which are zoonotic.[53] Although the transmission pathways for food-borne zoonoses are varied (with individual zoonotic agents often having multiple routes of infection), many are caused by faecal contamination of food or water (Cryptosporidia, *Escherichia coli*, Campylobacter, Leptospirosis, Q fever).[54-56] Other contamination pathways include milk (Brucellosis, Tuberculosis, Q fever),[56] parasites in uncooked meat (Trichenella) or bacteria on uncooked eggs (Salmonella).[56]

Emerging Zoonotic Disease (EZD) Surveillance

Surveillance Approaches for EZD

Traditional surveillance systems identify long-term trends in clearly defined diseases.[57] EZD surveillance focuses on detecting both range expansions of known viruses and the emergence of new pathogens, for which the causative agents, reservoirs or vectors may remain unknown. Novel surveillance approaches are therefore required, the suitability of which depends on the current understanding of the disease ecology (Fig. 2, modified figure from Buckeridge et al. (2006).[58]

Syndromic or rapid response surveillance focuses on detecting a set of symptoms instead of clinical or laboratory diagnosis.[59,60] The use of a broad case definition is assumed to allow for earlier outbreak detection.[60] The strengths of syndromic surveillance include: timeliness and completeness of data; ability to alleviate concern regarding the true absence of local outbreaks, when outbreaks are occurring elsewhere; and ability to detect emerging diseases, because of its focus on clinical symptoms.[60] However, the increased sensitivity, that comes with a broad case definition also gives syndromic surveillance a low specificity, resulting in high number of false positives.[60]

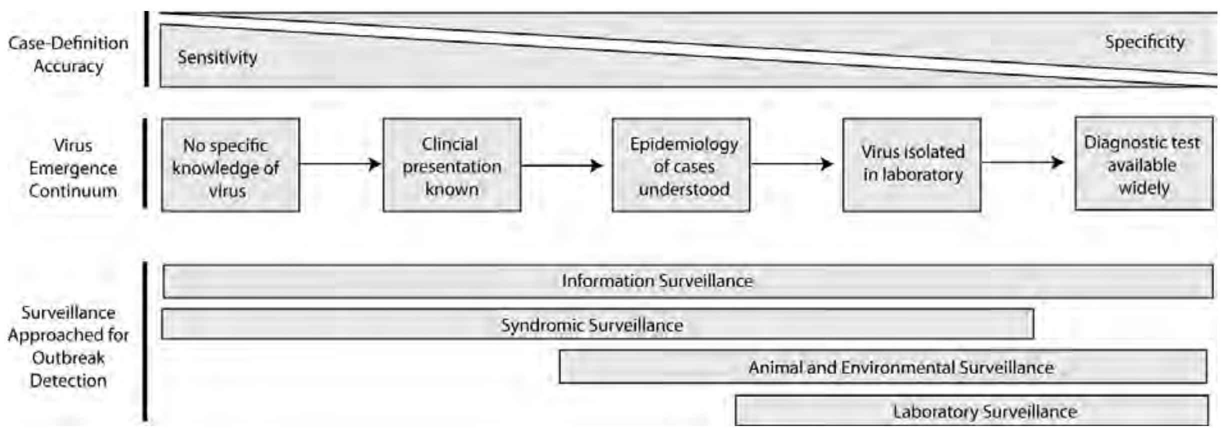

Figure 2: The continuum of emerging disease surveillance. Modified from Buckeridge et al., 2006.[58]

Information surveillance is a passive surveillance approach that uses email and web-based data aggregation to identify disease outbreaks. Examples include ProMEd and the Global Public Health intelligence Network (GPHIN).[58,61] ProMed is an international infectious diseases email chain in which > 45,000 members from 165 countries report outbreaks of infectious diseases and the media tracking of such outbreaks.[58,62] In contrast, GIPHIN is automated software that searches the internet for key words relating to emerging diseases.[61] GPHIN's value lies in the speed afforded it through its detachment from governmental bureaucracy and by its ability to cross jurisdictional boundaries.[61] Both systems suffer from broad case definitions and frequent false positives[58]; however, 65% of 578 outbreaks between July 1998 and August 2001, reported to the WHO, were initially detected by informal sources, with 56% detected by GIPHIN (it should be noted that these were not necessarily outbreaks of *emerging* disease).[63] Other recent examples of information surveillance include: HealthMap, which gathers data from 20,000 sources every hour to integrate, monitor, and present information on emerging infectious diseases[64,65]; and EpiSPIDER, which utilizes conventional data formatting approaches to facilitate the use of data with other software and services while also providing a visual representation of data presented on ProMED.[66]

Sentinel surveillance attempts to reduce costs by focusing resources on locations or groups representative of the greater population.[67] Sentinel herd surveillance is used to monitor cattle and swine diseases[68] and sentinel chicken populations can track human WNV risk over time.[69] Sentinel surveillance is best suited for situations where complete case counting is not required or where action is not dependent on a single case.[67] Sentinel surveillance is particularly effective if combined with a *targeted* or *risk-based surveillance* approach that maximizes detection probabilities in light of limited resources.[70] Zoonotic diseases typically emerge where animals and humans live in close proximity or in areas with large populations of disease reservoirs or vectors (e.g., farms).[11] Focusing surveillance in these areas can improve detection capabilities. Examples include: focusing surveillance on immunocompromised pet owners,[71] farm workers, aviary workers, zookeepers or slaughterhouse workers.[2] Similarly, WNV vector traps can be placed in areas with high vector abundance to facilitate detection of circulating arbovirus.[72] Predictive models that identify areas with an elevated risk of disease emergence can further focus national and global surveillance resources.[6]

Surveillance for zoonoses in animal populations, prior to spill over into human populations, can minimize disease in human populations. Such approaches can be expensive, as infected reservoirs may be asymptomatic, requiring the testing of apparently healthy individuals.[23] However, modeling efforts suggest that such approaches can be cost effective, despite initial costs. In some instances, *animal mortality surveillance* can act as an early warning system for zoonotic disease emergence. Dead bird surveillance initially played an important role in WNV surveillance,[73] while large-scale die-offs of prairie dogs can identify plague outbreaks.[74]

***Laboratory networks**,* with standard case definitions and testing procedures, are powerful surveillance tools for zoonotic disease,[75] especially once a causative agent is determined and diagnostic identification methods established. However, case definitions are rarely standardized, which reduces the effectiveness of EZD surveillance. Despite this, laboratory approaches can still eliminate potential causes of clinical illness in the initial stage of an outbreak investigation. Examples of laboratory surveillance networks in North America include: the National Animal Health Laboratory Network (NAHLN), the Laboratory Response Network (LRN), and the Food Emergency Response Network (FERN) in the U.S.; the Canadian Animal Health Surveillance Network (CAHSN), the Canadian Cooperative Wildlife Health Centre (CCWHC), the Canadian Public Health Laboratory Network, C-EnterNet, and the National Enteric Surveillance Program (NESP) in Canada.

Challenges of EZD Surveillance

- **Multi-species transmission necessitates co-operation between multiple agencies:** Zoonotic disease transmission involves multiple species, with wildlife,[76] companion animals[77,78] or agricultural species[79] serving as disease reservoirs. EZD surveillance requires co-operation between those who work in animal and human health, including agriculture, veterinary medicine, and public health.

- **Absence of regulated data sharing**: Separate reporting and communication procedures typically exist for animal and human cases[62] and the effectiveness of zoonotic disease surveillance is often limited by a lack of formal regulations for the sharing of data across sectors.[23,80] As of 2006, only 8 of 43 U.S. states surveyed required veterinarians to notify public health agencies regarding reportable zoonotic disease and, of these, two were only required to report rabies cases.[71]

- **Under-reporting of zoonotic outbreaks**: Many governmental agencies prohibit the reporting of unconfirmed outbreak information, which limits the effectiveness of early warning surveillance.[81] Also, there is also no economic incentive for private labs or animal production centres to share independent surveillance data with public health agencies.[82] In fact, an economic disincentive exists for some farmers or countries to report outbreaks of zoonoses that impact agriculture or tourism.[83]

- **Animal versus anthropogenic focus**: Animal surveillance typically focuses on agricultural animals, and to a lesser degree on wildlife, to identify infection in reservoirs prior to the species jump; doing so, may allow for implementation of cost-effective control measures and associated reductions in human illness.[84] However, early detection and prevention of disease in animals does not typically fall under the mandate of human health and EZD surveillance systems often focus on human disease as an indicator of zoonotic outbreaks.[80]

- **Limited understanding of disease at time of emergence and lack of case definition:** Perhaps the greatest challenge in EZD surveillance is the lack of a clear case definition or identified causative agent when looking for novel disease emergence. This uncertainty requires that EZD surveillance rely on epidemiological or clinical symptoms instead of laboratory identification. This can prove challenging, since the symptoms and signs of EZDs are often non-specific and may differ depending on viral strains and host genetics.[58]

Case Studies: EZD Surveillance in Canada

A brief review of national and provincial EZD surveillance approaches is presented below. Surveillance activities and reportable disease lists vary across provinces and case studies presented here aim to provide examples of differing surveillance approaches, not to reflect the entirety of EZD surveillance in a given province.

National

Public health surveillance and outbreak control fall under provincial jurisdiction and many zoonotic diseases are endemic only in select regions of the country. Therefore, EZD surveillance in Canada is primarily provincial in scope with each province carrying out unique surveillance activities. However, federal agencies do play a role in the reporting and detection of zoonotic disease in Canada.

The Canadian Food Inspection Agency (CFIA) is the primary federal organization dealing with animal diseases. Select *reportable* zoonotic diseases, that impact animal or human health, must be immediately reported to a CFIA district veterinarian in order to allow for implementation of control measures.[85] In contrast, *immediately notifiable* diseases are typically exotic diseases that laboratories must report to CFIA while *annually notifiable* diseases are those not classified as reportable or immediately notifiable, but which are reported yearly to the WHO (see Canadian Food Inspection Agency 2010[85] for complete disease lists). The CFIA also manages the CAHSN, a network of animal health diagnostic laboratories created to integrate data from multiple jurisdictions in order to improve Canada's ability to deal with zoonotic diseases.[86] However, this network is primarily focused on zoonotic disease only as it relates to the security of animal food animal production.[87]

The Canadian Cooperative Wildlife Health Centre (CCWHC) encompasses Canada's veterinary colleges[88] and serves as a national repository for wildlife data it generates, as well as data generated by other agencies. It has also been involved in the active surveillance of diseases, such as WNV, avian influenza, and chronic wasting disease.[88] Finally, the Public Health Agency of Canada (PHAC), in collaboration with the National Microbiology Laboratory in Winnipeg, collects limited data on zoonotic diseases while collating data submitted by individual provinces. PHAC also manages the National Enteric Surveillance Program (NESP) to quantify the incidence of food-borne illness, including those of zoonotic origins.

Alberta

The Alberta Veterinarian Surveillance Network (AVSN) is an EZD surveillance system that is a component of a well-developed poultry and cattle surveillance. Run by the Food Safety and Animal Health Division, this agency caries out continued surveillance of cattle, poultry, and food safety for public health events with the goal of early outbreak detection to allow a fast and effective response.[89,90] The AVSN is comprised of the Veterinary Practice surveillance system (VPS), Livestock Pathology Consultation Program (LPCP), and a Livestock Disease Investigation Network (LDIN).[90]

The VPS provides an internet-based framework for reporting livestock diseases, while the LPCP is made up of a team of veterinary pathologists who investigate animal health issues. The LDIN is a group of livestock epidemiologists and veterinarians who investigate disease outbreaks.[90] The AVSN carries out syndromic surveillance on cattle herds throughout the province and data is collected, analyzed, and distributed back to participating veterinarians. This system incorporates both laboratory and syndromic surveillance and recognizes outbreaks through increases in the levels of disease occurrence. Detection of unusual mortality, caused by diseases of unknown etiology, is followed by an outbreak investigation, including diagnostic pathology and pathogen identification at the National Microbiology Laboratory in Winnipeg, Manitoba. Data from participating veterinarians are submitted via the web to a data warehouse from which reports can be quickly generated and viewed by participants. Automated analysis is also undertaken, resulting in automated alerts for suspicious disease events. When detected, Federally Reportable Diseases are reported to the CFIA.[90]

Quebec

In order to facilitate monitoring of animal disease, the Directorate of Animal Health and Meat Inspection (DSAIV) in Quebec has created *le RAIZO*, the **R**eseau d'**A**lerte et d'**I**nformation **ZO**osanitaire (Animal Health Alert and Information Network).[91] Le RAIZO is comprised of regional veterinarians, sentinel networks, zoonotic disease surveillance, and a laboratory network and is mandated to continually monitor Quebec's livestock population health. The sentinel surveillance network is comprised of governmental veterinarians, specialists, and pathologists who communicate through periodic conference calls with the goal of identifying increases in disease incidence or disease severity in poultry, pigs, horses, cattle, sheep, bees, fish, and other wildlife.[91] A single veterinarian represents a regional group and is responsible for epidemiological surveys and biological sampling of potential zoonotic cases.[92] Information on potential zoonoses gathered through these meetings is shared according to a signed agreement between public health authorities and animal health agencies.[92] The laboratory network is comprised of three laboratories: the Quebec Animal Health Surveillance Laboratory (LEAQ), the Quebec Animal Pathology Laboratory (LEPAQ), and the Animal Pathology Regional Centre (CRP).[93] Data from these networks is combined through SILAB, a computer tool that collects all data from provincial laboratories and slaughterhouses. Focused surveillance exists for avian influenza, Salmonella in swine, *Salmonella enteritidis* in hens, rabies in racoons, skunks, and passive antibiotic resistant surveillance.[91]

British Columbia

The British Columbia Centre for Disease Control tracks potential cases of zoonotic disease by identifying unique cases of human illness and carrying out a detailed follow-up to gain information on travel history and animal contact.[94] Such passive surveillance approaches can effectively detect novel disease, as illustrated by the identification of a novel *Cryptococcus gattii* outbreak in BC in 1999.[95] Animal surveillance is currently not included in BC's animal health framework, and what is done is either mandated at the federal level or done in co-operation with industry.[96] The BC Ministry of Land and Agriculture's (MAL) Animal Health Centre (AHC) serves as the provincial animal laboratory and works in co-operation with agriculture industries, the CCHW, zoos, and aquariums to diagnosis disease in animal samples or cadavers.[94] Wildlife surveillance in BC is lead by the Ministry of Environment (MOE), in co-operation with the CCWHC and the Centre for Coastal Health; priorities include: monitoring wildlife health trends; new emerging issues, such as Chronic Wasting Disease; avian influenza; bovine tuberculosis; endemic diseases in high priority species; and diseases transmissible among wildlife and domestic animals.[97]

H5 and H7 influenza are currently the only animal diseases reportable to public health and improved communication between animal and human health has been identified as a gap in provincial EZD surveillance. Efforts are underway to make 14 additional animal diseases reportable to Public Health, including WNV.[98] BC's Zoonotic Disease Advisory Committee, which includes members of MAL, BCCDC, CFIA, and the MOE, meet quarterly to facilitate zoonotic disease prevention. Similarly, yearly zoonotic disease meetings function to strengthen lines of communication between public health, animal health, researchers, government officials, and students. Finally, an Integrated Salmonella Surveillance System has recently been created in BC which includes animal, food, and human health components.[99] This system may provide an ideal starting point for future integrated EZD surveillance.

Current Gaps in EZD Surveillance in Canada

- **Legal mandate for animal surveillance[80]**: Limited animal surveillance, especially outside the agricultural setting, limits zoonotic disease surveillance and control. If public health truly aims to prevent disease, a stronger focus needs to be placed on detecting zoonotic disease emergence prior to the species jump.

- **Legally mandated data sharing agreement between animal and human health**: Legally binding data sharing agreements, similar to those found in Quebec,[93] should become standard practice.

- **Appropriate funding:** It is easier to get funding for expensive emergency responses than for preventive surveillance.[62] Governments and funding bodies need to recognize the potential cost effectiveness of surveillance and early prevention of zoonotic disease.[100] It must also be recognized that cost-sharing measures may be required to access animal surveillance data from private labs.

- **Standardized methodologies and evaluation criteria**: This absence of standardized EZD surveillance methods stems in part from a failure to evaluate current systems. Critical appraisal of current approaches is needed to improve future surveillance efforts.[80]

Conclusion

EZD surveillance is challenging in light of limited public health resources.[83] The working group on *Sustaining Global Surveillance and Response to Emerging Zoonotic Diseases* failed to find a "single example (across the world) of a well-functioning, integrated, zoonotic disease surveillance system across human and animal health sectors."[62] Furthermore, only 30% of peer-reviewed EZD surveillance systems actually focus on unknown pathogens.[80]

Improvements in EZD surveillance in Canada are needed to address the issues identified above. However, such changes are unlikely to occur quickly and current EZD detection often results from an astute clinician or animal health expert who recognizes an abnormal disease cluster and contacts their animal or human health counterparts. Therefore, the practical effectiveness of EZD surveillance depends on the strength of relationships between public health, clinical, veterinary, and agricultural personnel. EZD surveillance in BC may be improved by implementing legally mandated data sharing between human and animal health, similar to that found in Quebec. In addition, dedicated surveillance of agricultural animals and key wildlife species, specifically those known to be vectors and reservoirs of multiple diseases, may serve as an early warning system for pathogen range expansions or the emergence of novel diseases. Such systems would require stable funding.

Despite the challenges, improvement in EZD surveillance can be expected as academic movements calling for improved interdisciplinary communication *(One Health*,[101] *One Medicine*,[102] *Conservation Medicine*,[103] and *EcoHealth*[104]) are implemented. Finally, it should also be recognized that the quality of pre-existing public and animal health infrastructure determines the ability for rapid identification, case follow-up, control, and future surveillance that will minimize the impact of emerging disease. Continued funding for public and animal health systems, complete with clearly defined reportable infectious disease surveillance, will ensure the existence of infrastructure required for future EZD surveillance.

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