

Linking Human and Animal Notifiable Zoonotic Disease Data in Washington State

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Abstract

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Introduction: Although zoonoses are of increasing public and veterinary health concern, and the ‘One Health’ initiative has intensified demand for collaborative zoonoses surveillance, most human and animal disease surveillance systems operate independently. The purpose of this study was to demonstrate the feasibility of integrated approaches to passive zoonoses surveillance in Washington (WA) State, and to explore their potential to improve disease prevention, control, and treatment actions. **Methods:** We linked and analyzed data on endemically acquired leptospirosis and psittacosis cases in animals and humans reported to the WA State Department of Agriculture and the WA State Department of Health, respectively, from 1993-2016. **Results:** A significantly higher average number of human and animal leptospirosis reports per month were made from August-December than from January-July. For both diseases, the majority of cases were reported in counties with higher human and pet population densities. Higher pet dog population was associated with increased risk of a human case of leptospirosis in the same

county and year, and higher pet bird population and the report of an avian case were associated with increased risk of a human case of psittacosis, although the positive predictive value and sensitivity for an avian case were low. The estimated incidence of psittacosis in pet bird owners and pet shop workers was substantially higher than for all state residents combined.

Conclusions: The results of this study may help WA State public and veterinary health officials target disease prevention and control interventions at seasons, counties, and populations at highest risk of infection.

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INTRODUCTION

INTEGRATED ZOO NOTIC DISEASE SURVEILLANCE

Zoonotic diseases – diseases that are transmissible between animals and humans – make up 58% of all recognized human pathogen species.¹ They are responsible for more than half of emerging infectious diseases that have appeared in humans over the past six decades,² and about 56% of disease outbreaks that have occurred around the world since 1980.³ Zoonotic diseases are of general public health concern, but in particular threaten the health and wellbeing of animal workers – such as veterinarians, animal lab technicians, wildlife biologists, farmers, and slaughterhouse workers – who come into close contact with different animals on a regular basis.⁴ There is growing concern that changes in climate, agricultural intensification, and expansion of human settlements and activities (e.g. recreation and farming) into wildlife habitats may trigger or are triggering an increase in the incidence of zoonoses in both humans and animals worldwide.^{5,6}

Over the past few decades, a multidisciplinary approach to improve the health of humans, animals, and the environment – referred to as ‘One Health’ – has gained international momentum.^{7,8} The ‘One Health’ initiative has fostered increased demand for collaboration in the field of disease surveillance,^{9,10} a vital tool in the monitoring of communicable diseases, including zoonoses.¹¹ Because humans and animals (especially domesticated animals, and to a lesser extent wildlife) often share the same environments and are susceptible to many of the same pathogens, integration of human and animal disease data is essential for effective ‘One Health’ disease surveillance.¹² A few systems exist that integrate human and animal surveillance data, either on global or regional scales, such as the United States (U.S.) Centers for Disease Control and Prevention’s (CDC’s) national arboviral surveillance system, ArboNET,¹³ and the

CDC's One Health Harmful Algal Bloom System (OHHABS).¹⁴ These and most other such systems were initiated in the past two decades, and some utilize existing data collected for different purposes.^{a,15} Furthermore, as the public and veterinary health communities become increasingly aware of the potential benefits of integrated human and animal disease surveillance systems, several studies have been conducted exploring their feasibility.^{10,16}

Nevertheless, in most parts of the world, human health surveillance systems and animal health surveillance systems operate as independent entities.^{12,17} At the federal level in the U.S., the CDC is responsible for gathering and analyzing reportable public health surveillance data collected by state departments of health.¹⁸ Likewise, the U.S. Department of Agriculture oversees a national animal disease reporting system, while each state also maintains its own local system for timely disease prevention and control purposes.¹⁹ Across the U.S., state-level public health, agricultural, and wildlife agency websites generally collect, store, and present their zoonoses data obtained through passive surveillance in different formats (e.g. Excel spreadsheet, PDF, text embedded directly into the webpage, etc.).²⁰ Furthermore, temporal gaps and potentially missing data exist in the disease surveillance databases of both human and animal health agencies at the state-level, but particularly with respect to animal health agencies. Gaps and missing data due to lack of consistent, standardized reporting methods across agencies are problematic because they may lead to an underestimation of zoonotic disease infection within human and animal populations. Inability to efficiently and thoroughly integrate data collection from public health, agricultural, and wildlife agencies, with appropriate data analysis, interpretation, and reporting, as well as gaps in communication between human and animal health agencies, all impede our ability to detect zoonotic disease outbreaks and identify trends,

^a ArboNet is an exception, as it is based on data collected expressly for its own use.

thus compromising our capacity to focus public and veterinary health prevention and control actions where they are needed most.

Communication of disease surveillance findings to the appropriate parties is a foundational component of functional disease surveillance systems. A chilling example of the potential consequences of inadequate communication between human and animal health agencies comes from the Netherlands.²¹ Q fever, caused by the intracellular bacterium *Coxiella burnetii*, causes minimal illness but may lead to abortions and stillbirths in the animals it naturally infects – such as goats, in this case. In humans, it mainly is seen as a rare occupational disease in farmers, veterinarians, and slaughterhouse workers, who likely become infected through contact with the birth fluids, urine, feces, or milk of infected animals. Between 2007-2009, the Netherlands saw an unprecedented wave of human Q fever cases, with 2,300 victims including six deaths by 2009, predominantly in individuals who never had animal contact. Although it is unclear whether goat-farming intensification in the country or a more virulent bacterial subtype incited the outbreak, it is evident that the preceding increase in *C. burnetii* goat infections observed within the veterinary community was not properly communicated to public health officials. Some speculate that this lack of transparency was due to concerns over potential economic losses. Ironically, the Dutch government culled 40,000 pregnant goats at more than 60 farms in 2009 in an effort to stop the outbreak, decimating many tribes. Collaboration and improved channels of communication between animal and human health agencies may have mitigated this economic fallout, and saved animal and human lives.

INTEGRATED SURVEILLANCE IN WASHINGTON STATE

Here in Washington (WA) State, as in most parts of the U.S., veterinary offices and laboratories report notifiable animal diseases²² to the Animal Services Division (ASD) of the

Washington State Department of Agriculture (WSDA) and human health practitioners and laboratories report notifiable human diseases²³ to the Washington State Department of Health (DOH). Many of these notifiable human and animal conditions are zoonotic and, therefore, are of both public and veterinary health relevance. Some zoonoses data are shared between WSDA and DOH, but at this time there is no official standard operating procedure related to data sharing, no common zoonotic disease reporting method, and no central data repository. Furthermore, until very recently, zoonoses data at each agency were stored in different formats, with animal case data at WSDA stored on paper records and human case data at DOH stored electronically, which made data integration across agencies extremely challenging. Consequently, to date, few descriptive comparisons and statistical analyses of linked animal and human zoonotic disease surveillance data in the state have been performed. We wished to reduce this research deficit and demonstrate the feasibility of integrated approaches to passive zoonoses surveillance, which has the potential to improve both public and veterinary health in WA State. In particular, we investigated the relationships between reported endemically acquired animal and human cases of leptospirosis and psittacosis in WA State from 1993-2016. Our decision to focus on these two diseases was based on an initial review of reported disease cases in animals (please see study objective 1 on page 9 for further details), which showed that leptospirosis and psittacosis were two of the most frequently reported diseases in animals from 1993-2016 that also were notifiable in humans. Furthermore, both diseases have associated public and veterinary health interventions for their effective prevention, treatment, and control.

LEPTOSPIROSIS

Leptospirosis is a bacterial disease caused by gram-negative spirochetes of the genus *Leptospira*.²⁴ It is considered an emerging infectious disease and is one of the most significant

zoonotic diseases around the world, although it is relatively rare in the U.S.²⁵ Infection manifests clinically in many mammals, including humans, dogs, horses, cows, sheep, and pigs.²⁴

Leptospira spirochetes exist subclinically in many wildlife species, most notably rats and other rodents, as well as raccoons, opossums, reptiles, and frogs.

In humans, the average incubation period is about 10 days but ranges from 2-30 days.²⁶ Clinical symptoms in humans may include acute onset uveitis, conjunctival suffusion, myalgias, fever, renal failure, and jaundice.²⁴ While most human infections are mild and self-resolving, approximately 10% of cases are severe and may be fatal. In dogs (which represent the majority of animal cases reported in WA State between 1993-2016; please see the results section beginning on page 18 for further details), the incubation period may range from 4-12 days²⁷ and clinical symptoms may include acute renal failure, fever, depression, lethargy, and uveitis.²⁴ Serological laboratory testing may be utilized in diagnosing both humans and animals. In humans, antibiotic prophylaxis may be an option for high-risk exposures over short periods. Treatment in humans and animals includes antibiotic initiation as early in the course of disease as possible, although this may not be curative, and possibly supportive care and hemodialysis.

Typically, humans are exposed to leptospire when they come into contact with water, moist soil, or food that is contaminated with the urine or other bodily secretions/excretions of an infected animal, or when they come into direct contact with an infected animal.²⁴ The bacteria then enter the body through mucous membranes or breaks in the skin. Both human and animal outbreaks are associated with rainfall and flooding, which increase the prevalence of the bacteria's preferred environments of moist soil and standing water. Historically, outbreaks in highly endemic tropical areas have occurred in rural and/or agricultural areas following heavy precipitation, which force leptospire out of the soil and into natural and built water sources.²⁸

Since the turn of the century, outbreaks in non-endemic regions as well as in urban centers of endemic regions have become increasingly common. This escalation largely is attributed to the growing popularity of recreational activities in natural bodies of water, such as adventure racing and endurance events, as well as tourism and international travel.²⁹ Leptospirosis also poses an important occupational risk for many animal workers, including farmers, dairy and slaughterhouse workers, butchers, hunters, dog handlers, and veterinary health professionals.²⁴

A number of key public health actions are associated with leptospirosis, including performing descriptive epidemiology in humans and animals, educating the public about modes of disease transmission, controlling rodent populations, educating veterinary and human health professionals as well as pet owners about prevention in high risk groups and symptoms of infection in humans, promoting and maintaining a high level of canine vaccination as part of routine veterinary vaccination protocols in the U.S. pet dog population, educating occupational health providers about high risk workers and disease recognition, promoting use of personal protective equipment (PPE) in workers at risk, and disinfecting contaminated environments.²⁴ Other associated veterinary public health and animal health actions include quarantining and treating infected animals, vaccinating other at-risk animals such as cows and pigs, seeking appropriate occupational health care if exposed to an infected animal in clinic, encouraging owners of infected pets to contact their medical provider if they develop symptoms or for further advice, contacting the medical provider directly if the veterinarian suspects human infection, and reporting animal cases to the appropriate authority if required by state law.

PSITTACOSIS

Psittacosis, also known as ornithosis, avian chlamydiosis, and parrot fever, is caused by the intracellular bacterium *Chlamydophila psittaci*.²⁴ The disease occurs in humans worldwide

and, although relatively few human cases are reported each year in the U.S., because of the broad spectrum of clinical manifestations, many human cases likely go undetected and therefore unreported. *C. psittaci* appears in most birds and especially psittacine birds (members of the parrot family such as parakeets, cockatiels, macaws, conures, and budgerigars), which are popular as pets. It also may infect turkeys, ducks, occasionally chickens, other wild birds including seabirds and raptors, and various mammals including dogs, cats, horses, cows, goats, sheep, pigs, muskrats, and wild ungulates.^{24,30,31} In both birds and mammals, many infections are subclinical.

In humans, the incubation period is 5-15 days³² and symptoms of infection may range from mild flu-like illness with headache, myalgias, cough, and photophobia, to severe pneumonia, acute respiratory distress syndrome, and sepsis.²⁴ In birds (which represent all animal cases reported in WA State between 1993-2016 for which animal type was specified; please see the results section beginning on page 18 for further details), the incubation period varies from three days to several weeks with latent infections possible. Although many infected birds do not exhibit clinical symptoms, the disease may cause significant morbidity and mortality in psittacine birds in particular, including lethargy, diarrhea, malaise, and conjunctivitis. In humans, diagnosis typically is confirmed by serology, and in birds, a combination of culture, antibody testing, and antigen detection generally is used. Treatment in both humans and birds primarily involves antibiotic administration.

Humans may be exposed to *C. psittaci* either through direct contact with an infected animal (e.g. beak-to-mouth contact when kissing a pet bird) or through contact with food or environments contaminated with the bodily secretions/excretions of an infected animal.^{24,33} The pathogen may enter the body through mucous membranes, ingestion, or aerosol inhalation.

Human-to-human transmission through close contact has been documented.³⁴ Environmental factors that increase the risks of infection and transmission include crowded and stressed bird populations as well as poor sanitation and ventilation.²⁴ *C. psittaci* is capable of surviving for prolonged periods of time in the environment under certain conditions, which may increase the likelihood of reinfection. Owners of pet birds are at increased risk of infection, as are a number of occupational groups including workers in pet stores that sell birds, pet bird breeders, veterinarians, zookeepers, poultry workers, and diagnostic laboratory workers.

Public health responsibilities related to psittacosis include determining risk of infection in community members from pet shops that sell birds, pet bird ownership, aviaries, and poultry production,²⁴ assimilating the National Association of State Public Health Veterinarians *Compendium of Measures to Control Chlamydia psittaci Infection Among Humans (Psittacosis) and Pet Birds (Avian Chlamydiosis)*,^{24,30} investigating and detecting human cases and sources of infection, such as through the surveilling of pet shops and poultry operations,²⁴ overseeing the treatment or culling of infected birds and ensuring the disinfection of contaminated environments, working with agricultural agencies to control the infection in bird populations, and educating pet shop and poultry workers about the occupational risk of psittacosis and proper implementation of exposure controls and PPE. Associated veterinary animal and public health actions include diagnosing and treating infected birds, teaching bird owners to recognize psittacosis symptoms in their pets and ways to reduce the risk of pet bird exposure and transmission to humans, following official reporting requirements in their state, and finally training other veterinary staff to employ biosecurity measures such as use of PPE and personal hygiene to prevent zoonotic transmission and spread to other animals.

STUDY OBJECTIVES

The objectives of this study were as follows:

- **Objective 1:** Describe the notifiable animal conditions reported to WSDA from 1993-2016
- **Objective 2:** Characterize the temporal and/or spatial relationships between reported endemically acquired (i.e. acquired in-state) animal and human cases of leptospirosis and psittacosis in WA State from 1993-2016
- **Objective 3:** For leptospirosis and psittacosis, determine whether the number of reported endemically acquired human cases per year was associated with the reported number of endemically acquired animal cases per year in WA State from 1993-2016
- **Objective 4:** For leptospirosis and psittacosis, determine whether an endemically acquired animal disease report in a given year and WA State county could be used to predict the occurrence of an endemically acquired human case in that same year and county, accounting for other plausible human risk factors including human and animal population densities and climate
- **Objective 5:** Estimate and compare the incidence of endemically acquired psittacosis in WA State residents with that in WA State pet bird owners and pet shop workers from 1993-2016

We identified and addressed these objectives to explore their potential usefulness in assisting WA State public and veterinary health officials in the monitoring of the occurrence of leptospirosis and psittacosis in animals and humans in the state, targeting seasons, counties, and populations at highest risk, undertaking more timely disease outbreak detection, increasing the effectiveness of outbreak response, and improving disease prevention, control, and treatment

actions. In addition, achievement of the fourth objective may help human health agencies determine if there is sentinel value in awareness of leptospirosis or psittacosis in animals (i.e. animals as sentinels for human disease risk).

METHODS

We developed and analyzed an integrated dataset containing information from cases of endemically acquired animal and human leptospirosis and psittacosis reported in WA State from 1993-2016, as well as county and state-level demographic and climate data. All analyses were performed in R.³⁵

DATA ASCERTAINMENT

We abstracted data on reported cases of notifiable animal diseases from paper records at WSDA. WSDA receives reports of notifiable animal diseases from veterinary offices and laboratories via fax, phone, and occasionally email, and historically has kept separate records for each data stream. Faxed data typically are monthly reportable disease forms, in which veterinary offices and labs indicate the total number of each disease diagnosed in the past month, almost always without any additional details such as animal type. These faxes historically were kept on paper and extend back to 2004. WSDA also receives phone calls from veterinary offices and labs of a notifiable condition in one or more animals. These data also historically were recorded on paper and extend back to the end of 1992. Variables recorded for each phone call are date of phone call, animal type, animal origin, number of infected animals, disease, and location of veterinary office or laboratory. To protect owner privacy, WSDA does not record any geographic information related to owner and/or animal residency. Email reports are relatively infrequent and historically neither were consistently sent to the WSDA staff members responsible for notifiable

animal disease recordkeeping (e.g. email reports may have been sent from veterinary offices directly to WSDA's State Veterinarian or one of the regional veterinarians) nor systematically recorded. Although there may be some overlap between cases reported via fax, phone, and email (e.g. some cases called into WSDA may also be represented on monthly reportable disease forms faxed to the agency), there is no way to determine which cases are duplicates. Because the phone records are by far the richest of the three data streams, both in terms of number of reports and number of variables per report, these are the only data we used for this study. We began data abstraction at 1993, as this was the first full year for which phone data were available, and ended at 2016, as this was the most recent year for which human notifiable zoonotic disease data were available.

Data on endemically acquired human cases of leptospirosis and psittacosis reported to DOH from 1993-2016 were obtained directly from the DOH Office of Communicable Disease Epidemiology. Both probable and confirmed cases were included for both diseases, based on the Council of State and Territorial Epidemiologist case definitions in the year of report.^{36,37} Human case variables included reporting local health jurisdiction (LHJ), which represented the patient's county of residence, as well as year and month of disease onset. The DOH data manager determined that this data request qualified for Institutional Review Board (IRB) exempt status, and therefore did not require IRB approval. To protect patient confidentiality, unique identification numbers void of protected health information were used to identify patient data. Raw data were stored on a password-protected computer in a password-protected file accessible only to members of the study team.

A number of important assumptions were made about the animal and human disease data. Note that the date associated with each animal case reflected the date of report to WSDA, while

the date associated with each human case reflected the date of disease onset. In addition, the geographic information for each animal case represented the location of the treating veterinarian, while the geographic information for each human case represented the location of patient residence. In the following analyses, we assumed that for both animal and human cases, the date represented the date of disease onset and the location represented the place of exposure and residence. Although laboratory records were not available for any animal cases of leptospirosis and psittacosis, based on personal communication with WSDA ASD staff, it is our understanding that most if not all cases of these diseases reported to WSDA were laboratory confirmed; therefore, we assumed all animal cases of both diseases used in this study were laboratory-confirmed. Finally, the animal origin variable in the animal disease dataset indicated the last known place of residence of the animal before WA State (e.g. a pet dog adopted in a WA State shelter may have been transferred from a shelter in Texas (TX), in which case the animal origin would be “TX”). However, WSDA does not record the length of time an animal of out-of-state origin has been in WA State, so it is difficult to discern the likelihood that the animal was infected outside the state. Because the vast majority of animals with reported leptospirosis and all birds with reported psittacosis were either of unknown or WA State origin (see results section beginning on page 18), in this study we assumed that all animal cases of both leptospirosis and psittacosis reported to WSDA from 1993-2016 were endemically acquired.

State and county-level demographic data for each year from 1993-2016 were obtained from the Washington State Office of Financial Management (OFM).³⁸ For population count and density data, intercensal estimates were used from 1993-2010, and postcensal estimates from 2011-2016. For housing data, postcensal estimates of total housing units were used for all years. Estimates of total annual precipitation per county were obtained from the Northwest Alliance for

Computational Science and Engineering's PRISM Climate Group, based at the University of Oregon.³⁹ Precipitation estimates were available only up to 2015, so data for 1993-2015 were abstracted.

As we were unable to find data on the number of pet dogs and birds in WA State by county, we estimated these values using methods recommended by the American Veterinary Medical Association (AVMA).⁴⁰ The recommended formulas are shown below:

Number of dogs = $0.584 * \text{total number of households in county}$

Number of birds = $0.071 * \text{total number of households in county}$

To use these formulas, we assumed the local demographics and rates of pet ownership in WA State counties from 1993-2016 were similar to the national demographics and rates of pet ownership upon which the formulas are based.

CHARACTERIZATION OF NOTIFIABLE ANIMAL CONDITIONS

In order to describe the notifiable animal conditions reported to WSDA from 1993-2016, we reviewed the number of each notifiable disease reported in that time frame according to WSDA's phone records (see data ascertainment section beginning on page 10 for further information). Based on this review, we focused the remaining analyses on leptospirosis and psittacosis, as these were two of the most frequently reported diseases in animals from 1993-2016 that also were notifiable in humans; moreover, both have associated public and veterinary health interventions for effective disease prevention, treatment, and control (see sections dedicated to leptospirosis on page 4 and psittacosis on page 6 for further details).

TEMPORAL AND SPATIAL COMPARISONS OF HUMAN AND ANIMAL SURVEILLANCE

To investigate any temporal relationships between reported endemically acquired animal and human cases of leptospirosis and psittacosis in WA State from 1993-2016, we graphed statewide animal and human case counts per year for each disease. In addition, to investigate any seasonal trends, we collapsed the years and plotted the total number of animal, human, and cumulative (animal and human combined) cases each month from 1993-2016. For leptospirosis, we also calculated the average number of cumulative cases reported per month from January to July and from August to December, and performed a two-sided t-test allowing for unequal variances to compare these means.

To investigate any spatial relationships between reported endemically acquired animal and human cases of leptospirosis and psittacosis, we mapped the total number of animal and human reports per county in WA State from 1993-2016 for each disease. For leptospirosis, only the total numbers of canine cases were mapped (canine cases represented the majority of animal cases reported in WA State between 1993-2016; please see the results section beginning on page 18 for further details). We also mapped the average human, pet dog, and pet bird population densities per county from 1993-2016. Annual pet population densities were calculated by dividing the estimated number of pets per county per year by the area of the county. For county area, we used the average of the three area estimates given in the human population density dataset from OFM. Finally, for each county we mapped the incidence of leptospirosis in humans and dogs and the incidence of psittacosis in humans and birds by dividing the total number of cases reported from 1993-2016 by the average population (for humans, pet dogs, and pet birds, accordingly) over that time frame.

LINEAR REGRESSIONS OF ANNUAL STATEWIDE COUNTS

To determine whether there was an association between the annual number of reported endemically acquired human cases and the annual number of reported endemically acquired animal cases of leptospirosis and psittacosis in WA State, for each disease we plotted the statewide number of human cases against the statewide number of animal cases per year from 1993-2016, and performed a bivariate linear regression of the number of human cases on the number of animal cases reported in that year, as well as a multivariate linear regression of the number of human cases on the number of animal cases reported and the estimated statewide human population that year. Statistical significance was evaluated at the $\alpha = 0.05$ level.

MULTIVARIATE RISK MODELING OF HUMAN CASES

To explore whether animal disease reports of endemically acquired leptospirosis or psittacosis could be used to predict the occurrence of an endemically acquired human case, we fit bivariate and multivariate logistic regression models for each disease on a number of risk factors for human infection. The outcome for each model was the binary occurrence of a human case in a given year and county in WA State. Independent covariates were the binary occurrence of an animal case (canine for leptospirosis and avian for psittacosis) reported in that same year and county and the estimated human and pet population densities (pet dogs for leptospirosis and pet birds for psittacosis) in that year and county. Because leptospirosis is a climate sensitive disease, annual county-level precipitation also was included as a covariate in the leptospirosis models. As stated above, precipitation data were available only until 2015, so the leptospirosis models included data from 1993-2015, while the psittacosis models included data from 1993-2016. Any independent variables that showed a significant association ($p \leq 0.1$) with the occurrence of a

human case in the bivariate analyses were included in the multivariate analysis. Because human population density was highly correlated with both pet dog and pet bird population density, human population density was left out of the multivariate models. The statistical significance of each odds ratio (OR) was evaluated at the $\alpha = 0.05$ level. Because these diseases are rare in WA State, for both we assumed that the OR was a reasonable approximation of the relative risk (RR).

POSITIVE PREDICTIVE VALUE AND SENSITIVITY OF AN INTEGRATED SYSTEM

To further explore whether animal disease reports could be used to predict the occurrence of human disease reports, for both leptospirosis and psittacosis we calculated the positive predictive value (PPV; a measure of predictive utility) and sensitivity (a measure of test validity) of the integrated disease surveillance data. In these analyses, PPV was the probability of a reported human disease case in the same year and county given a reported animal disease case ($PPV = A/(A+B)$, see table below); sensitivity was the probability of a reported animal disease case in the same year and county given a reported human disease case (sensitivity = $A/(A+C)$, see table below), i.e. sensitivity was the proportion of “true” human cases captured by an integrated system treating animal disease reports as a tool for predicting human disease reports in the same year and county. For leptospirosis, both equine and canine cases were included in the animal case counts.

Reference table for positive predictive value (PPV) and sensitivity calculations.
 $PPV = A/(A+B)$; sensitivity = $A/(A+C)$.

		Human Case		Total Cases
		Yes	No	
Animal Case in Same Year & County	Yes	A	B	A+B
	No	C	D	C+D
Total Cases		A+C	B+D	

EXPLORATORY ANALYSES OF PSITTACOSIS INCIDENCE

Finally, to explore whether pet bird owners and pet shop workers might be at higher risk of psittacosis, we calculated and compared the incidence of endemically acquired psittacosis in all WA State residents and in WA State pet bird owners and pet shop workers from 1993-2016. The incidence in state residents was calculated by dividing the total number of human cases reported from 1993-2016 by the average estimated statewide population over that time frame.

The number of cases in pet bird owners and pet shop workers was estimated to be 88% of all cases reported, based on information communicated directly to the study team by the DOH Office of Communicable Disease Epidemiology. The number of pet bird owners in the state each year was calculated by multiplying the estimated number of pet bird-owning households by the estimated number of persons per household. As we were unable to find data on the number of pet bird-owning households in WA State per year, we estimated these values using the method recommended by AVMA.⁴⁰ The recommended formula is shown below:

$$\text{Number of bird-owning households} = 0.031 * \text{total number of households in WA State}$$

To use this formula, we assumed the local demographics and rates of bird ownership in WA State between 1993-2016 were similar to the national demographics and rates of bird ownership upon which the formula is based. We used OEM demographic data to estimate the number of persons per household each year by dividing the estimated statewide population by the estimated total number of households. To calculate incidence, the average number of pet bird owners in Washington State per year from 1993-2016 was used as a proxy for the number of pet bird owners and pet shop workers combined, as the number of pet shops that sell birds in the

state is relatively small, and therefore the number of pet shop workers at risk likely is a relatively small fraction of the true total.

RESULTS

FREQUENCIES OF ANIMAL DISEASES REPORTED TO WSDA

Figure 1 shows the number of cases for each notifiable animal disease reported to WSDA from 1993-2016 in a bar chart. During this time frame, there was only a single case reported for most reportable animal diseases. However, psittacosis, heartworm, and leptospirosis were reported notably more frequently than other diseases, with 94, 103, and 117 case reports, respectively. Although all three of these diseases are zoonotic,^{24,41} only psittacosis and leptospirosis also were notifiable conditions in humans in WA State during this time frame. Therefore, the following analyses of linked animal and human notifiable zoonotic disease data focused on leptospirosis and psittacosis.

DESCRIPTIVE STATISTICS OF LEPTOSPIROSIS AND PSITTACOSIS

Table 1 summarizes the cases of leptospirosis and psittacosis in animals and humans reported to WSDA and DOH, respectively, from 1993-2016. One hundred ten reports totaling 117 cases of animal leptospirosis were made to WSDA during this period (some reports indicated more than one affected animal). An average of 4.9 animal cases were reported in WA State each year, with a standard deviation of 6.3 and a range of 0-24. In eight of these years, no animal cases were reported. One hundred fifteen cases were in dogs, representing the vast majority of all cases reported (98%). The other two cases (2%) were in horses. Of the dogs, one originated in Arizona, one in Texas, 57 in WA State, and 56 were of unknown origin; of the

horses, one originated in Pennsylvania and the other was of unknown origin (data not shown). Again, we assumed all animal cases were endemically acquired (see methods section beginning on page 10 for further details). Twenty reports of endemically acquired human leptospirosis were reported to DOH between 1993-2016, totaling 20 cases. An average of 0.8 human cases were reported in WA State each year, with a standard deviation of 1.4 and a range of 0-5. In 15 of these years, no human cases were reported.

Forty-four reports totaling 94 cases of animal psittacosis were made to WSDA from 1993-2016. An average of 3.9 animal cases were reported in WA State each year, with a standard deviation of 10.8 and a range of 0-53. In 10 of these years, no animal cases were reported. Ninety-one cases were in birds, representing the vast majority of all cases reported (97%). The other three cases (3%) were in unspecified animals. However, because psittacosis predominantly is a disease of birds, for all analyses conducted in this study, we assumed these three cases also were avian cases. Table 2 provides further breakdown of the details of case reports that specified avian patients. The majority of cases were in unspecified birds, but a number of reports indicated psittacine birds, including eight (9%) cockatiels, four (4%) macaws, and three (3%) Amazon parrots. In addition, a few reports specified non-psittacine birds, including one dove, one finch, and one racing pigeon. Sixty-five birds originated in WA State and 29 were of unknown origin (data not shown). Again, we assumed all avian cases were endemically acquired (see methods section beginning on page 10 for further details). Twenty-six reports of endemically acquired human psittacosis were reported to DOH from 1993-2016, totaling 26 cases. An average of 1.1 human cases were reported in WA State each year, with a standard deviation of 1.9 and a range of 0-7. In 15 of these years, no human cases were reported.

TEMPORAL AND SPATIAL PATTERNS IN ANIMAL AND HUMAN CASES

Figure 2 shows graphs of the number of endemically acquired animal and human cases of leptospirosis and psittacosis reported in WA State each year between 1993-2016. For leptospirosis, we generally found more animal cases than human cases reported per year. Over time, we observed an increase in the number of cases reported in latter years, especially for animals, with no cases reported in many of the earlier years. In addition, we observed different patterns of disease occurrence between humans and animals, with many years in which one or more animal cases were reported but no human cases, and vice versa. For psittacosis, our observations related to disease occurrence were similar, with generally more avian cases than human cases reported per year and different patterns of disease occurrence between humans and birds. However, in contrast to what we observed for leptospirosis, over time we saw a decrease in the number of cases reported for both birds and humans, with no cases reported in many of the later years. In 1998, the spike in avian cases was due to a single report of 50 infected birds from Spokane County in April. Although official details of this report were not available to the study team, based on personal communication with WSDA ASD staff, it is our understanding that these 50 avian cases occurred in a pet shop.

Figure 3 shows the number of animal, human, and total (animal and human combined) cases of each disease reported per month in WA State from 1993-2016. For leptospirosis, the total number of cases reported appears to increase in later months, from August to December. From January to July, an average of 8.3 total cases of leptospirosis were reported per month from 1993-2016 (SD = 3.5 reports/month); from August to December, an average of 15.8 cases were reported per month (SD = 3.9). Based on the results of a two-sided t-test allowing for unequal variances, we concluded these means were significantly different from one another ($\alpha = 0.05$, $t =$

-3.4, $df = 8.1$, $p = 0.009$). For psittacosis, no monthly patterns were discernible. Again, note that the spike of bird cases in April was due to a single report of 50 infected birds in Spokane County in 1998.

Figure 4 shows a map of WA State counties, which we used to display reported disease occurrence spatially, and which facilitated interpretation of the data. Figure 5 shows the total number of canine and human leptospirosis cases reported in each county from 1993-2016, as well as the estimated average pet dog and human population densities, and canine and human incidences over that time frame. These visualizations show that the majority of both canine and human cases of leptospirosis were reported in Western WA State (especially King, Pierce, Thurston, and Kitsap Counties for dogs, and King and Clark for humans), and in counties with higher pet dog and human population densities. They also show that while there was a fair amount of overlap in the counties where canine and human cases were reported from 1993-2016, there also were a number of counties in which a canine case was reported but no human cases were reported, and vice versa. The maps of estimated incidence paint a notably different picture than the maps of total case counts, with higher incidences in Pacific, Kittitas, and Asotin for dogs, and Skamania for humans.

Similarly, Figure 6 shows the total number of avian and human psittacosis cases reported in each county from 1993-2016, as well as the estimated average pet bird and human population densities, and avian and human incidences over that time frame. These visualizations show that the majority of both avian and human cases of psittacosis also were reported in Western WA State, especially King County for birds, and Snohomish, King, and Clark for humans, and in counties with higher pet bird and human population densities. The exception is Spokane County in Eastern WA State, in which a single report of 50 infected birds was made to WSDA in April

of 1998, as described above. As with leptospirosis, while there was a fair amount of overlap in the counties where avian and human cases of psittacosis were reported from 1993-2016, there also were a number of counties in which an avian case was reported but no human cases, and vice versa. Again, the maps of estimated psittacosis incidence paint a notably different picture than the maps of total case counts, with higher incidences in Whatcom and Okanogan for birds, and Okanogan and Skagit for humans.

TEMPORAL COMPARISONS AT THE STATE LEVEL

Figures 7 presents scatter plots and results of the linear regressions of the number of endemically acquired human leptospirosis cases regressed on the number of endemically acquired canine leptospirosis cases reported per year, and the number of endemically acquired human psittacosis cases regressed on the number of endemically acquired avian psittacosis cases reported per year in WA State from 1993-2016. We failed to detect a linear relationship between variables for either disease. Table 3 shows the results of these bivariate linear regressions, as well as the results of multivariate linear regressions that include annual estimated human population density in WA State as an additional covariate. At $\alpha = 0.05$, we failed to detect a significant linear association between the number of canine leptospirosis cases reported per year and the number of human leptospirosis cases reported per year in the state, including when we adjusted for human population size. We did observe a significant bivariate association between the number of avian cases and the number of human cases of psittacosis reported per year ($p = 0.003$), but this correlation disappeared when adjusted for human population size. In the multivariate model, we observed a significant negative association between human population size and the number of cases of human psittacosis reported per year in the state ($p = 0.003$).

PREDICTORS FOR HUMAN CASE OCCURRENCE AT THE COUNTY LEVEL

Table 4 shows the results of bivariate and multivariate logistic regression models of the binary occurrence of an endemically acquired human case of leptospirosis or psittacosis in a particular county and year regressed on various risk factors for human disease. Recall that because leptospirosis and psittacosis are rare diseases in WA State, we assumed that the OR was a reasonable approximation of the RR for each disease. At $\alpha = 0.05$, we observed a significant bivariate association between the risk of a human case of leptospirosis and both higher county-level human population density and higher county-level pet dog population density ($p < 0.0001$ for both). In the multivariate model, pet dog population density was positively associated with the risk of a human case. Our results showed that for counties with the same annual precipitation and canine case report status but that differed by one dog/km² in density, the county with the higher pet dog population density was 1.05 times more likely to receive a report of a human case of leptospirosis that year (95% confidence interval (CI) = 1.02-1.07, $p < 0.0001$). We did not find a significant bivariate or multivariate association between the report of a canine case and the risk of a human case in the same year and county. Although the association between the risk of a human case of leptospirosis and annual county-level precipitation was statistically significant in both the bivariate and multivariate models, the estimated ORs for both were 1.00 with 95% CIs including 1.00. Therefore, we concluded that there was no difference in the risk of a human case of leptospirosis between counties that differed in cumulative annual precipitation, including after adjusting for pet dog population density and canine case report status.

We observed significant bivariate associations between the risk of a human case of psittacosis and (1) the report of an avian case of psittacosis in the same year and county, (2) higher county-level human population density, and (3) higher county-level pet bird population

density ($p < 0.0001$ for all). In the multivariate model, both the report of an avian case and pet bird population density remained significantly associated with the risk of a human case of psittacosis. We estimated that for counties with the same pet bird population density, those with a report of at least one avian case of psittacosis were 5.68 times more likely to receive a report of a human case of psittacosis in the same year than those with no reports of an avian case (95% CI = 1.42-22.77, $p = 0.01$). We estimated that for counties with the same annual avian case report status but that differed by one bird/km² in density, those with the higher pet bird population density were 1.27 times more likely to receive a report of a human case of psittacosis in the same year (95% CI = 1.11-1.45, $p = 0.0007$).

The PPV and sensitivity for the occurrence of an animal case of leptospirosis (equine and canine combined) predicting the occurrence of a human case in the same county are given for each year as well as the entire study period (1993-2016) in Tables 5 and 6, respectively. The annual PPV ranged from 0.0% to 75.0% during this time period. Over the entire 24-year period, the PPV was 6.3%, suggesting that if a county had a report of an animal case of leptospirosis, the probability of that county also having a report of a human case in the same year was about 1 in 16. The sensitivity ranged from 0.0% to 50.0% per year, and over all years was 15.0%. Thus, the proportion of “true” human leptospirosis cases (which were represented by reported human cases in this analysis) captured by an integrated system treating animal disease reports as a tool for predicting human disease reports in the same year and county was about 1 in 7.

The PPV and sensitivity for the occurrence of an avian case of psittacosis predicting the occurrence of a human case in the same county are given for each year as well as the entire study period (1993-2016) in Tables 7 and 8, respectively. The annual PPV ranged from 0.0% to 50.0% during this time period. Over the entire 24-year period, the PPV was 10.6%, suggesting that if a

county had a report of an avian case of psittacosis, the probability of that county also having a report of a human case in the same year was just over 1 in 10. The sensitivity ranged from 0.0% to 100.0% per year, and over all years was 26.9%. Thus, the proportion of “true” human psittacosis cases (which were represented by reported human cases in this analysis) captured by an integrated system treating avian disease reports as a tool for predicting human disease reports in the same year and county was slightly over 1 in 4.

PSITTACOSIS INCIDENCE COMPARISON

The results of the comparison of the incidence rates of endemically acquired human psittacosis in all WA State residents and in pet bird owners and pet shop workers from 1993-2016 are given in Table 9. The estimated incidence in all residents was 4.2 cases per 1,000,000 persons, and in pet bird owners and pet shop workers was 118.4 cases per 1,000,000 persons. The incidence was about 28 times greater in pet bird owners and pet shop workers than in all WA State residents combined.

DISCUSSION

POTENTIAL IMPLICATIONS FOR PUBLIC AND VETERINARY HEALTH PRACTICE

The results of this study may help WA State public and veterinary health officials target prevention and disease control interventions at seasons, counties, and populations at highest risk of leptospirosis and psittacosis infection. This study failed to detect a temporal relationship between the number of animal cases and the number of human cases of either disease reported per year in WA State from 1993-2016, or any statistically significant linear relationship between the two variables (after adjusting for human population). Although reports of animal and/or

human psittacosis did not appear to occur more frequently during certain times of year in WA State, we did find a significantly higher average total number of leptospirosis cases (animals and humans combined) reported per month from August to December than from January to July. This higher average monthly rate of *Leptospira* infections in animal and human populations during the second half of the year may be related to the first flush phenomenon, which refers to the rapid increase in pollutant concentration during the initial period of storm runoff.^{42,43} Based on these results, state and local public and veterinary health officials may wish to strengthen leptospirosis control efforts beginning in August, as well as educate the public and relevant occupational groups about the potential increased risk of infection from August to December, and encourage veterinary and human health professionals to be particularly vigilant in their testing and diagnosis during this time of year.

We observed some county-level spatial overlap in animal and human case reporting in WA State from 1993-2016. For both leptospirosis and psittacosis, the majority of animal and human cases were reported in Western WA State, in which humans and their pets are more densely populated. Although the generally higher number of cases reported in more populated counties may simply be the result of a greater number of people and animals at risk of infection, it also may reflect regional differences in the quality of passive disease surveillance and reporting. In some WA State counties, the resources for surveillance and diagnosis of animal infections may be more robust than those for human infections, in which case animals may serve as sentinels for zoonotic diseases in humans. Other counties may experience the opposite, with the resources for human disease detection superior to those for animal disease detection, in which case humans may serve as sentinels for the presence of infection in proximate animals. Continuing analysis of the spatio-temporal overlap of human and animal cases of leptospirosis

and psittacosis in WA State may help identify the shortcomings of existing surveillance systems and improve quality assurance efforts, such as reduction of exposure and outcome misclassification. Regional variability in the number of disease cases may be due to differences in other risk factors apart from human and animal population densities, such as the magnitude of zoonotic exposures faced by occupational groups like veterinarians, pet shop employees, and poultry workers. Finally, public and veterinary health officials may wish to consider human and animal disease incidence in addition to case counts when identifying WA State counties in greatest need of prevention and intervention efforts, as these two measures paint distinct pictures of regional differences in disease occurrence. Counties at highest risk of canine leptospirosis may include Pacific, Thurston, Kitsap, Kittitas, and Asotin, and of human leptospirosis may include Clallam, Mason, Cowlitz, Clark, and Skamania. Counties at highest risk of avian psittacosis may include Clallam, Kitsap, Whatcom, Okanogan, and Spokane, and of human psittacosis may include Clark, Snohomish, Skagit, Okanogan, and Benton.

We found that the report of an endemically acquired canine case of leptospirosis in a given year and county was not significantly associated with the report of an endemically acquired human case in that same year and county, after adjusting for pet dog population density and annual precipitation. However, we found that counties with the same pet bird population density but with at least one avian case of psittacosis reported were more likely to receive a report of a human case of psittacosis that year than counties with no reports of an avian case. With a notably high OR of 5.68 (recall that because of the rarity of the disease, we assumed the OR approximated the RR), these results support the utility of avian psittacosis cases to predict human infection risk, as well as human health officials heightening their focus on counties where a bird case already has been reported that year. For both leptospirosis and psittacosis, we found

significant, positive, multivariate associations between pet dog and pet bird population densities, respectively, and the report of a human disease case in the same county and year. These results support public health agencies emphasizing surveillance and prevention efforts in counties with higher pet population densities. In general, we found that the associations between human and avian psittacosis were stronger than the associations between human and animal leptospirosis. This overall observation may reflect the higher exposure risk of avian psittacosis compared to canine or equine leptospirosis in terms of the likelihood of transmission, i.e. transmission of psittacosis from birds to humans may be more likely than the transmission of leptospirosis from dogs or horses to humans.

PPV and sensitivity are epidemiologic tools commonly used to measure the screening performance of medical diagnostic tests. Predictive models for zoonotic disease occurrence, and disease surveillance programs in general, should be subject to the same evidence-based assessments to ensure they are providing useful information in an efficient manner.⁴⁴⁻⁴⁶ PPV and sensitivity have been used by a number of previous studies to evaluate the effectiveness of surveillance systems for epidemic detection,⁴⁷ vaccine-preventable disease case capture,⁴⁸ hospital discharge code validity,⁴⁹ and to assess the utility of using zoonotic disease outbreaks in animals to predict cases in humans.⁴⁵ Furthermore, both the CDC and the World Health Organization (WHO) recommend PPV and sensitivity among various attributes to evaluate surveillance systems.^{50,51}

The PPV and sensitivity values, respectively, for leptospirosis suggested that only 6.3% of animal cases reported in WA State from 1993-2016 corresponded to a human case in the same county and year, and that 85% of human cases occurred without a corresponding animal case in the same county and year. If we consider animal disease reports as a tool for predicting human

disease reports, only 6.3% of counties that tested positive for an animal leptospirosis case in a given year had a reported human case in that same year. In terms of test validity, among counties that had a report of human leptospirosis in a given year, animal reports were associated with human reports only 15% of the time. Similarly, the PPV and sensitivity values, respectively, for psittacosis suggested that 10.6% of avian cases corresponded to a human case in the same county and year, and about 73% of human cases occurred without a corresponding avian case in the same county and year. That is, only 10.6% of counties that tested positive for an avian psittacosis case in a given year had a reported human case in that same year, and, among counties that had a report of human psittacosis in a given year, avian reports were associated with human reports only about 27% of the time. These results serve as an important reminder that human leptospirosis and psittacosis infections are relatively rare in WA State, even when these diseases are present in proximate animal populations.

Nevertheless, the wide PPV and sensitivity ranges for each disease from 1993-2016 suggest annual fluctuations in the effectiveness of disease reporting and control. Furthermore, in the absence of standardized systems for integrated disease surveillance program evaluation,⁴⁴ action thresholds based on PPV and sensitivity may vary among public health agencies, depending on available resources and other factors. For example, for some public health officials, a predictive tool for psittacosis with PPV greater than 10% and sensitivity greater than 25% may be sufficiently compelling to consider birds as sentinels for human disease risk, prompting them to increase disease prevention and control activities in nearby human populations when an avian case has been reported that year. DOH employees may wish to consider the results of this study in determining if the PPVs and sensitivities for animal cases of

leptospirosis and avian cases of psittacosis fall within their action thresholds, and establish data sharing practices with WSDA accordingly.

Finally, we found that the estimated incidence of psittacosis in pet bird owners and pet shop workers in WA State was substantially higher than the estimated incidence in all state residents combined from 1993-2016. Although additional data may be required to more accurately estimate psittacosis incidence in these subpopulations (see next steps section beginning on page 32 for further discussion), we suggest that the results of this exploratory analysis support targeted public, veterinary, and occupational health education and disease prevention efforts in WA State residents who own pet birds and/or work in pet shops that sell birds.

LIMITATIONS

This study had several limitations. One of the primary limitations was missing report data. Based on personal communications with DOH and WSDA ASD staff, it is our understanding that zoonotic disease cases likely are notably underreported to both agencies, especially WSDA, although the extent of underreporting is unknown and challenging to quantify. Therefore, the total number of reports analyzed in this study may be substantially lower than the true number of zoonotic disease cases in the state between 1993-2016. In addition, the reporting practices of animal and human health offices and laboratories may have differed across counties and changed over time, depending on how active DOH and WSDA were at encouraging and enforcing reporting, how compliant clinicians and laboratory managers were with reporting requirements, whether there had been a zoonotic disease incident that peaked public interest, etc. Furthermore, as passive surveillance relies on the clinical recognition of notifiable conditions, subclinical and asymptomatic cases in both humans and animals very likely went unreported.

Probable cases in animals that were not laboratory confirmed also may have been unreported. In the same vein, we only counted animal cases listed in the WSDA phone records, not in email or fax records. While there undoubtedly is some overlap between these data streams, there also almost certainly are cases of leptospirosis and psittacosis that appear in the email and/or fax records but not in the phone records, and we did not include these in our analyses.

Another limitation was the lack of clear temporality for animal cases. Although DOH records date of disease onset for human cases, WSDA only records date of phone report for animal cases. Based on personal communication with WSDA ASD staff, it is our understanding that the timing of reports by veterinary offices and laboratories is inconsistent, with some phone reports made months after diagnosis. However, as WSDA does not record when phone reports are made in relation to diagnoses, we were unable to identify such instances in this study. Consequently, with the exception of our investigation of seasonal trends, in which we collapsed years and plotted total case counts each month between 1993-2016, year was the unit of time in all analyses in this study. However, there may be value in utilizing a more granular time variable, such as the incorporation of incubation period into multivariate models and PPV and sensitivity analyses, as other studies have done.⁴⁵ The lack of temporal clarity for animal cases also increased the likelihood of outcome misclassification, particularly for cases that were reported to WSDA early in the year, but may actually have occurred at the end of the previous year. That said, because there are so few cases of leptospirosis and psittacosis reported in animals and humans in WA State per year, using a more granular time variable also might create significant analytical challenges.

This study also was limited by potential exposure misclassification, which could have occurred in a number of ways. As described above, in an effort to protect owner privacy, WSDA

only records the location of the reporting veterinary office or laboratory, not the location of animal residence. As veterinarians may treat animals that reside outside the county in which their practice is located, it is possible that some animals were classified as being infected in the incorrect county. Furthermore, much of the animal leptospirosis and psittacosis data were missing information on animal origin. Of the leptospirosis cases that indicated an animal origin outside WA State, no information was available about the length of time the animal had resided in WA State prior to infection. In this study, we assumed all reported animal cases were acquired in WA State, but it is possible that some were acquired out-of-state, or even internationally. As DOH records information related to travel, we are confident all human cases included in this study were acquired in WA State. However, recall that the reporting LHI is recorded for human cases, and it is possible that some patients were exposed in counties other than their home county. Finally, in order to estimate pet dog and pet bird population sizes at the county level as well as the number of pet bird owners in WA State following AVMA recommendations, we assumed the local demographics and rates of pet ownership in WA State and its counties from 1993-2016 were similar to the national demographics and rates of pet ownership upon which the AVMA formulas are based, which may not be the case in reality.

Despite these limitations, we suggest that our analyses of integrated WSDA and DOH zoonotic disease surveillance data have yielded results that will be useful to disease prevention and control officials and agencies in WA State.

NEXT STEPS

There are many additional analyses that could be performed with these linked animal and human leptospirosis and psittacosis surveillance data, other than those carried out in this study. Given the abundance of years in which no cases of animal and/or human leptospirosis or

psittacosis were reported in WA State between 1993-2016, we believe it is imperative to explore statistical models for zero-inflated time series data, as failing to account for zero-inflation may lead to spurious associations.⁵² In addition, more formal time series⁴⁵ and cluster analyses⁵³ may lend additional insight into the risk of leptospirosis and psittacosis infection in humans and animals in the state. Furthermore, investigating the burden of these diseases in human populations in WA State (e.g. in Disability Adjusted Life Years, or DALYs) may provide information that is more valuable to local and state public health policy makers than information provided by raw case counts alone.^{54,55} These linked data also could be used to determine whether an endemically acquired human disease report in a given year and WA State county could be used to predict the occurrence of an endemically acquired animal case in that same year and county, which may be of particular interest to WSDA.

Although DOH records occupation for all reported human disease cases, individual-level occupation data were not available for this study without further IRB review. Closer investigation of the incidence of leptospirosis and psittacosis in certain animal worker groups, such as pet shop workers, shelter workers, and veterinary professionals, is feasible and may help public health professionals target prevention activities towards occupational groups at highest risk. In an effort to minimize potential exposure misclassification, the analyses carried out in this study could be rerun excluding the leptospirosis reports that indicated out-of-state animal origin; however, the challenges related to timing of exposure and classifying animals of unknown origin, as described above, would remain. To maximize the number of reported animal cases captured in these analyses, techniques to combine phone, fax, and email records while removing probable duplicates could be explored, although investigators would need to account for the fact that the consistency with which reports are recorded and the length of time for which historical

records are kept differ between these data streams. Finally, comparable analyses could be performed in a single county in WA State, with integrated data from other states or countries, and for notifiable zoonotic diseases other than leptospirosis and psittacosis.

CONCLUSIONS

This study highlights the feasibility of combining human and animal notifiable zoonotic disease data with other publicly available data, such as those related to population demographics and local climate. Furthermore, it identifies potential benefits and challenges of comparing animal and human surveillance data streams for leptospirosis and psittacosis at the county and state levels in WA State. Better data sharing and other communications between human and animal health agencies may be essential to improving integrated zoonotic disease surveillance and response. In addition to contributing to more timely and effective disease prevention and control actions at state and county levels, enhanced integrated surveillance may result in increased understanding of zoonotic disease relationships in animal and human populations, such as seasonality factors and occupational risk in animal workers, as well as improved identification of populations at highest risk. Furthermore, there may be sentinel value in human health agency awareness of zoonoses in animals (i.e. animals as sentinels for human disease risk). Although not explored in this study, it stands to reason that there also may be sentinel value in animal health agency awareness of zoonoses in humans.

Barriers to implementing integrated surveillance include the lack of a common data tracking, analysis, reporting, dissemination, and communication platform, in addition to the lack of a standardized system of disease nomenclature. Based on personal correspondence with DOH and WSDA ASD staff, it is our understanding that communication between these two state

agencies regarding notifiable zoonotic diseases historically has been poor, and has been limited by funding and manpower. However, the potential importance of regular data sharing is well-recognized by current employees of both agencies, and efforts are underway to strengthen communication channels, including revision of the Washington Administrative Codes^{22,23} to mandate prompt data sharing between DOH and WSDA when reports of certain zoonotic diseases are made to either agency.

The utility of combined animal and human zoonotic disease surveillance data to WA State public and veterinary health officials and policy makers relies heavily on the strength of the passive surveillance systems used to capture these data. Infrastructure to foster high quality data collection by human and veterinary health providers and laboratories must be developed and maintained, in addition to efficient and user-friendly procedures for notifiable disease reporting to the appropriate state agency. The study limitations described above argue for more robust data collection practices on the part of WSDA in particular. Over the past year, WSDA has made notable improvements to their reportable animal disease data intake and management systems and protocols. This development, in combination with the ongoing strengthening of inter-agency communication channels described above, lead us to believe that our ability to seamlessly combine human and animal notifiable zoonotic disease data in WA State, as well the confidence with which we may draw inferences from these combined data, only will increase in the future.

In conclusion, we believe the results of this study support greater collaboration between WA State animal and human health agencies in the passive surveillance of leptospirosis and psittacosis, including coordinated case investigations and the continuous integration of animal and human surveillance data streams with one another and with demographic variables. Such efforts, in turn, may help public and veterinary health officials improve disease prevention,

control, and treatment activities, thereby reducing both human and animal morbidity and mortality.

FIGURES AND TABLES

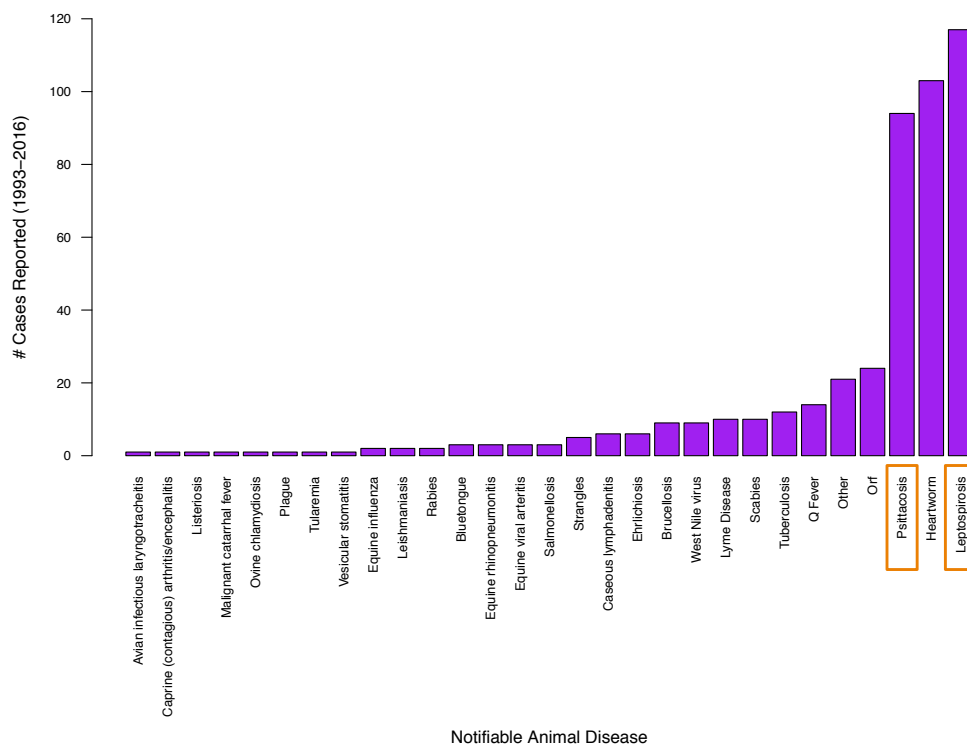


Figure 1. Number of cases of notifiable animal diseases reported to the Washington State Department of Agriculture (WSDA) from 1993-2016, ranked in ascending order. The “other” category represents animal diseases that were reported to WSDA but are not notifiable animal conditions in Washington State. Leptospirosis and psittacosis (outlined in orange) were two of the most commonly reported animal diseases in this time frame that also were notifiable in humans; both have associated public and veterinary health actions.

Table 1. Summary of cases of leptospirosis and psittacosis in animals and humans reported to the Washington State Departments of Agriculture and Health, respectively. Some reports made to the Department of Agriculture indicated more than one affected animal, i.e. animal case. Animal cases also are stratified by animal group. All descriptive statistics shown are for years analyzed.

		Years Available	Years Analyzed	Reports (n)	Reported Cases (n)*	Reported Cases/Year (n)			Reported Cases by Group (n(%))	
						Range	Mean \pm SD	Zeros		
Leptospirosis	Animal	1993-present	1993-2016	110	117	0 - 24	4.9 \pm 6.3	8	Canine: 115 (98%)	Equine: 2 (2%)
	Human	1986-2016	1993-2016	20	20	0 - 5	0.8 \pm 1.4	15		
Psittacosis	Animal	1993-present	1993-2016	44	94	0 - 53	3.9 \pm 10.8	10	Avian: 91 (97%)	Unspecified: 3 (3%)
	Human	1985-2016	1993-2016	26	26	0 - 7	1.1 \pm 1.9	15		

*Only human cases acquired in Washington State are counted; we assume all animal cases reported were endemically acquired

Table 2. Avian cases of psittacosis reported to the Washington State Department of Agriculture from 1993-2016, by common name of the infected bird.

Avian Detail	Reported Cases (n (%))
African grey parrot	2 (2%)
Amazon parrot	3 (3%)
Australian parakeet	1 (1%)
Bird (uns)	57 (63%)
Budgerigar	2 (2%)
Cockatiel	8 (9%)
Cockatoo	3 (3%)
Conure	2 (2%)
Dove	1 (1%)
Finch	1 (1%)
Lovebird	2 (2%)
Macaw	4 (4%)
Parrot (uns)	2 (2%)
Psittacine bird (uns)	2 (2%)
Racing pigeon	1 (1%)



Figure 2. Number of cases of endemically acquired animal and human leptospirosis (upper) and psittacosis (lower) reported in Washington State, by year, from 1993-2016.

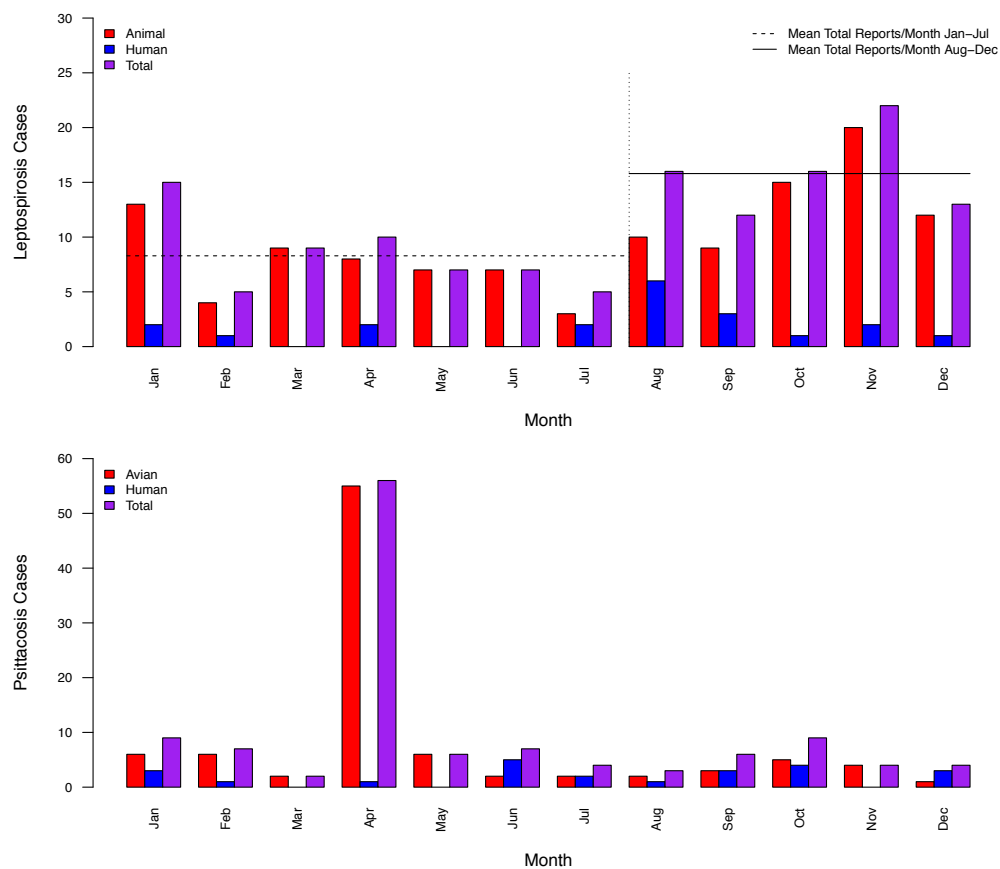


Figure 3. Number of endemically acquired animal and human cases of leptospirosis (upper) and psittacosis (lower) reported each month in Washington State from 1993-2016. Note that three human cases of psittacosis are missing data for month of disease onset. For leptospirosis, the average numbers of total reports (animal and human combined) per month for January-July and for August-December are shown (Jan-Jul mean \pm SD = 8.3 ± 3.5 reports/month; Aug-Dec mean \pm SD = 15.8 ± 3.9 reports/month). Based on the results of a two-sided t-test allowing for unequal variances, we conclude these means are statistically significantly different from one another ($\alpha = 0.05$, $t = -3.4$, $df = 8.1$, $p = 0.009$).

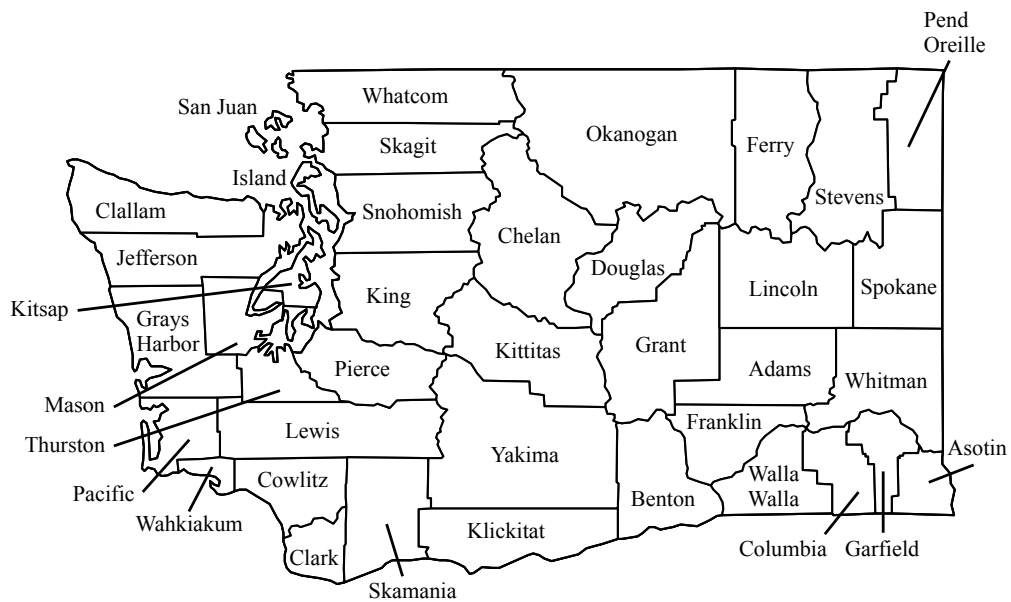
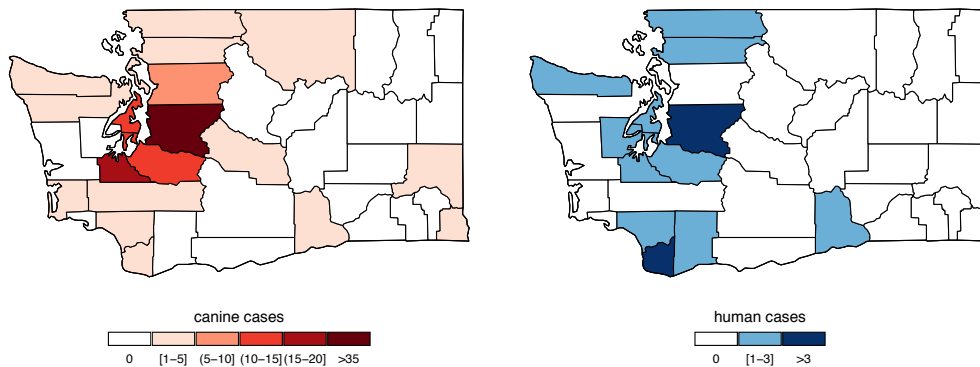
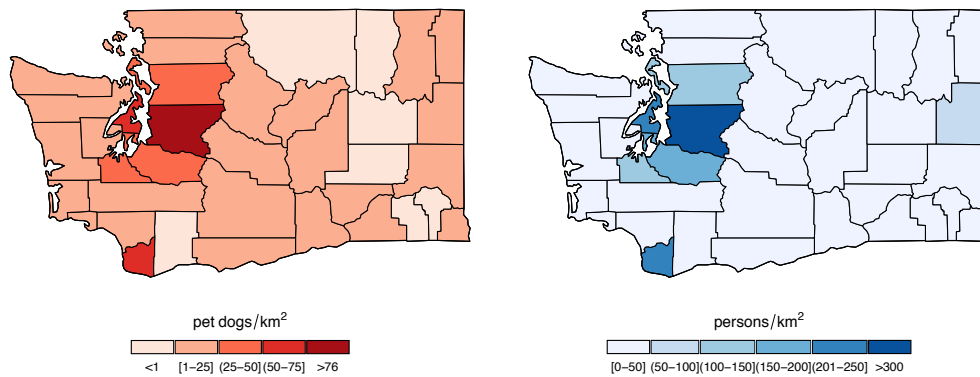


Figure 4. Washington State counties.

Leptospirosis, by WA State County, 1993–2016
Total Cases Reported



Estimated Population Density



Estimated Incidence

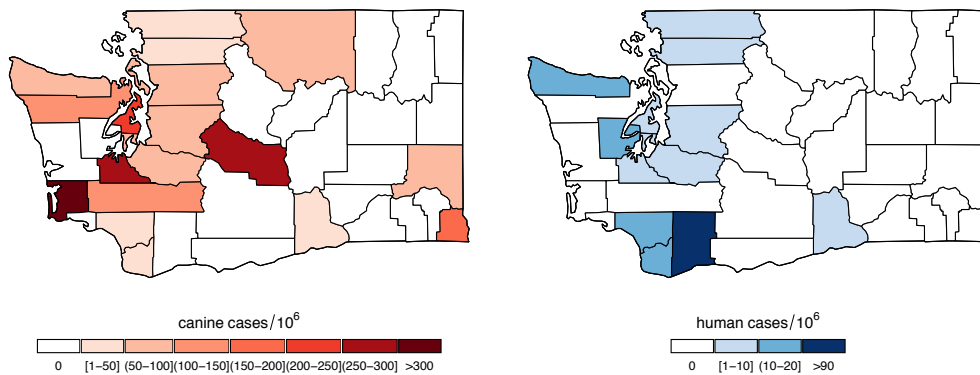
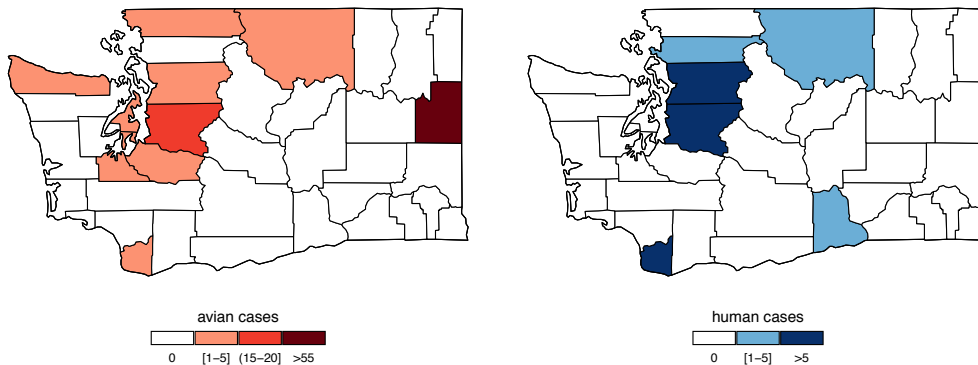
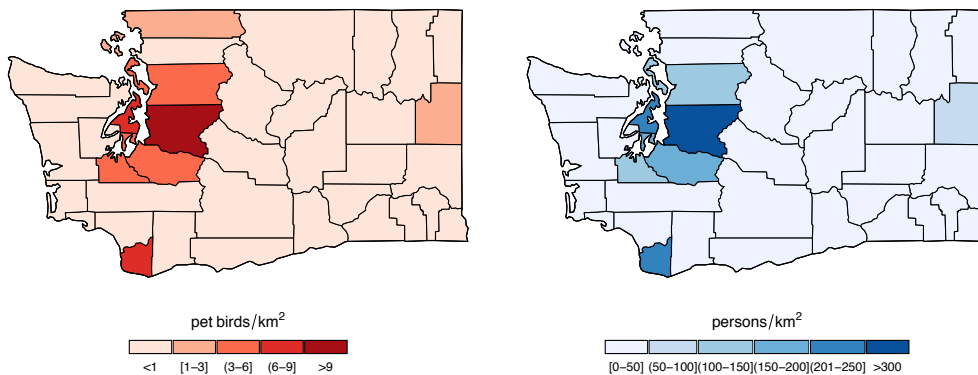


Figure 5. Total numbers of reported endemically acquired canine leptospirosis cases (top left) and human leptospirosis cases (top right), estimated average pet dog population densities (middle left) and average human population densities (middle right), and estimated canine leptospirosis incidence (bottom left) and human leptospirosis incidence (bottom right) in Washington State from 1993-2016, stratified by county.

Psittacosis, by WA State County, 1993–2016
Total Cases Reported



Estimated Population Density



Estimated Incidence

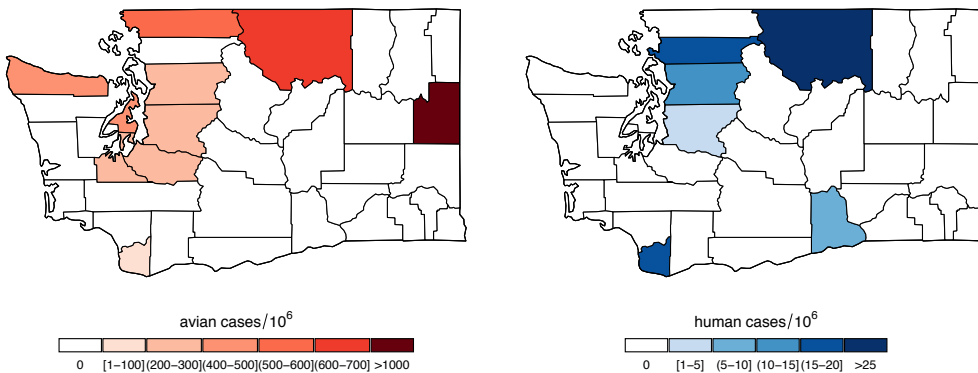


Figure 6. Total numbers of reported endemically acquired avian psittacosis cases (top left) and human psittacosis cases (top right), estimated average pet bird population densities (middle left) and average human population densities (middle right), and estimated avian psittacosis incidence (bottom left) and human psittacosis incidence (bottom right) in Washington State from 1993-2016, stratified by county.

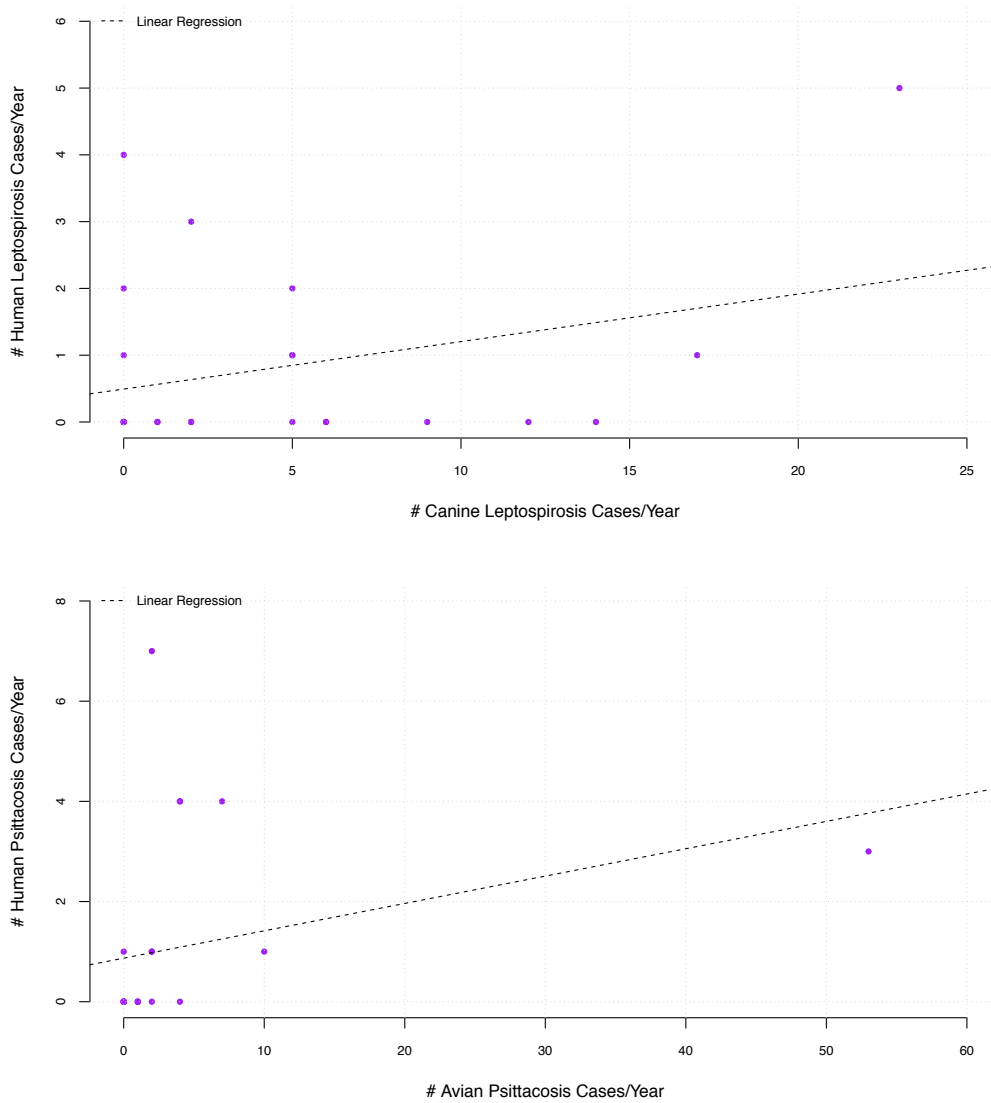


Figure 7. Scatter plots of the number of endemically acquired human leptospirosis cases reported per year vs. the number of endemically acquired canine leptospirosis cases reported per year (upper) and of the number of endemically acquired human psittacosis cases reported per year vs. the number of endemically acquired avian psittacosis cases reported per year (lower) in Washington State from 1993-2016. Linear regressions also are presented for each plot.

Table 3. Results of linear regression models of the number of endemically acquired human cases of leptospirosis (upper) and psittacosis (lower) per year in Washington State from 1993-2016, regressed on the number of endemically acquired animal cases reported in that year alone (bivariate) and in combination with the estimated human population in the state that year (multivariate). P-values < 0.05 are highlighted in yellow.

Leptospirosis								
Covariate	Bivariate				Multivariate			
	Estimate	95% CI		p-value	Estimate	95% CI	p-value	
# canine cases reported/year	0.07	-0.08	0.22	0.3	0.09	-0.08	0.27	0.3
Estimated human population					-4.13E-07	-1.46E-06	6.38E-07	0.4
Psittacosis								
Covariate	Bivariate				Multivariate			
	Estimate	95% CI		p-value	Estimate	95% CI	p-value	
# avian cases reported/year	0.05	0.02	0.09	0.003	0.01	-0.02	0.04	0.5
Estimated human population					-2.18E-06	-3.52E-06	-8.36E-07	0.003

Table 4. Results of bivariate and multivariate logistic regression models of the occurrence of an endemically acquired human case of leptospirosis (upper) and psittacosis (lower) in a given year and county in Washington State between, regressed on the occurrence of an endemically acquired animal case reported in that same year and county and the estimated human and pet population densities in that year and county. Because leptospirosis is a climate sensitive disease, annual county-level precipitation also was included as a covariate in the leptospirosis models. Precipitation data were available only until 2015, so the leptospirosis models include data from 1993-2015, while the psittacosis models include data from 1993-2016. Any independent variables that showed a significant association ($p \leq 0.1$) with the occurrence of a human case in the bivariate analyses were included in the multivariate analysis. Because human population density is highly correlated with both pet dog and pet bird population density, human population density was left out of the multivariate models. P-values < 0.05 are highlighted in yellow.

Leptospirosis								
Covariate	Bivariate				Multivariate			
	OR	95% CI		p-value	OR	95% CI	p-value	
Canine case reported (binary)	3.00	0.84	10.70	0.09	0.42	0.06	2.78	0.4
Human pop. density (persons/km ²)	1.01	1.01	1.01	<0.0001				
Pet dog pop. density (dogs/km ²)	1.04	1.03	1.05	<0.0001	1.05	1.02	1.07	<0.0001
Annual precipitation (mm)	1.00	1.00	1.00	0.0009	1.00	1.00	1.00	0.01
Psittacosis								
Covariate	Bivariate				Multivariate			
	OR	95% CI		p-value	OR	95% CI	p-value	
Avian case reported (binary)	15.03	4.87	46.40	<0.0001	5.68	1.42	22.77	0.01
Human pop. density (persons/km ²)	1.01	1.01	1.01	<0.0001				
Pet bird pop. density (birds/km ²)	1.36	1.21	1.52	<0.0001	1.27	1.11	1.45	0.0007

Table 5. Positive predictive value (PPV) for an endemically acquired animal case of leptospirosis predicting the occurrence of an endemically acquired human case of leptospirosis in the same county and year.

Year*	# Animal Cases†	# w/ Human Case in Same Year & County	Positive Predictive Value
1998	2	0	0.0
2000	1	0	0.0
2003	1	0	0.0
2004	6	0	0.0
2005	2	0	0.0
2006	5	0	0.0
2007	24	4	16.7
2008	5	0	0.0
2009	12	0	0.0
2010	17	0	0.0
2011	5	0	0.0
2012	4	3	75.0
2013	8	0	0.0
2014	12	0	0.0
2015	5	0	0.0
2016	3	0	0.0
Total	112	7	6.3

*Years 1993-2016 were evaluated; only years in which one or more animal cases were reported are shown

†Both canine and equine cases are included; five canine cases were reported in unknown counties, which are excluded

Table 6. Sensitivity for an endemically acquired animal cases of leptospirosis predicting the occurrence of an endemically acquired human case of leptospirosis in the same county and year.

Year*	# Human Cases	# w/ Animal Case in Same Year & County†	Sensitivity
1996	2	0	0.0
1997	1	0	0.0
2001	4	0	0.0
2005	3	0	0.0
2007	5	2	40.0
2008	1	0	0.0
2010	1	0	0.0
2012	2	1	50.0
2015	1	0	0.0
Total	20	3	15.0

*Years 1993-2016 were evaluated; only years in which one or more human cases were reported are shown

†Both canine and equine cases are included

Table 7. Positive predictive value (PPV) for an endemically acquired avian case of psittacosis predicting the occurrence of an endemically acquired human case of psittacosis in the same county and year.

Year*	# Avian Cases	# w/ Human Case in Same Year & County	Positive Predictive Value
1993	4	0	0.0
1994	7	2	28.6
1995	2	0	0.0
1996	4	1	25.0
1997	10	5	50.0
1998	53	2	3.8
1999	4	0	0.0
2000	2	0	0.0
2002	1	0	0.0
2005	2	0	0.0
2006	1	0	0.0
2007	2	0	0.0
2008	1	0	0.0
2012	1	0	0.0
Total	94	10	10.6

*Years 1993-2016 were evaluated; only years in which one or more avian cases were reported are shown

Table 8. Sensitivity for an endemically acquired avian cases of psittacosis predicting the occurrence of an endemically acquired human case of psittacosis in the same county and year.

Year*	# Human Cases	# w/ Avian Case in Same Year & County	Sensitivity
1993	4	0	0.0
1994	4	2	50.0
1995	7	0	0.0
1996	4	2	50.0
1997	1	1	100.0
1998	3	2	66.7
2000	1	0	0.0
2005	1	0	0.0
2014	1	0	0.0
Total	26	7	26.9

*Years 1993-2016 were evaluated; only years in which one or more human cases were reported are shown

Table 9. Comparison of the estimated incidence of human psittacosis from 1993-2016 between all residents in Washington State vs. pet birds owners and workers in pet shops that sell birds in Washington State.

Population at Risk in Washington State	Years	# Human Cases Reported*	Estimated Population Size†	Estimated Incidence per 1,000,000
All Residents	1993-2016	26	6,233,596	4.2
Pet Bird Owners & Pet Shop Workers	1993-2016	23	193,241	118.4

*Endemically acquired cases only reported to the Washington State Department of Health (DOH); the number of human cases of psittacosis in pet bird owners and pet shop workers was estimated to be 88% of all cases reported, per information communicated directly to the authors by DOH

†Calculated as the average of annual estimated populations between 1993-2016, see methods for additional details; the estimated number of pet bird owners in Washington State was used as a proxy for the number of pet bird owners and pet shop workers combined, as the number of pet shops that sell birds in the state is relatively small, and therefore the number of pet shop workers at risk likely is a relatively small fraction of the true total

BIBLIOGRAPHY

1. Woolhouse ME, Gowtage-Sequeria S. Host range and emerging and reemerging pathogens. *Emerg Infect Dis*. 2005;11(12):1842-1847.
2. Jones KE, Patel NG, Levy MA, et al. Global trends in emerging infectious diseases. *Nature*. 2008;451(7181):990-993.
3. Smith KF, Goldberg M, Rosenthal S, et al. Global rise in human infectious disease outbreaks. *J R Soc Interface*. 2014;11(101):20140950.
4. LeJeune J, Kersting A. Zoonoses: an occupational hazard for livestock workers and a public health concern for rural communities. *J Agric Saf Health*. 2010;16(3):161-179.
5. Mills JN, Gage KL, Khan AS. Potential Influence of Climate Change on Vector-Borne and Zoonotic Diseases: A Review and Proposed Research Plan. *Environmental Health Perspectives*. 2010;118(11):1507-1514.
6. Jones BA, Grace D, Kock R, et al. Zoonosis emergence linked to agricultural intensification and environmental change. *Proceedings of the National Academy of Sciences of the United States of America*. 2013;110(21):8399-8404.
7. One Health Initiative. About the One Health Initiative. <http://www.onehealthinitiative.com/about.php>. Accessed May 31, 2017.
8. American Veterinary Medical Association. One Health: A New Professional Imperative. https://www.avma.org/KB/Resources/Reports/Documents/onehealth_final.pdf. Published 2008. Accessed May 31, 2017.
9. Stark KD, Arroyo Kuribrena M, Dauphin G, et al. One Health surveillance - More than a buzz word? *Prev Vet Med*. 2015;120(1):124-130.
10. National Research Council Committee on Achieving Sustainable Global Capacity for Surveillance and Response to Emerging Diseases of Zoonotic Origin. In: Keusch GT, Pappaioanou M, Gonzalez MC, Scott KA, Tsai P, eds. *Sustaining Global Surveillance and Response to Emerging Zoonotic Diseases*. Washington (DC): National Academies Press (US); 2009.
11. Perez A, Alkhamis M, Carlsson U, et al. Global animal disease surveillance. *Spat Spatiotemporal Epidemiol*. 2011;2(3):135-145.
12. Scotch M, Odofin L, Rabinowitz P. Linkages between animal and human health sentinel data. *BMC Veterinary Research*. 2009;5:15-15.
13. ArboNET. https://wwwn.cdc.gov/arboNET/maps/ADB_Diseases_Map/index.html. Accessed July 12, 2018.
14. One Health Harmful Algal Bloom System (OHHABS). Centers for Disease Control and Prevention. <https://www.cdc.gov/habs/ohhabs.html>. Published 2017. Accessed July 18, 2018.
15. Wendt A, Kreienbrock L, Campe A. Zoonotic disease surveillance--inventory of systems integrating human and animal disease information. *Zoonoses Public Health*. 2015;62(1):61-74.
16. Mauer WA, Kaneene JB. Integrated Human-Animal Disease Surveillance. *Emerging Infectious Diseases*. 2005;11(9):1490-1491.
17. Bisson IA, Ssebide BJ, Marra PP. Early detection of emerging zoonotic diseases with animal morbidity and mortality monitoring. *Ecohealth*. 2015;12(1):98-103.

18. Centers for Disease Control and Prevention. National Notifiable Diseases Surveillance System (NNDSS). In:2018.
19. United States Department of Agriculture Animal and Plant Health Inspection Service. U.S. National List of Reportable Animal Diseases (NLRAD) National Animal Health Reporting System (NAHRS) Operational Manual. In:2016.
20. Scotch M, Baarson B, Beard R, Lauder R, Varman A, Halden RU. Examining the Differences in Format and Characteristics of Zoonotic Virus Surveillance Data on State Agency Websites. *Journal of Medical Internet Research*. 2013;15(4):e90.
21. Enserink M. Infectious diseases. Questions abound in Q-fever explosion in the Netherlands. In: *Science*. Vol 327. United States2010:266-267.
22. Chapter 16-70 Washington Administrative Code: Animal Diseases - Reporting. In: Washington State Legislature, ed2014.
23. Chapter 246-101 Washington Administrative Code: Notifiable Conditions. In: Washington State Legislature, ed2014.
24. Rabinowitz PM, Conti LA. *Human-Animal Medicine*. 2010.
25. Bharti AR, Nally JE, Ricaldi JN, et al. Leptospirosis: a zoonotic disease of global importance. *Lancet Infect Dis*. 2003;3(12):757-771.
26. Heymann D. *Control of communicable diseases manual*. 19 ed. Washington DC: American Public Health Association; 2008.
27. Kahn CM. *The Merck veterinary manual*. 9 ed. Whitehouse Station, N.J.: Merck & Co.; 2005.
28. Victoriano AF, Smythe LD, Gloriani-Barzaga N, et al. Leptospirosis in the Asia Pacific region. *BMC Infect Dis*. 2009;9:147.
29. Evangelista KV, Coburn J. Leptospira as an emerging pathogen: a review of its biology, pathogenesis and host immune responses. *Future Microbiology*. 2010;5(9):1413-1425.
30. Balsamo G, Maxted AM, Midla JW, et al. Compendium of Measures to Control Chlamydia psittaci Infection Among Humans (Psittacosis) and Pet Birds (Avian Chlamydiosis), 2017. *J Avian Med Surg*. 2017;31(3):262-282.
31. Psittacosis/Avian Chlamydiosis. In: The Center for Food Security and Public Health, Iowa State University; 2017.
32. Baud D, Regan L, Greub G. Emerging role of Chlamydia and Chlamydia-like organisms in adverse pregnancy outcomes. *Curr Opin Infect Dis*. 2008;21(1):70-76.
33. Acha PN, Szyfres B. *Zoonoses and communicable diseases common to man and animals: vol.2: chlamydioses, rickettsioses, and vrioses*. 3 ed. Washington DC: Pan American Health Organization; 2003.
34. Hughes C, Maharg P, Rosario P, et al. Possible nosocomial transmission of psittacosis. *Infect Control Hosp Epidemiol*. 1997;18(3):165-168.
35. R Core Team. R: A language and environment for statistical computing. In. *Vienna, Austria: R Foundation for Statistical Computing*; 2018.
36. Leptospirosis (*Leptospira interrogans*). <https://wwwn.cdc.gov/nndss/conditions/leptospirosis/>. Accessed July 18, 2018.
37. Psittacosis/Ornithosis (*Chlamydophila psittaci*). Centers for Disease Control and Prevention: National Notifiable Diseases Surveillance System (NNDSS). <https://wwwn.cdc.gov/nndss/conditions/psittacosis/>. Accessed July 18, 2018.
38. Population & demographics. In: Washington State Office of Financial Management; 2018.

39. PRISM Climate Group. In: Oregon State University: Northwest Alliance for Computational Science and Engineering; 2018.
40. U.S. Pet Ownership Statistics. American Veterinary Medical Association. <https://www.avma.org/KB/Resources/Statistics/Pages/Market-research-statistics-US-pet-ownership.aspx>. Published 2018. Accessed July 15, 2018.
41. Simon F, Morchon R, Gonzalez-Miguel J, Marcos-Atxutegi C, Siles-Lucas M. What is new about animal and human dirofilariosis? *Trends Parasitol.* 2009;25(9):404-409.
42. Deletic A. The first flush load of urban surface runoff. *Water Research.* 1998;32(8):2462-2470.
43. Gupta K, Saul AJ. Specific relationships for the first flush load in combined sewer flows. *Water Research.* 1996;30(5):1244-1252.
44. Drewe JA, Hoinville LJ, Cook AJC, Floyd T, StÄrK KDC. Evaluation of animal and public health surveillance systems: a systematic review. *Epidemiology and Infection.* 2012;140(4):575-590.
45. Rabinowitz PM. Comparison of Human and Animal Surveillance Data for H5N1 Influenza A in Egypt 2006–2011. In: Vol 7.2012.
46. German R. Sensitivity and predictive value positive measurements for public health surveillance systems. In. *Epidemiology.* Vol 112000:720-727.
47. Hashimoto S, Murakami Y, Taniguchi K, Nagai M. Detection of epidemics in their early stage through infectious disease surveillance. *International Journal of Epidemiology.* 2000;29(5):905-910.
48. Nsubuga F, Ampaire I, Kasasa S, Luzze H, Kisakye A. Positive predictive value and effectiveness of measles case-based surveillance in Uganda, 2012-2015. *PLoS One.* 2017;12(9):e0184549.
49. Rosamond WD, Chambless LE, Sorlie PD, et al. Trends in the Sensitivity, Positive Predictive Value, False-Positive Rate, and Comparability Ratio of Hospital Discharge Diagnosis Codes for Acute Myocardial Infarction in Four US Communities, 1987-2000. *American Journal of Epidemiology.* 2004;160(12):1137-1146.
50. German RR, Lee LM, Horan JM, Milstein RL, Pertowski CA, Waller MN. Updated Guidelines for Evaluating Public Health Surveillance Systems: Recommendations from the Guidelines Working Group. *Morbidity and Mortality Weekly Report: Recommendations and Reports.* 2001;50(RR-13):i-35.
51. World Health Organization. Communicable disease surveillance and response systems: guide to monitoring and evaluating. In:2006.
52. Yang M, Cavanaugh JE, Zamba GKD. State-space models for count time series with excess zeros. *Statistical Modelling.* 2014;15(1):70-90.
53. Alvarez J, Whitten T, Branscum AJ, et al. Understanding Q Fever Risk to Humans in Minnesota Through the Analysis of Spatiotemporal Trends. *Vector Borne Zoonotic Dis.* 2018;18(2):89-95.
54. Abela-Ridder B, Sikkema R, Hartskeerl RA. Estimating the burden of human leptospirosis. *Int J Antimicrob Agents.* 2010;36 Suppl 1:S5-7.
55. de Gier B, Hogerwerf L, Dijkstra F, van der Hoek W. Disease burden of psittacosis in the Netherlands. *Epidemiol Infect.* 2018;146(3):303-305.