Sick City: A Literature Review of Global Studies Surveying Circulating Zoonotic Pathogens Across Urban-Rural Gradients

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Introduction

Anthropocene

In the broadest brushstrokes of observing the geological history of Earth, the changes observed in the comparatively infinitesimally small time frame in which human evolution and human influence has erupted onto the Cenozoic area, have already monumentally shaped the evolutionary histories of many organisms on the Earth today (Zalasiewicz *et al.*, 2011). The effects of human evolution and the predominant impact that humans have exerted upon their environment has drawn a new epoch in Earth's history; that of the Anthropocene. The Anthropocene epoch is a proposed nomenclature to discuss the "era of humans". (Crutzen, 2002). The Anthropocene epoch focuses on the recent diversification of human infrastructure, specifically the monumental changes to environmental landscape over the last three centuries. While Nobel Prize winning chemist, Paul J Crutzen introduced the Anthropocene to modern discourse (Crutzen, 2002), studies of the impact humanity has had on its natural environment have been observed and recorded as early as the late 1800's (Stoppani, 1873.; Arrhenius, 1896.; Chamberlain, 1897). As evidenced with the eruption of scientific literature surrounding the effects of human civilizations on the natural world being a relatively modern conceptualization, a natural association can be made with a simultaneously unfolding human phenomena; the rise of urbanization.

Urbanization

Urbanization, at its core, is the transition from rural and agricultural worlds where humans manipulated and worked with the native flora and fauna within their community to terraformed natural landscapes and urban anthropocentric communities (Satterthwaite, 2011). Although the effects of human-guided changes in the biosphere demonstratively began with the advent of agriculturalism (Ruddiman, 2003), urban sprawl introduced unparalleled challenges and changes to the animal world that are of paramount importance to urban ecologists, genomicists, and wildlife investigators. Topics arising from urbanization include genetic diversity stemming from urban guided pressures on selection, urban adaptation, and the effects of increased human-animal interaction owing to urban changes (Harris *et al.*, 2016). The exact definition of urbanicity, a statistically quantifiable number to express an area's degree of urbanization, varies between standards of human, architectural, and landscape development (Suarez-Rubio and Krenn, 2018; Allender, et al., 2011; Dahly, Adair, 2008; Hahs and McDonnell, 2006). Standards of human development include features such as population density; which was sub-defined as the number of households per defined measurement (eg: 2km X 2km in one study) and population numbers; which was sub-defined as the number of individuals per defined measurement (Suarez-Rubio and Krenn, 2018). Standards of architectural or physical development include varied urban features such as the density of paved roads, density of home dwellings such as houses and apartments, proximity to sewer and waste management centers, proximity to airports, proximity to hospitals and other healthcare related buildings, and infrastructures such as subways, garbage dumps, and clean water accessibilities (Dahly, Adair, 2008). Landscape development can include the remnant of natural features that exist within the developed land, such as canopy coverage of trees, landscape shape index (LSI),

presence of unprocessed water reservoirs, lakes, or rivers, and dominant land cover (Hahs, and McDonnell, 2006). Through an integrative combination of investigating multiple standards that contribute towards urbanicity, an urban-rural gradient can be considered in the conceptualization of many anthropogenic changes to a landscape. By identifying an entire gradient of urbanization, a more direct correlation between urbanization on a scale with a number of variables can be made; such a comparison between a binary division of urban or rural is a reductive investigation (Hahs, and McDonnell, 2006).

Animal Behaviors and Urbanization

One emerging field of study relative to urbanization, is the effect of urbanization on native species. In broad terms, species native to areas which have undergone anthropogenic changes, have faced pressures in adapting or surviving against the sudden human infrastructure (Hendry, Gotanda, and Stevensson, 2017). Examples of the anthropogenic changes that humanity introduces to native occupants of modern landscapes dominated by civilization are pollution and waste, commercialized fishing, hunting, and foraging of natural fauna and flora, introduction antimicrobial agents, pesticide usage in natural environments, and the introduction of new species in potentially invasive roles (Hendry, Gotanda, and Stevensson, 2017). More narrowly, these changes drastically restructure the landscape from their original terraformation, separating natural fauna into three categories: urban exploiters, urban adaptors, and urban avoiders (Fisher, Schneider, Ahlers, and Miller, 2015). Urban exploiters and urban avoiders are solidly identifiable as existing on the fringes of the urban-rural gradient; either they occupy the spaces where urbanization has reached full penetrance or avoid modern civilization all together. Examples of urban exploiters to the New York City area, for example, may include the eastern gray squirrel

(*Sciurus carolinensis*), the rock pigeon (*Columba livia*), and the brown rat (*Rattus norvegicus)*, all of whom are definitively benefiting from urban infrastructure for habitat, protection from predation and exposure, and for novel scavenging (McKinney, 2002). Conversely, urban avoider species live on the far periphery of cityscapes, chiefly found in sparsely altered terrain; examples of which are the American black bear (*Ursus americanus*), and the copperhead (*Agkistrodon contortix*). The third, and more intermediate class of animals fall under the urban adaptor domain, who occupy multiple roles across the urban-rural gradient. Examples of urban adaptors in the New York City area, for example, include the northern raccoon (*Procyon lotor*), the Virginia opossum (*Didelphis virginiana*), and the American robin (*Turdus migratorius*), all of whom are differentiated by an ability to exploit and capitalize on human-dense environments for a number of benefits, but are not as beholden to them for survival unlike the urban exploiters or human obligates (Ditchkoff, Saalfeld, and Gibson, 2006). Although species existing to the extremes of the urban response are studied with regards to the cascading effects of anthropogenic shift, it is the urban adaptors that predominate many studies across disciplines of genomics, urban ecology, and epidemiology(Munshi-South, 2012; Wilson, et al., 2016; Hendry, Gotanda, and Stevensson, 2017; Gortat, et al., 2017).

Urban adaptors seemingly demonstrate commensalism through their interactions with human societies (Gardner-Santana, et al., 2009). Commensalism is a form of symbiosis in which one participant, in these cases the urban adaptor species, benefits from a relationship where the other, in this case the humans providing the resources as secondary to their own lifestyle, neither benefits nor is hindered in the relationship. Using food as an example, many urban adaptors are mammals who benefit from the garbage left outside of urban dwellings during their scavenging

hours. Ubiquitous to many cities are the presence of raccoons and mice who can occasionally be found routing through open trash cans or dumpsters. Unlike similar behaviors observed with city rats, who are notable urban exploiters, these urban adaptive species retreat back to less anthropocentric dwellings in adjacent forests (Ditchkoff, Saalfeld, and Gibson, 2006., Hulme-Beaman, Dobney, Cucchi, and Searle, 2016). The definition of the commensal relationship, however, is challenged by emerging literature discussing the urban directed changes to the urban adaptive species, described in terms of behavior and in ecology (Hendry, Gotanda, and Stevensson, 2017., Wilson, et al., 2016., Gardner-Santana, et al., 2009.) Studies indicate how early commensal relationships between humans and urban adaptive animals are complicated by pathogen vector status, where animals unintentionally act as surrogate parasites by predating human spaces and communicating illness.

Urbanization is closely linked to changes in behaviors with animals that live in the periphery and subsist off of commensal interaction with urban centers. In one cohesive set of studies depicting the modulation of behavior in an urban adaptive species, the European blackbird (*Turdus merula*), the effects of urbanization on urban blackbirds were identified in being correlative for a number of deviations in behavior and personality from their rural counterparts (Miranda, 2014). Features such as increased inter- and intraspecies aggression, and risk-taking behavior were increased in urban birds (Dabelsteen and Pedersen, 1990; Lowry, Lill, and Wong, 2011; Jozkowicz and Gorska-Klek, 1996), and related studies indicated similar trends in urban mammals (Bowers, and Breland, 1996). Additionally, exploration and lack of inhibition around human activity is likewise heightened in urban bird species (Atwell, et al., 2012). Inversely, behaviors of alarm or startle mechanics, and escape behaviors (qualitatively

measured in flight initiation distance) are decreased in urban species of both birds (Knight, Grout, and Temple, 1987) and mammals (Engelhardt, and Weladji, 2011). A number of explanations are supported by the evidence within the literature to explain the modifications in animal behavior. Some attribute the habituation of human involvement and the conceptualization of a non-predator status of humans cohabitating urban spaces (Chapman, Rymer, and Pillay, 2012). Some suggest that because major apex predators tend to be urban avoiders, there is a devolving sense of predator avoidance as they are uncontested in urban spaces (Knight, Grout, and Temple, 1987; Atwell, et al., 2012), and some suggest that the niche availability of human refuse and sheltering spaces are so advantageous that they override hesitation with engaging in human avoidances (Atwell, et al., 2012; Lowry, Lill, and Wong, 2011). Demonstratively urban adaptive animals are engaging in behaviors that bring them closer and closer to human domiciles, whether they occupy garbage cans or enter apartment complexes and scavenge inside human homes. Urban adaptors engage in much higher cross-species interactions with humans due to these features of urbanization linked behavior shifts, leading to an epidemiological consideration of vector relationships, one that challenges the aforementioned commensal understanding of these urban adaptors.

It is no small coincidence that mammals, namely those of order *Rodentia,* and birds make up a plurality, if not majority, of urban adaptive animals. Urban centers characteristically are associated with an increase in temperature relative to even adjacent but more sparsely populated environments due to the urban-heat-island phenomena (Scheffers *et al.*, 2016). With increased heat of an urban center relative towards less developed areas in which an urban adaptor may subsist, there is a much higher prevalence of smallness associated (Merckx, et al., 2018). This

directional selection of small phenotype is a result of thermodynamic considerations for the animal, with larger bodies with higher surface area requiring a higher metabolic rate than those who are selectively smaller with lower surface area. Rodents are particularly suited mammals for this adaptation owing to their generally small bodies which are thermodynamically considerate for both heat loss prevention and lower metabolic requirements (Mueller, and Diamond, 2001). In addition, both small mammals and birds are under selective pressures to navigate sparse feeding and habitat availabilities, known as habitat fragmentation, and have to navigate non-natural infrastructural features such as skyscrapers and closely packed buildings, as well as vehicles (Alberti, Marzluff, and Hunt, 2017). Smallness directly lends itself to higher instances of cross-species interaction between urban adaptive animals and humans as they share space in urban environments. Smaller rodents can more easily traverse through ducts and passages in human domiciles and interact with more intimate human spaces like individual kitchens (Williams, et al., 2018).

Urban Epidemiology

In epidemiology, the closer proximity between smaller animals and human domeciles, a direct result of urbanization presents a troubling dynamic; it is likewise not a coincidence that small mammals, especially rodents, are historically noteworthy vectors for diseases (Morand, Jittapalapong, and Kosoy, 2015). Literature depicts how across Europe (Strand, and Lundkvist, 2019), Asia (Bordes, et al., 2013), and North America (Panti-May, et al., 2017; Han, Schmidt, Bowden, and Drake, 2015), rodents have acted as animal agents of disease transmission throughout human history. Rodents are well-known vectors; organisms which carry pathogens that are typically unimpactful in the carrier but are demonstrated to be pathogenic to a host

(Meerberg, Singleton, and Kijlstra, 2009). Because rodents have a propensity to carry pathogenic diseases that are relevant towards transmission to other mammals, including humans, their equally close association with invading human spaces in urban environments is a problem in dense cities (Himsworth, Parsons, Jardine, and Patrick, 2013). Urban ecology and urban epidemiology both consider this impact of species proximity that facilitates disease communication to human populations (Davis, Calvet, and Leirs, 2005). On an ecological scale, patterns of animal distribution surrounding the advent of urbanization are of interest as these patterns influence behaviors that bring together cross-species interaction (Chapman, Rymer, and Pillay, 2012; Engelhardt, and Weladji, 2011; Atwell, et al., 2012). On an epidemiological scale, the cross-species interaction is studied in terms of zoonotic pathogen communication, of which the quantification has been of major epidemic interest in the latter half of the 20th century (Jones, et al., 2008).

A zoonotic pathogen is an infectious agent, either bacteria, virus, or parasite, that is able to communicate disease to other animals through the usage of another animal as a vector (Mills, Gage, and Khan, 2010). Relevantly, zoonotic diseases are most commonly applied to diseases in which humans are the terminal subject. In a human model for zoonotic disease, the pathogen in question goes through another animal vector, and it is the job of the vector to communicate the pathogen to humans. A number of different animals can act in the role of a vector, but mammals as vectors are the most represented in human-relevant zoonoses (Jones, et al., 2008), though examples of non-mammalian vectors of disease like birds are relevant in both rural and urban settings (Tsiodras *et al.*, 2008).

Mammals make for proficient vectors for human zoonotic pathogens for a number of reasons, including the multiple different ways that humans interact with terrestrial mammals in their daily lives, both consciously and unwittingly (Jones, et al., 2008). Intentionally, the practice of agriculture in rural settings, and the consumption of animal derived products such as animal meat, dairy products, and fur and wool working, have brought together novel opportunity for zoonotic pathogens to be communicated between human cultivators of animal goods and the animals themselves (Larssen, Ståhl, and Enemark, 2014). Farmers engage in numbers of proximal behaviors with animal blood and feces and are of heightened risk for adverse interactions such as bites and scratches from the vector animal. This risk permeates across the urban-rural gradient and the agricultural domestication of large rural mammals introduce zoonotic pathogen risk to even urban consumers of farms with animals (Grant et al., 2008; Foley, et al., 2013). Unintentionally, the human lifestyle brings other sources of close proximity to potential animal vectors. As pets, both cats and dogs are potent carriers for relevant zoonotic pathogens (Maia, et al., 2014; Miró, et al., 2017). Across an urban-rural gradient, household pets are at extreme risk for interactions with other vector species, especially in circumstances where they are allowed to occupy both outside spaces and indoor homes (Maggi, and Krämer, 2019). Cats, for example, are well known to predate rodents when given opportunity outside of homes and as a result are key animal vectors for diseases such as toxoplasmosis in humans (Calero-Bernal, and Gennari, 2019). Toxoplasmosis, a disease caused by infestation of the protozoan *Toxoplasma gondii*, uses intermediate hosts such as rodents, to infest cats as their definitive hosts, who are obligate for the life cycle of *T. gondii* (Calero-Bernal, and Gennari, 2019). Humans themselves are uniquely not the intended definitive host, unlike many zoonotic diseases, but are likewise infected by both cats and dogs. Risk factors increase with the activity outdoors

the pet has because they experience increased exposure to outdoor vectors, such as free-living rodents, stray cats and dogs, and fecal remnants of animal vectors. As dogs and cats occasionally engage in coprophagia, the consumption of fecal matter, activities outdoors allow for heightened exposure to fecal pathogens (Calero-Bernal, and Gennari, 2019). Studies indicate that across urban-rural gradients, pets in urban centers are paradoxically more disposed to encountering certain zoonotic pathogens despite a reduced number in the population diversity of immediate animal vectors that a rural center would have (Miró, et al., 2017., Maia, et al., 2014). Because urban adaptive rodents can exist in urban centers that provide both human dwellings (Williams, et al., 2018), and natural canopy forests (Williams, et al., 2018., Himsworth, et al., 2014), these findings make contextual sense. If urban centers have higher proximities of rodent vectors invading human domiciles, then they would come into contact with both pets and their owners with problematic occurrence. In theme with the unintentional exposure to zoonotic vectors, rodents are a demonstrated major source for the broad diversity of human zoonotic pathogens across the entire urban-rural gradient(Davis, Calvet, and Leirs, 2005., Han, Schmidt, Bowden, and Drake, 2015., Panti-May, et al., 2017). Rodents themselves are the most frequent vectors in terms of zoonotic pathogen numbers (Morand, Jittapalapong, and Kosoy, 2015), owing to factors of their aforementioned proximity and involvement with human spaces, especially in urban environments, as well as their physiological similarities to humans (Perlman, 2016).

Pathogen Host-Switching and Zoonoses

In the antiquity of zoonoses, each was likely to be an isolated pathogen with a very narrow range of potential hosts, or host range (Parrish, et al., 2008). A host range consists of usually limited terminal, or definite hosts, and few intermediate vectors. In rare occurrences, an

accidental transfer of a pathogen from an intended host range into a species outside of these tentatively defined parameters into a novel host creates an opportunity for a new infection (Menachery, Graham, and Baric, 2017). In order to become not only virulent in a new host, but to continue outside of single infections or limited epidemics, a pathogen must overcome obstacles related to survival in a novel host (Parrish, et al., 2008). A number of variables that influence if a novel pathogen may generate past epidemic infection in a novel host include: the types and impact of contact between the native reservoir species and the new potential host, barriers that the new host's innate immunity and cellular defenses use to resist a novel infection, the ability of the pathogen to survive and propagate in the novel host, and how effective the new host could be with communicating the pathogen across its own host population (Parrish, et al., 2008). To summarize, there are four major steps that are met in the evolution of a successful host-switching event as depicted in Figure 1. Figure 2 depicts a mock-pathway in which a pathogen has circumvented through the four major steps and has emerged successful in host-switching. Upon successful host-switching and capitalization on novel hosts, a true zoonotic epidemic can be realized. Examples of events where successful novel host switching has led to an emerging epidemic are depicted in Table 1.

Figure 1: Diagram of the Four Major Steps Involved in Host-Switching for Pathogens

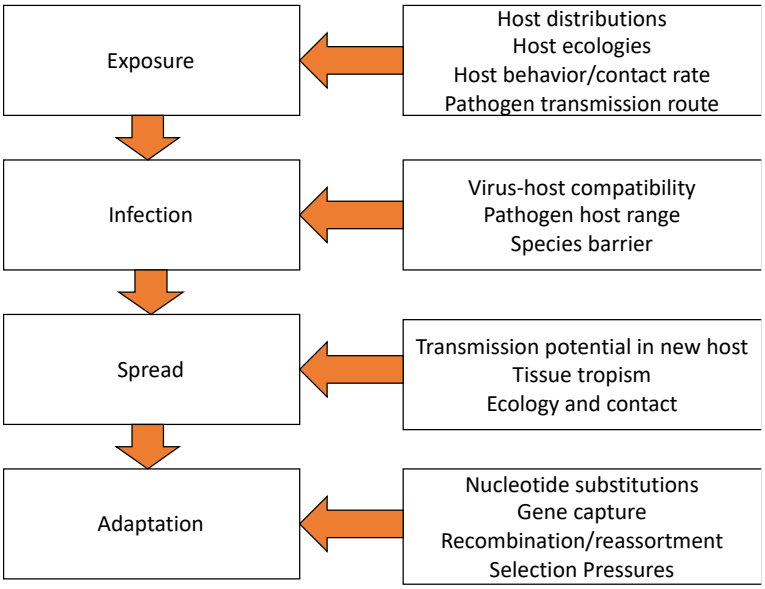
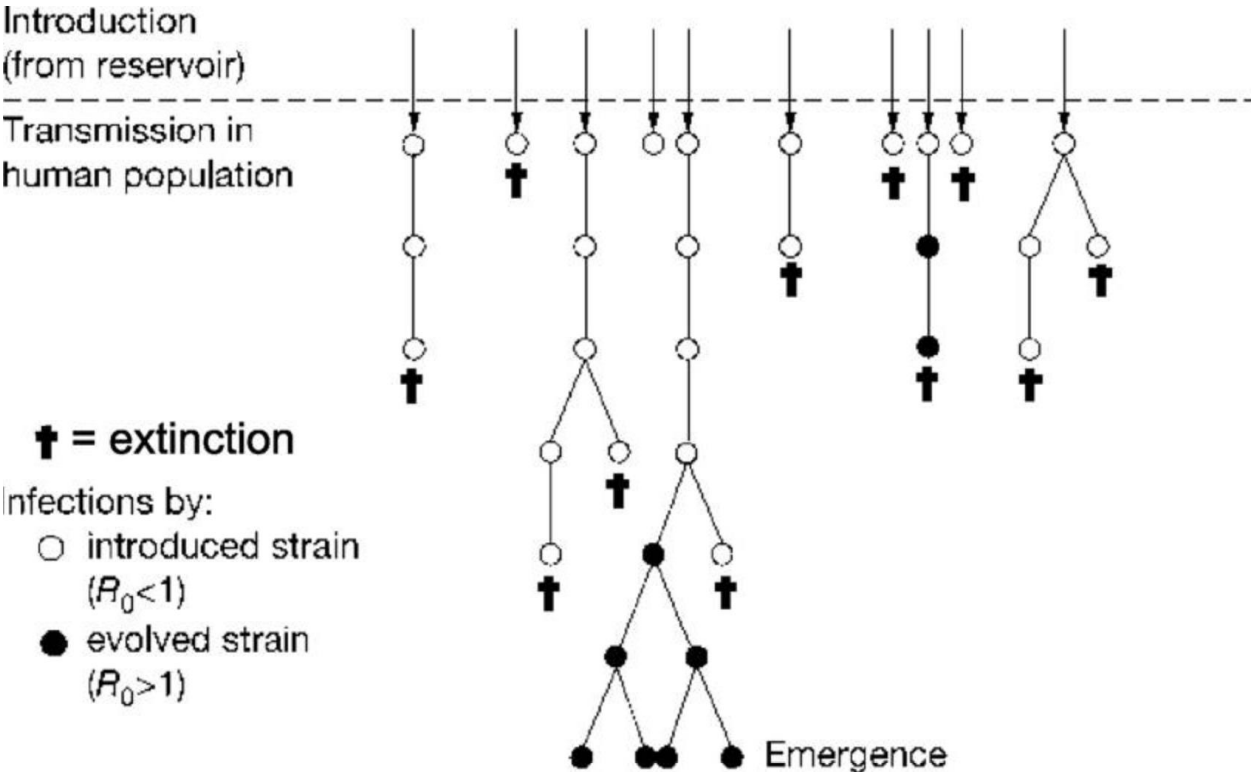


Figure 2: Illustration of a Successful Host-Switching event leading to a new Emergence



(Parish, *et al.* 2008).

Table 1: List of Pathogens that have evolved New Host Ranges through Host-Switching

Pathogen	**Relevant Disease Caused**	**Speculated Original Host Range**	**Newly Developed Host**
Borellia burgdorfi	Lyme disease	Rodents, Ungulates	Humans
Corynebacterium diphtheriae	Dipththeria	Domesticated Ungulates, Cattle	Humans
Dengue virus	Dengue Fever	Old World Primates	Humans
Ehrlichia spp.	Ehrlichosis	Rodents	Humans, Dogs, Cats
Human immunodeficiency virus type 1 (HIV-1)	Acquired immune deficiency syndrom (AIDS)	Chimpanzees	Humans, Gorillas
Human metapneumovirus (HMPV)	Human metapneumovirus infection	Poultry (primarily Turkeys, to a lesser extent, Chickens)	Humans
Influenzavirus A	Influenza A	Birds	Humans, Pigs, Bats, Horses
Measles morbilivirus	Measles	Cattle	Humans
Orthohantavirus	Nephropathica epidemica	Rodents, Soricomorphs (shrews)	Humans
Plasmodium falciparum	Malaria	Either Birds or Old World Primates	Humans
Plasmodium vivax	Malaria	Southeast Asian Macaques	Humans

Pathogen	Relevant Disease Caused	Speculated Original Host Range	Newly Developed Host
Severe acture respiratory syndrome coronavirus (SARS-CoV)	Severe Acute Respiratory Syndrome (SARS)	Himalayan palm civet (Paguma larvata), Racoon dog (Nyctereutes procyonoides), Bats	Humans
Trypanosoma brucei	Sleeping Sickness	African rumanents	Humans
Variola virus (VARV)	Smallpox	African rumanents (possibly Camels)	Humans
Yersinia pestis	Bubonic, Septicemic, and Pneumonic Plague	Rodents	Humans

An emerging area of interest in epidemiology is to qualitatively survey the pathogen load of known vectors of human disease to assess what circulating pathogens a civilization may be at risk for (Firth, et al., 2014., Kimura, et al., 2007). As mammals are extraordinarily relevant to disease in human populations for the many reasons positioned earlier, it is not surprising that many avenues of current research involves the detection and qualification of pathogens carried by mammals(Rojas, et al., 2010.; Chomel, and Kasten, 2010.; Smith, et al., 2012.; Kamani, et al., 2013). Furthermore, rodents are of exceptional interest to studies synthesizing urban epidemiology and urban ecology (Firth, et al., 2014). Studies investigating carrier status of vector mammals initially involve a number of sources for obtaining pathogenic data, either through collection of fecal pellets (Kimura, et al., 2007), or urine (Rojas, et al., 2010), both of which can be used to collection of bacterial, helminthic shedding, or through culling and gross dissection to remove virally and/or bacterially infected cells(Firth, et al., 2014.; Kimura, et al., 2007.; Chomel, and Kasten, 2010). A design around testing for specific and relevant pathogens

to a geographic area allows for a more targeted isolation, replication, and analysis of target sequences that are associated with known pathogens (Firth, et al., 2014). Specific polymerase chain reaction (PCR) assays operate by the selection of specific DNA/RNA primers to known pathogen sequences, upon which positive replication of genetic material, later confirmed with sequencing data, can identify the presence of a whole spectra of known pathogens (Firth, et al., 2014). Tissues selected for observation vary between pathogens of interest, with those reliant on the circulatory system for communication through the host system finding prevalence in filtration organ tissues such as the liver (Talwani, Gilliam, and Howell, 2013), or spleen, but a number of other host tissues may be of target interest for collection, such as the lung (Kunst *et al.*, 2009), digestive tract (Diaz, *et al.*, 2018) and the brain (Parikh, Tucci, and Galwankar, 2012). As pathogens have specificity in their target tissues, known as tissue tropism, investigative search for a particular pathogen would involve selection of known tissue reservoirs for the disease (McCall, Siqueira-Neto, and McKerrow, 2016). Pathogens, however, can evolve new ranges for tissue tropism, even to tissues of their non-native hosts, as Figure 1 demonstrates. For broad tissue tropic pathogens, or for surveys of potentially multiple carrier status, a range of tissues may be collected. Additionally, pathogens vary in their strategies for host penetration; some pathogens may be aerosolic, transferring through coughing, sneezing, or exhalations, thus respiratory tissues would be of investigative interest, such as the lungs, and the mucosa of the mouth and nose. Other pathogens may be communicated through fecal-oral contact, thus tissues of the stomach, upper gastrointestinal tract, and accessory organs such as the pancreas, liver, and kidneys would be of interest.

Pathogen detection could be very useful evidence to explore differences of risk for zoonotic pathogen transference across an urban-rural gradient. By comparatively assessing the sheer numbers, comorbid carrying of different pathogens, and the total diversity of pathogens faced in populations across the urban-rural gradient, a comprehensive literature review of pathogens across urban-rural gradients can suggest relationships between the urban-rural scale and relative risk for its inhabitants. Given the context of research indicating the relationships between urbanization, vector population, and cross-species pathogen jumping, results of a literature review of all pathogen detection of animal vectors across a gradient can be a useful observation in explaining the features of disease and epidemics that are observed in urban environments. It can be hypothesized that in an encompassing review of pathogen detection across an urban-rural gradient that results of urban vectors will demonstrate higher numbers of infected subjects, a higher comorbidity, and a higher diversity of represented zoonotic pathogens.

Results

Search

To determine relevant studies for consideration in literature review, definitive search criteria were employed. Specifically, both the search medium and the terminology were carefully reviewed and finalized in order to ascertain the highest yield of relevant studies. Searches were conducted using two college-level library database systems: Purchase College Library and Binghamton University Library, which have access to 9 and 16 databases respectively. In addition to two academic library systems, the ProQuest Summon® search engine and Google Scholar were used to locate abstracts of studies for later search through library provided databases. To narrow the results to relevant studies, the following search terms were used ubiquitously across searches using Google Scholar and ProQuest Summon®: “urbanization,” “urban (areas),” “zoonotic/zoonoses,” “vector,” “parasitic/parasite,” “urban(-rural) gradient,” “host-switching/species jumping,” “pathogen(s),” and “survey.” In various compositions, these terms were applied to find studies relevant. In total 17 search attempts were made across the four platforms, linking together the search terms in varying compositions. Search attempts are defined as unique entries into the search bar of a specific search engine; duplicate phrases were applied to different search engines. Relevancy was determined superficially at first by selecting articles of interest and searching within the text for these search terms. A number of studies were consulted and for the purposes of this literature review, 31 studies were selected.

Geographical Survey

31 studies were selected to represent urban-rural gradients across the world, selected primarily based on relevance to the urban-rural focus of the literature review. As depicted in Figure 3, studies on zoonses across urban-rural gradients were found five continents. Antarctica was excluded based on the inviability of human-animal interactions that could facilitate disease in humans, though anecdotally instances of pathogen communication from humans to Antarctic

animals is observed, (Griekspoor, Olsen, and Waldenström, 2009). Australia was excluded based on the lack of relevant studies that indicate animals as vectors for zoonotic disease, as well as for a lack of relevant studies that indicate an urban-rural gradient consideration. Of the five continents that were selected, North America and Europe were the most highly represented with 11 studies in each. Asia was represented by five studies, South America with three studies, and Africa represented by a single study.

In North America three countries were represented; Canada, Mexico, and the United States. Canada was represented by two studies in Southwestern Saskatchewan and Southeastern Saskatchewan, (Leighton, Artsob, Chu, and Olson, 2001), and in Northern Saskatchewan, (Himsworth, et.al., 2010). Both studies conducted in Canada were determined to fit in the rural demographic. No studies were urban, nor fit an urban-rural demographic. Mexico was represented by one study on the eastern Yucatán Peninsula, (Panti-May, et.al., 2017). The study was conducted across multiple neighborhoods ranging from urban to suburban, thus is within the parameters of the gradient of investigation. The United States was represented by eight studies in New York City, New York, (Firth, et.al., 2014; Frye, et.al., 2015; Williams, et.al., 2018), California and Wisconsin, (Case, Chomel, Nicholson, and Foley, 2006), California and Colorado, (Carver, et.al., 2012), Baltimore, Maryland, (Easterbrook, et.al., 2007; Kabrane-Lazizi, et.al.,1999), New Orleans, Louisiana and Oahu and Hawaii, Hawaii, (Kabrane-Lazizi, et.al.,1999), and Chicago, Illinois, (Hamer, Lehrer, and Magle, 2012). Five of these studies were conducted in exclusively urban environments, and three of them consisted of investigation conducted across an urban-rural gradient. No studies were exclusively rural in demographic.

In Europe ten countries were represented; Albania, Austria, Croatia, Denmark, Germany, Hungary, the Netherlands, Switzerland, and the United Kingdom. Albania was represented by one study which was conducted in an urban/suburban city of Tirana, (Silaghi, et.al., 2014). Austria was represented by one study which was conducted in rural settings, (Schmidt, et.al., 2014). Croatia was represented by one study which was conducted in rural settings, (Tadin, et.al., 2016). Denmark was represented by one study which was conducted in the urban capital city of Copenhagen, (Heuser, et.al., 2016). German was represented by three studies, sampling urban cities of Hamburg, (Johne, et.al., 2010; Heuser, et.al., 2016), Berlin, (Heuser, et.al., 2016), Brandenburg, (Heuser, et.al., 2016), and suburban and rural areas of Saxony, Saxony-Anhalt, North Rhine-Westphalia, Baden-Wuerttemberg, Ahlen, Stuttgart, and Esslingen, (Heuser, et.al., 2016). One study was urban in its demographic, (Johne, et.al., 2010), two studies surveyed across an urban-rural gradient, (Heuser, et.al., 2016; Menn, Lorentz, and Naucke, 2010). No studies were exclusively rural in demographic.

In Asia two countries were represented; Japan and South Korea. Japan was represented by four studies, three of which were indicated as exclusively rural, and one of which spanned an urban-rural gradient. Two studies were conducted in the urban capital city of Tokyo, (Koizumi, et.al., 2009; Hayashimoto, et.al., 2015,). One study was conducted in urban cities in seven prefectures: Tokyo, Kanagawa, Gifu, Aichi, Osaka, Hiroshima, and Hokkaido, (Tanaka, Miyazawa, Watarai, and Ishiguro, 2005). One study was conducted across veterinary clinics across all 47 prefectures of Japan, sampling across an urban-rural gradient, (Sasaki, et.al., 2012).

In Africa, only one country was represented by a single study; Nigeria. In Nigeria, collections and surveying were conducted across an urban-rural gradient across four states of Nigeria, Plateau, Kaduna, Kwara, and Rivers, (Kamani, et.al., 2013).

Pathogens Detected and Carriers

A total of 105 distinct types of pathogens were discovered over the span of 31 studies. The different pathogens were separated into categorization of their biological classification type: Animal, Bacteria, Protozoan, and Virus. Additionally, a single fungal pathogen was detected in an urban house mice (*Mus musculus*), *Pneumocystis murina*.

Table 2: Observed Animal Parasite Pathogens and Identified Carriers in Scientific Literature

Pathogen	Pathogen Type	Identified Carriers	Percent of Studies Referencing Pathogen
Ancylosoma spp.	Animal	Bobcat	3.23%
Aspiculuris tetraptera	Animal	House Mouse	3.23%
Calodium hepatica	Animal	Norway Rat	6.45%
Echinococcus spp. *E.granulosus* *E.multilocularis*	Animal	Domestic Dog Water Vole Meadow Vole Red-backed Vole	6.45%
Eucoleus spp.	Animal	Bobcat	3.23%
Heterakis spumosa	Animal	Norway Rat	3.23%
Hymenolepis spp. *H.diminuta* *H.nana*	Animal	House Mouse Norway Rat	12.9%
Mastophorus muris	Animal	Norway Rat	3.23%
Mesocestoides spp.	Animal	Meadow Vole	3.23%
Onchocercidae	Animal	Domestic Dog	3.23%
Physaloptera felis	Animal	Bobcat	3.23%
Syphacia obvelata	Animal	House Mouse	3.23%
Taenia spp. *T. taeniaeformis* *T. crassiceps* *T. martis*	Animal	Water Vole Meadow Vole Red-backed Vole Eurasian Field Mice	3.23%
Toxascaris leonina	Animal	Bobcat	3.23%

Pathogen	Pathogen Type	Identified Carriers	Percent of Studies Referencing Pathogen
Toxocara canis	Animal	Domestic Dog Eurasian Field Mice Water Vole Meadow Vole Red-backed Vole	6.45%
Toxocara cati	Animal	Bobcat Eurasian Field Mice Water Vole Meadow Vole Red-backed Vole	6.45%
Trichuris spp.	Animal	Bobcat (L.rufus)	3.23%

Animal Pathogens

Of the 105 pathogens described, 17 were animal parasites. 13 animal parasites belonged to the phylum Nematoda, also known as the roundworms, and 4 animal parasites belonged to the phylum Platyhelminths and in class Cestoda, also known as the flatworms. Of the 17 animal parasites, 6 were discovered in surveyed bobcats (*Lynx rufus*), 3 were discovered in surveyed domestic dogs (*Canis lupus familiaris*), 3 were discovered in house mice (*Mus musculus*), 4 were discovered in Norway rats (*Rattus norvegicus*), and 13 were discovered across three genera of voles (*Myodes*, *Arvicola*, and *Microtus*) and one genus of mouse (*Apodemus*). Five animal pathogens were unique to bobcats across the studies, and one animal pathogen, was also observed in the Eurasian field mice (genus *Apodemus*). Two animal pathogens were unique to house mice, with one animal parasite shared with the Norway rat. Three animal pathogens were unique to the Norway rat. The Eurasian field mice and three genera of voles had only one unique animal pathogen discovered in *Microtus*, with 12 others shared between the voles and the Eurasian field mouse.

Table 3: Observed Bacterial Pathogens and Identified Carriers in Scientific Literature

Pathogen	Pathogen Type	Identified Carriers	Percent of Studies Referencing Pathogen
Anaplasma spp. *A.platys* *A.phagocytophilium* *A.phagocytophilum*	Bacteria	Domestic Dog Domestic Cat Eurasian Field Mice Red-backed Vole	22.58%
Bartonella spp. *B. henselae* *B. clarridgeiae* *B. elizabethae* *B. queenslandensis* *B. tribocorum*	Bacteria	Norway Rat Domestic Dog Domestic Cat Eurasian Field Mice Red-backed Vole	25.81%
Borrelia afzelii	Bacteria	Eurasian Field Mice Red-backed Vole	6.45%
Borrelia burgdorferi	Bacteria	Numerous Bird Species*	6.45%
Borrelia miyamotoi	Bacteria	Eurasian Field Mice	3.23%
Brucella canis	Bacteria	Domestic Dog	3.23%
Campylobacter spp. *C. jejuni* *C. difficile* *C. perfringens* *C. upsaliensis*	Bacteria	Norway Rat Domestic Dog Domestic Cat	9.68%
Chlamydia spp. *C. psittaci* *C. pecorum*	Bacteria	Pigeon	3.23%
Ehrlichia spp. *E. canis* *E. muris* *E. chaffeensis* HF strain.	Bacteria	Domestic Dog Domestic Cat Eurasian Field Mice	16.13%
Enteropathic *E. coli*	Bacteria	Norway Rat Pigeon	6.45%
Francisella tularensis	Bacteria	Domestic Dog Domestic Cat Eurasian Field Mice	9.68%
Heliobacter spp. *H.hepaticus* *H. fennelliae* *H. ganmani* *H. rodentium* *H. japanicum* (sp. MIT 01-6451)	Bacteria	House Mouse	3.23%

Pathogen	Pathogen Type	Identified Carriers	Percent of Studies Referencing Pathogen
Klebsiella spp. *K. oxytoca* *K. pneymoniae*	Bacteria	House Mouse	3.23%
Leptospira spp. *L. interrogans*	Bacteria	Norway Rat Eurasian Field Mice Red-backed Vole Meadow Vole	32.26%
Mycobacterium spp. *M. terrae* *M.gordonae* *M.szulgai* *M.hiberniae* *M.porcinum*	Bacteria	Pigeon	3.23%
Mycoplasma spp. *M.haemofelis* *M. pulmonis*	Bacteria	Domestic Cat House Mouse	6.45%
Pasteurella pneumotropica	Bacteria	House Mouse	3.23%
Rickettsia spp. *R. rickettsii* *R. akari* *R.felis* *R.typhi* *R.helvetica* *R.burgdorferi* *R.conorii*	Bacteria	Domestic Dog Domestic Cat Norway Rat	25.81%
Salmonella spp. *S.enterica*	Bacteria	Norway Rat Pigeon Numerous Bird Species	9.68%
Shigella	Bacteria	Norway Rat	3.23%
Staphylococcus aureus	Bacteria	House Mouse	3.23%
Streptobacillus moniformis	Bacteria	Norway Rat	3.23%
Yersinia enterocolitica	Bacteria	Norway Rat	3.23%
Yersinia pestis	Bacteria	Domestic Dog Domestic Cat	3.23%

Bacterial Pathogens

Of the 105 pathogens described, 24 were bacterial pathogens. Of the 24 bacterial pathogens, 8 were discovered in domestic dogs (*Canis lupis familiaris*), with 1 unique bacterial

agent discovered in dogs alone. Domestic cats (*Felis catus*) shared all 7 other bacterial pathogens identified in dogs, as well as sharing one pathogen with house mice (*Mus musculus*), displaying 8 total pathogens. 7 bacterial pathogens were discovered in Eurasian mice (genus *Apodemus*), with 6 pathogens observed in at least one other subject, and 1 unique pathogen. 4 pathogens were discovered across the three genera of voles, with genus *Myodes* appearing twice without genera *Microtus* or *Arvicola*, however, the voles display no unique bacterial pathogens. 9 bacterial pathogens were discovered in the Norway rat (*Rattus norvegicus*), three of which were unique to them. 2 bacterial pathogens were discovered in numerous birds (class *Aves*), one of which was unique to them, West Nile Virus. 4 pathogens were discovered in pigeons (*Columba livia*), 2 of which were unique to them. 5 bacterial pathogens were discovered in the house mice (*Mus musculus*), 4 of which were unique.

Table 4: Observed Protozoan Pathogens and Identified Carriers in Scientific Literature

Pathogen	Pathogen Type	Identified Carriers	Percent of Studies Referencing Pathogen
Babesia microti	Protist	Eurasian Field Mice Red-backed Vole Meadow Vole	3.23%
Babesia rossi	Protist	Domestic Dog	3.23%
Babesia vogeli	Protist	Domestic Dog	6.45%
Cryptosporidium spp. *C.parvum*	Protist	Norway Rat Bobcat Domestic Dog	9.68%
Cystoisospora felis	Protist	Bobcat	3.23%
Eimeria spp.	Protist	Bobcat	3.23%
Entamoeba	Protist	House Mouse	3.23%
Giardia spp. *G.muris* *G.duodenalis*	Protist	House Mouse Bobcat Domestic Dog	9.68%
Hepatozoon canis	Protist	Domestic Dog	6.45%
Isospora spp.	Protist	Bobcat	3.23%

Pathogen	Pathogen Type	Identified Carriers	Percent of Studies Referencing Pathogen
Leishmania infantum	Protist	Domestic Dog	3.23%
Neospora caninum	Protist	Domestic Cat	3.23%
Octomitus pulcher	Protist	House Mouse	3.23%
Spironucleus muris	Protist	House Mouse	3.23%
Theileria spp.	Protist	Domestic Dog	3.23%
Toxoplama gondii	Protist	Domestic Cat Bobcat Water Vole Meadow Vole Eurasian Field Mice	9.68%
Tritrichomonas muris	Protist	House Mouse	3.23%
Trypanosoma cruzi	Protist	House Mouse Norway Rat	3.23%

Protozoan Pathogens

Of the 105 pathogens described, 18 were protists. Of the 18 protozoan pathogens, 7 were discovered in domestic dogs (*Canis lupus familiaris*), 5 of which were unique to dogs, and two of which were discovered in other hosts. 2 protozoan pathogens were discovered in domestic cats, 1 of which was solely discovered amongst cats. 6 protozoan pathogens were discovered in bobcats (*Lynx rufus*), 3 of which were unique to them. 2 protozoan pathogens were discovered in Eurasian field mice (genus *Apodemus*), both of which were also detected in other hosts, namely the voles. 2 protozoan pathogens were detected in the voles (genera *Myodes*, *Arvicola*, and *Microtus*), both of which were detected in other hosts. 2 protozoan pathogens were detected in the Norway rat (*Rattus norvegicus*), both of which were detected in other subjects. 4 protozoan pathogens were detected in the house mice (*Mus musculus*), three of which were unique to them and one of which was discovered in other subjects.

Table 5: Observed Protozoan Pathogens and Identified Carriers in Scientific Literature

Pathogen	Pathogen Type	Identified Carriers	Percent of Studies Referencing Pathogen
Bloomfield virus	Virus	House Mouse	3.23%
Canine parvovirus 2	Virus	House Mouse	3.23%
Chelsea phelbo-like virus	Virus	House Mouse	3.23%
Chicken anemia virus	Virus	House Mouse	3.23%
Dobrava-Belgrade orthohantavirus	Virus	Eurasian Field Mice	6.45%
Feline immunodeficiency virus (FIV)	Virus	Domestic Cat	3.23%
Fresh Meadows densovirus 1	Virus	House Mouse	3.23%
Fresh Meadows densovirus 2	Virus	House Mouse	3.23%
Fresh Meadows densovirus 3	Virus	House Mouse	3.23%
Fresh Meadows densovirus 4	Virus	House Mouse	3.23%
Hantavirus spp.	Virus	Eurasian Field Mice Meadow Voles Red-backed Vole Norway Rat	16.13%
Hepatitis E Virus	Virus	Norway Rat	9.68%
Lactate dehydrogenase-elevating virus (LaDV)	Virus	House Mouse	3.23%
Mouse adenovirus Type 2 (Strain K8)	Virus	House Mouse	3.23%
Mouse hepatitis virus	Virus	House Mouse	6.45%
Mouse papillomavirus 1	Virus	House Mouse	3.23%
Mouse parvovirus 2	Virus	House Mouse	3.23%
Murine adeno-associated virus 1 (Murine AAV1)	Virus	House Mouse	3.23%
Murine adeno-associated virus 2 (Murine AAV2)	Virus	House Mouse	3.23%

Pathogen	Pathogen Type	Identified Carriers	Percent of Studies Referencing Pathogen
Murine adenovirus 2 (MAd-2)	Virus	House Mouse	3.23%
Murine astrovirus 1 (MuAst-1)	Virus	House Mouse	3.23%
Murine astrovirus 2 (MuAst-2)	Virus	House Mouse	3.23%
Murine bocavirus (MuBV)	Virus	House Mouse	3.23%
Murine chapparvovirus (MuCPV)	Virus	House Mouse	3.23%
Murine circovirus	Virus	House Mouse	3.23%
Murine feces-associated gemycircularvirus 1 (Murine FaGv-1)	Virus	House Mouse	3.23%
Murine feces-associated gemycircularvirus 2 (Murine FaGv-2)	Virus	House Mouse	3.23%
Murine feces-associated hepe-like virus (MuFAHLV)	Virus	House Mouse	3.23%
Murine feces-associated rhabdovirus (MuFARV)	Virus	House Mouse	3.23%
Murine kobuvirus (MuKoV)	Virus	House Mouse	3.23%
Murine norovirus (MNV)	Virus	House Mouse	6.45%
Murine picobirnavirus 1	Virus	House Mouse	3.23%
Murine picobirnavirus 2	Virus	House Mouse	3.23%
Murine picobirnavirus 3	Virus	House Mouse	3.23%
Murine picornavirus (MuPiV)	Virus	House Mouse	3.23%
Murine rotavirus (MuRotaV)	Virus	House Mouse	3.23%

Pathogen	Pathogen Type	Identified Carriers	Percent of Studies Referencing Pathogen
Murine sapovirus (MuSaV)	Virus	House Mouse	3.23%
Murine-associated porcine bocavirus (MuAPBV)	Virus	House Mouse	3.23%
Mus musculus polyomavirus 3e (MmusPyV-3)	Virus	House Mouse	3.23%
Orthopoxyvirus	Virus	Red-backed Vole	3.23%
Puumala virus	Virus	Eurasian Field Mice Red-backed Vole	3.23%
Rat polyomavrius	Virus	Norway Rat House Mouse	6.45%
Theiler's encephalomyelitis virus (TMEV)	Virus	House Mouse	6.45%
Tula orthohantavirus	Virus	Eurasian Field Mice Red-backed Vole Meadow Vole	6.45%
West Nile Virus	Virus	Numerous Bird Species	3.23%
Wuchang cockroach virus 3	Virus	House Mouse	3.23%

Viral Pathogens

Of the 105 pathogens described, 46 were viruses. Of the 46 viral pathogens discovered, 36 were discovered in house mice (*Mus musculus*). Of these 38, 37 were unique to house mice and only 1 of which was shared with another subject, the Norway rat (*Rattus norvegicus*). 3 viral pathogens were discovered in the Norway rat, one of which was unique to them. 4 viral pathogens were detected across subjects of three genera of voles (*Myodes*, *Arvicola*, and *Microtus*), 2 of which were unique to both the voles and to the genus *Myodes*. 1 pathogen was detected in domestic cats (*Felis catus*) and was unique to them.

Pathogens by Host

Across 31 studies, 11 different categories of animal hosts were identified, sampled, and assessed for pathogen carrier status. Of the 11 subjects, 6 fell under the classification of the Order *Rodentia*, or rodents. 4 of which were described on the basis of genus level description, being genera *Apodemus*, *Myodes*, *Microtus*, and *Arvicola*, the Eurasian field mouse, Red-backed vole, Meadow vole, and Water vole, respectively. The two other rodents identified were specific species, the house mouse (*Mus musculus*), and the Norway rat (*Rattus norvegicus*). Of the 11 subjects, three fell under the classification of the Order *Carnivora*, or the carnivores. Two of the carnivores more specifically fell under the suborder *Feliformia*, and were specific species; both the domestic cat (*Felis catus*) and the bobcat (*Lynx rufus*). One of the carnivores fell under the suborder *Caniformia*, and was a specific species, the domestic dog (*Canis lupus familiaris*). Of the 11 subjects, two of which were non-mammalian, falling under the class *Aves*. One of which was a specific species of bird, the common pigeon or rock dove (*Columba livia*), and the other of which was a broad collection of wild birds.[1]

Bobcats hosted a total of 12 pathogens, 6 of which were animal parasites and 6 were protozoan pathogens. None of the pathogens detected in bobcats were either bacterial pathogens or viral pathogens. 33.3% of the animal parasites carried in surveyed bobcats were relevant to known human diseases, 2 out of 6. 50% of the protozoan pathogens carried in surveyed bobcats were relevant to known human diseases, 3 out of 6.

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[1] 32 different species of bird across Class *Aves* were considered.
Three tested positive for *B.burgdorfi*, Red-winged blackbird (*Agelaius phoeniceus*), Rose-breasted grosbeak (*Pheucticus ludovicianus*), House wren (*Troglodytes aedon*).
Five tested positive for *West Nile Virus,* Brown-headed cowbird (*Molothrus ater*), Common grackle (*Quiscalus quiscula*), Northern cardinal (*Cardinalis cardinalis*), Rose-breasted grosbeak (*Pheucticus ludovicianus*), Wood thrush (*Hylocichla mustelina*)
One tested positive for *Salmonella* spp, Red-winged blackbird (*Agelaius phoeniceus*)
See Appendix – 2 for complete list of the numerous bird species.

Domestic cats hosted a total of 11 pathogens, 8 of which were bacterial pathogens, 2 of which were protozoan pathogens, and 1 of which was a viral pathogen. None of the pathogens detected in domestic cats were animal parasites. 100% of the bacterial pathogens carried by domestic cats were relevant to known human diseases, 8 out of 8. 50% of the protozoan pathogens carried by domestic cats were relevant to known human diseases, 1 out of 2.

Domestic dogs hosted a total of 18 pathogens, 3 of which were animal parasites, 8 of which were bacterial pathogens, and 7 of which were protozoan pathogens. None of the pathogens detected in domestic dogs were viral pathogens. 66.7% of the animal parasites carried in surveyed domestic dogs were relevant to known human diseases, 2 out of 3. 100% of the bacterial pathogens carried by domestic dogs were relevant to known human diseases, 8 out of 8. 57.1% of the protozoan pathogens carried in surveyed domestic dogs were relevant to known human diseases, 4 out of 7.

Eurasian field mice hosted 16 pathogens, 3 of which were animal parasites, 7 of which were bacterial pathogens, 2 of which were protozoan pathogens, and 4 of which were viral pathogens. 85.7% of the bacterial pathogens carried by Eurasian field mice were relevant to known human diseases, 6 out of 7. 100% of the protozoan pathogens carried in surveyed Eurasian field mice were relevant to known human diseases, 2 out of 2.

The house mice hosted 53 pathogens, 3 of which were animal parasites, 8 of which were bacterial pathogens, 6 of which were protozoan pathogens, and 38 of which were viral pathogens. Additionally, house mice also hosted one fungal pathogen, *Pneumocystis murina*. 33.3% of the animal parasites carried in surveyed in house mice were relevant to known human diseases, 1 out of 3. 80% of the bacterial pathogens carried by house mice were relevant to known human diseases, 4 out of 5. 50% of the protozoan pathogens carried by house mice were relevant to known human diseases, 3 out of 6. 25% of the viral pathogens carried by house mice were relevant to known human diseases, 1 out of 4.

The meadow vole hosted 10 pathogens, 5 of which were animal parasites, 1 of which

was a bacterial pathogen, 2 of which were protist pathogens, and 2 of which were viral pathogens. 40% of the animal parasites carried in surveyed meadow voles were relevant to known human diseases, 2 out of 5. 100% of the bacterial pathogens carried by meadow vole were relevant to known human diseases, 1 out of 1. 100% of the protozoan pathogens carried by meadow voles were relevant to known human diseases, 2 out of 2.

The Norway rat hosted 18 pathogens, 4 of which were animal parasites, 9 of which were bacterial pathogens, 2 of which were protozoan pathogens, and 3 of which were viral pathogens. 50% of the animal parasites carried in surveyed Norway rats were relevant to known human diseases, 2 out of 4. 100% of the bacterial pathogens carried by Norway rats were relevant to known human diseases, 9 out of 9. 100% of the protozoan pathogens carried by Norway rats were relevant to known human diseases, 2 out of 2.

Numerous bird species hosted 3 pathogens, 2 of which were bacterial pathogens and 1 of which was a viral pathogen. None of the pathogens presented in the numerous birds were animal parasites or protozoan pathogens. 0% of all pathogens surveyed across the numerous birds were relevant to known human diseases, 0 out of 3.

Pigeons hosted 4 pathogens, all 4 of which were bacterial in nature. None of the pathogens presented in the pigeons were animal parasites, protozoan pathogens, or viral pathogens. 100% of the bacterial pathogens carried by pigeons were relevant to known human diseases, 4 out of 4.

The red-backed vole hosted 13 pathogens, 4 of which were animal parasites, 4 of which were bacterial pathogens, 1 of which was a protozoan pathogen, and 4 of which were viral pathogens. 25% of the animal parasites carried in surveyed red-backed voles were relevant to known human diseases, 1 out of 4. 75% of the bacterial pathogens carried by red-backed voles were relevant to known human diseases, 3 out of 4. 25% of the viral pathogens carried by red-backed vole were relevant to known human diseases, 1 out of 4.

The water vole hosted a total of 5 pathogens, 4 of which were animal parasites and 1 of

which was a protozoan pathogen. None of the pathogens presented in the water vole were bacterial pathogens or viral pathogens. 25% of the animal parasites carried in surveyed water voles were relevant to known human diseases, 1 out of 4. 100% of the protozoan pathogens carried by water voles were relevant to known human diseases, 1 out of 1.

Table 6: Percentage of Pathogens Identified in 11 Host Species that are Infectious Agents in Human Pathology

	Animal Parasites	Bacterial	Protist	Viral
Bobcat	33.33%	0%	50%	0%
Domestic cat	0%	100%	50%	0%
Domestic Dog	66.67%	100%	57.14%	0%
Eurasian field Mice	0%	85.71%	100%	25%
House Mouse	33.33%	80%	50%	0%
Meadow Vole	40%	100%	100%	0%
Norway Rat	50%	100%	100%	0%
Numerous Bird Species	0%	0%	0%	0%
Pigeon	0%	100%	0%	0%
Red-backed Vole	25%	75%	0%	25%
Water Vole	25%	0%	100%	0%

Pathogens by Demographic

31 studies were selected to represent literature across a global scale, which were divided into three categories based on the demography of where principle survey were conducted. Studies that were exclusively conducted in urban environments were given with the category of “urban,” and studies that were exclusively conducted in either rural or largely non-anthropocentric environments were given with the category of “rural.” A third category accounted for studies in which either multiple sampling sites spanned between urban and rural domains, or for when a suburban domain was considered, thus was given the category of “urban-rural gradient.” Urban studies composed 18 out of the 31 studies selected, composing roughly 58% (58.06%) of the studies. Urban-rural gradient studies composed 8 out of the 31

studies selected, composing roughly 26% (25.81%) of the studies. Rural studies composed 5 out of the 31 studies selected, composing roughly 16% (16.13%) of the studies.

Tables 7-10 depict the prevalence of all 106 identified pathogens based on demographic history of the studies and where relevant carrier hosts were found. Values are depicted as percentages based on the comparative numbers within their categories; for example, 12.5% of the urban-rural gradient studies indicate carrier status of *Ancylostoma* spp. in their subjects. Raw numerical data concerning the numbers and identities of the studies indicated across each category is included in the appendix section.

Table 7: Demographics of Animal Parasitic Pathogens and Carrier Species

	Percentage of Studies Identifying Carriers			**Species Identified**		
Pathogen	Urban	Urban-Rural Gradient	Rural	Urban	Urban-Rural Gradient	Rural
Ancylostoma spp.		12.50			Bobcat	
Aspiculuris tetraptera	5.56			House Mouse		
Calodium hepatica	11.11			Norway Rat		
Echinococcus spp.	5.56		20.00	Red-backed Vole Meadow Vole Water Vole		Domestic Dog
Eucoleus spp.		12.50			Bobcat	
Heterakis spumosa	5.56			Norway Rat		
Hymenolepis spp.	22.22			Norway Rat House Mouse		
Mastophorus muris	5.56			Norway Rat		
Mesocestoides spp.	5.56			Meadow Vole		
Onchocercidae		12.50			Domestic Dog	
Physaloptera felis		12.50			Bobcat	
Syphacia obvelata	5.56			House Mouse		
Taenia spp.	5.56			Eurasian Field Mice Red-backed Vole Meadow Vole Water Vole		
Toxascaris leonina		12.50			Bobcat	

Pathogen	Percentage of Studies Identifying Carriers			Species Identified		
	Urban	Urban-Rural Gradient	Rural	Urban	Urban-Rural Gradient	Rural
Toxocara canis		12.50	20.00		Eurasian Field Mice, Red-backed Vole, Meadow Vole, Water Vole	Domestic Dog
Toxocara cati		25.00			Bobcat, Eurasian Field Mice, Red-backed Vole, Meadow Vole, Water Vole	
Trichuris spp.		12.50			Bobcat	

Table 8: Demographics of Bacterial Pathogens and Carrier Species

Pathogen	Percentage of Studies Identifying Carriers			Species Identified		
	Urban	**Urban-Rural Gradient**	**Rural**	**Urban**	**Urban-Rural Gradient**	**Rural**
Anaplasma spp.	5.56	50.00	40.00	Domestic Cat	Ticks, Domestic Dog	Domestic Dog, Eurasian Field Mice, Red-backed Vole
Bartonella spp.	22.22	25.00	60.00	Norway Rat, Domestic Cat	Domestic Cat, Tick	Domestic Dog, Domestic Cat, Eurasian Field Mice
Borellia spp.	5.56	12.50	40.00	Birds	Domestic Dog	Eurasian Field Mice, Red-backed Vole
Brucella canis		12.50			Domestic Dog	
Campylobacter spp.	5.56	12.50	20.00	Norway Rat	Domestic Dog, Domestic Cat, Ticks	Domestic Dog
Chlamydia spp.	5.56			Pigeon		
Ehrlichia spp.	5.56	25.00	40.00	Domestic Dog	Domestic Dog, Domestic Cat, Ticks	Eurasian Field Mice
Enteropathic E. coli	11.11			Norway Rat, Pigeon		

	Percentage of Studies Identifying Carriers			Species Identified		
Pathogen	**Urban**	**Urban-Rural Gradient**	**Rural**	**Urban**	**Urban-Rural Gradient**	**Rural**
Francisella tularensis		12.50	40.00		Domestic Dog	Domestic Dog, Domestic Cat, Eurasian Field Mice
Heliobacter spp.	5.56			House Mouse		
Klebsiella spp.	5.56			House Mouse		
Leptospira spp.	44.44		40.00	Norway Rat, Eurasian Field Mice, Red-backed Vole, Meadow Vole		Eurasian Field Mice, Red-backed Vole, Meadow Vole
Mycobacterium spp.	5.56			Pigeon		
Mycoplasma spp.	5.56	12.50		House Mouse	Domestic Cat	
Pasteurella pneumotropica	5.56			House Mouse		
Rickettsia spp.	11.11	50.00	20.00	Domestic Cat, Norway Rat	Domestic Dog, Domestic Cat, Ticks	Domestic Dog
Salmonella spp.	11.11			Norway Rat, Pigeon		
Shigella	5.56			Norway Rat		
Staphylococcus aureus	5.56			House Mouse		
Streptobacillus moniformis	5.56			Norway Rat		
Yersinia enterocolitica	5.56			Norway Rat		
Yersinia pestis			20.00			Domestic Dog, Domestic Cat

Table 9: Demographics of Protozoan Pathogens and Carrier Species

	Percentage of Studies Identifying Carriers			Species Identified		
Pathogen	**Urban**	**Urban-Rural Gradient**	**Rural**	**Urban**	**Urban-Rural Gradient**	**Rural**
Babesia spp.	5.56		40.00	Domestic Dog		Domestic Dog, Eurasian Field Mice, Rec-backed Vole, Meadow Vole
Cryptosporidium spp.	5.56	12.50	20.00	Norway Rat	Bobcat	Domestic Dog
Cystoisopora felis		12.50			Bobcat	
Eimeria spp.		12.50			Bobcat	
Entamoeba	5.56			House Mouse		
Giardia spp.	5.56	12.50	20.00	House Mouse	Bobcat	Domestic Dog
Heptaozoon canis		12.50	20.00		Domestic Dog	Domestic Dog
Isospora spp.		12.50			Bobcat	
Leishmania infantum		12.50			Domestic Dog	
Neospora caninum		12.50			Domestic Cat	
Octomitus pulcher	5.56			House Mouse		
Spironucleus muris	5.56			House Mouse		
Theileria spp.			20.00			Domestic Dog
Toxoplasma gondii	5.56	25.00		Eurasian Field Mice, Meadow Vole, Water Vole	Bobcat, Domestic Cat	
Tritrichomonas muris	5.56			House Mouse		
Trypanosoma cruzi	5.56			Norway Rat, House Mouse		

Table 10: Demographics of Protozoan Pathogens and Carrier Species

	Percentage of Studies Identifying Carriers			Species Identified		
Pathogen	**Urban**	**Urban-Rural Gradient**	**Rural**	**Urban**	**Urban-Rural Gradient**	**Rural**
Bloomfield virus	5.56			House Mouse		
Canine parvovirus 2	5.56			House Mouse		
Chelsea phelbo-like virus	5.56			House Mouse		
Chicken anemia virus	5.56			House Mouse		
Dobrava-Belgrade orthohantavirus	5.56		20.00	Eurasian Field Mice		Eurasian Field Mice
Feline immunodeficiency virus (FIV)	5.56			Domestic Cat		
Fresh Meadows densovirus 1-4	5.56			House Mouse		
Hantavirus spp.	22.22		20.00	Norway Rat		Eurasian Field Mice, Red-backed Vole, Meadow Vole
Hepatitis E virus	16.67			Norway Rat		
Lactate dehydrogenase-elevating virus (LaDV)	5.56			House Mouse		
Mouse adenovirus Type 2 (Strain KB)	5.56			House Mouse		
Mouse hepatitis virus	11.11			House Mouse		
Mouse papillomavirus 1	5.56			House Mouse		
Mouse parvovirus 2	5.56			House Mouse		
Murine adeno-associated virus 1 and 2 (Murine AAV1, Murine AAV2)	5.56			House Mouse		
Murine adenovirus 2 (MAd-2)	5.56			House Mouse		
Murine astrovirus 1 and 2 (MuAst-1, MuAst-2)	5.56			House Mouse		
Murine bocavirus (MuBV)	5.56			House Mouse		
Murine chapparvovirus (MuCPV)	5.56			House Mouse		
Murine circovirus	5.56			House Mouse		

	Percentage of Studies Identifying Carriers			Species Identified		
Pathogen	**Urban**	**Urban-Rural Gradient**	**Rural**	**Urban**	**Urban-Rural Gradient**	**Rural**
Murine feces-associated gemycircularvirus 1 and 2 (Murine FaGv-1, Murine FaGv-2)	5.56			House Mouse		
Murine feces-associated hepe-like virus (MuRAHLV)	5.56			House Mouse		
Murine feces-associated rhabdovirus (MuFARV)	5.56			House Mouse		
Murine kobuvirus	5.56			House Mouse		
Murine norovirus MNV)	11.11			House Mouse		
Murine picobirnavirus 1-3	5.56			House Mouse		
Murine picornavirus (MuPiV)	5.56			House Mouse		
Murine rotavirus (MuRotaV)	5.56			House Mouse		
Murine sapovirus (MuSaV)	5.56			House Mouse		
Murine-associated porcine bocavirus (MuAPBV)	5.56			House Mouse		
Mus musculus polyomavirus 3e (MmusPyV-3)	5.56			House Mouse		
Orthopoxyvirus			20.00			Red-backed Vole
Puumala virus			20.00			Eurasian Field Mice, Red-backed Vole
Rat polyomavirus	11.11			Norway Rat, House Mouse		
Theiler's encephalomyelitis virus (TMEV)	11.11			House Mouse		
Tula orthohantavirus	5.56		20.00			Eurasian Field Mice, Red-backed Vole, Meadow Vole
West Nile Virus	5.56			Birds		
Wuchang cockroach virus 3	5.56			House Mouse		

Urban Demographics

Of the 17 animal parasites observed across all of the reviewed studies, 9 were identified in urban studies; 7 of them were identified by 5.56% of all of the urban studies sampled, 1 of them was identified by 11.11% of all of the urban studies sampled, and 1 of them was identified by 22.22% of all of the urban studies sampled. 7 animal parasites of them were not identified by any of the urban studies. Of the 22 bacterial pathogens observed across all of the reviewed studies, 20 were identified in urban studies; 14 of them were identified by 5.56% of all of the urban studies sampled, 3 of them were identified by 11.11% of all of the urban studies sampled, 1 was identified by 22.22% of all of the urban studies sampled, and 1 was identified by 44.44% of all of the urban studies sampled. 2 bacterial pathogens were not identified by any of the buran studies. Of the 16 protozoan pathogens observed across all of the reviewed studies, 9 were identified in urban studies; all 9 of which were identified by 5.56% of all urban studies sampled. Of the 38 viral parasites observed across all of the reviewed studies, 36 were identified in urban studies; 32 of them were identified by 5.56% of all of the urban studies, 4 of them were identified by 11.11% of all of the urban studies sampled, 1 of them was identified by 16.67% of all of the urban studies sampled, and 1 of them was observed in 22.22% of all of the urban studies sampled. 2 viral pathogens were not identified in any of the urban studies.

Urban-Rural Gradient Demographics

Of the 17 animal parasites observed across all of the reviewed studies, 8 were identified in urban-rural gradient studies; 7 of which were identified by 12.50% of all of the urban-rural gradient studies sampled, and 1 of which was identified in 25.00% of all of the urban-rural gradient studies sampled. 9 animal parasites were not identified by any of the urban-rural

gradient studies. Of the 22 bacterial pathogens observed across all of the reviewed studies, 9 bacterial pathogens were identified; 5 of which were identified by 12.50% of all of the urban-rural gradient studies sampled, 2 of which were identified by 25.00% of all of the urban-rural gradient studies sampled, and 2 of which were identified by 50.00% of all of the urban-rural gradient studies sampled. 13 bacterial pathogens were not identified in any of the urban-rural gradient studies. Of the 16 protozoan pathogens observed across all of the reviewed studies, 9 were identified in urban-rural gradient studies; 9 of which were identified by 12.50% of all of the urban-rural gradient studies sampled, and 1 of which was identified by 25.00% of all of the urban-rural gradient studies sampled. 7 protozoan pathogens were not identified by any of the reviewed studies. Of the 38 viral parasites observed across all of the reviewed studies, none of them were identified within any of the urban-rural gradient studies.

Rural Gradient Demographics

Of the 17 animal parasites observed across all of the reviewed studies, 2 were identified in rural studies; both of which were observed across 20.00% of all of the rural studies sampled. Of the 22 bacterial pathogens observed across all of the reviewed studies, 9 were identified in rural studies; 3 of which were identified in 20.00% of all rural studies, 5 of which were identified in 40.00% of all rural studies, and 1 of which was observed in 60.00% of all studies. Of the 16 protozoan pathogens observed across all of the reviewed studies, 5 were identified in rural studies; 4 of which were identified in 20.00% of all of the rural studies sampled, and 1 of which was identified in 40.00% of all of the rural studies sampled. Of the 38 viral parasites observed across all of the reviewed studies, 5 were identified in rural studies, all 5 were observed within 20.00% of all of the rural studies sampled.

Demographics Summary

As there were 18 urban studies, 8 urban-rural gradient studies, and 5 rural studies, the percentages given conform to the following fractions:

Urban: 1/18 = 5.56%, 2/18 = 11.11%, 3/18 = 16.67%, 4/18 = 22%, 8/18 = 44.44%

Urban-Rural: 1/8 = 12.5%, 2/8 = 25.00%, 4/8 = 50.00%

Rural: 1/5 = 20.00%, 2/5 = 40.00%, 3/5 = 60.00%

Figure 4: Numbers of Studies Identifying Animal Parasites in Urban, Urban-Rural, and Rural Demographics

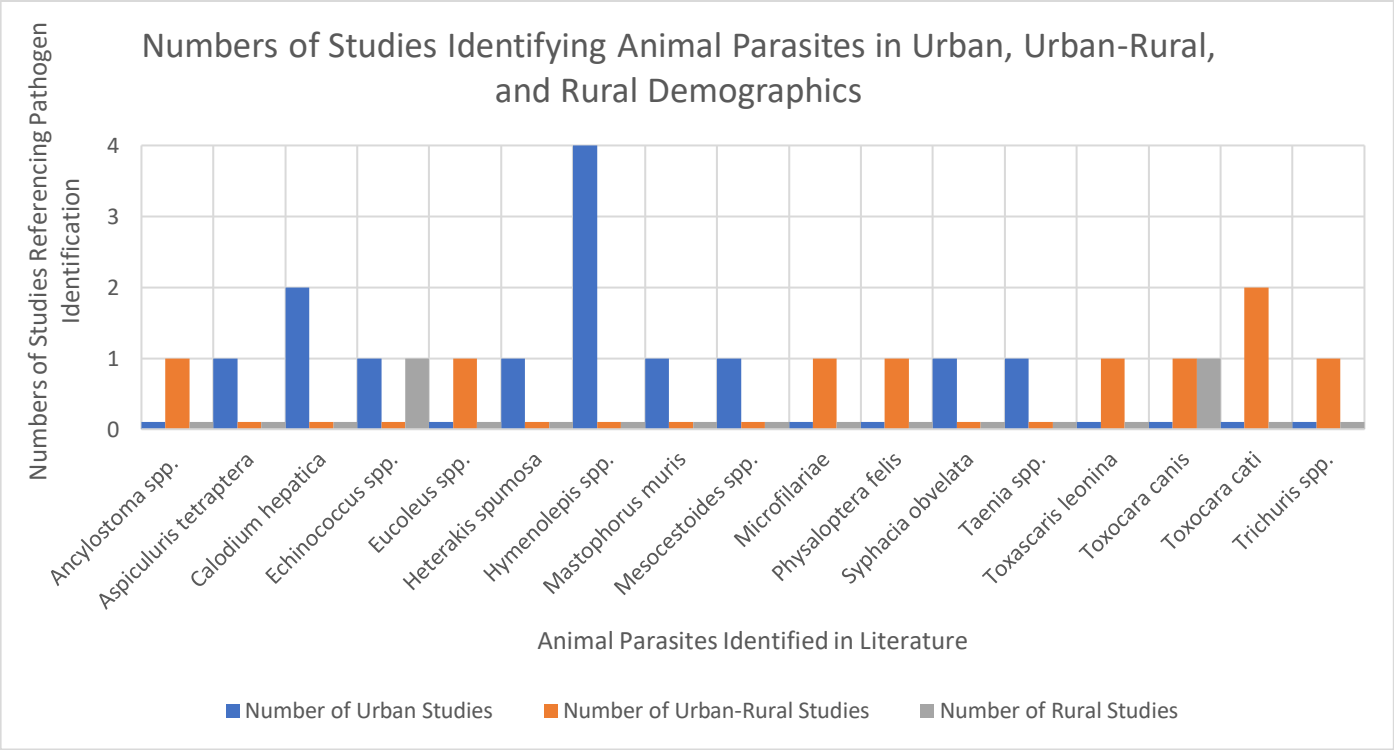


Figure 5: Numbers of Studies Identifying Bacterial Parasites in Urban, Urban-Rural, and Rural Demographics

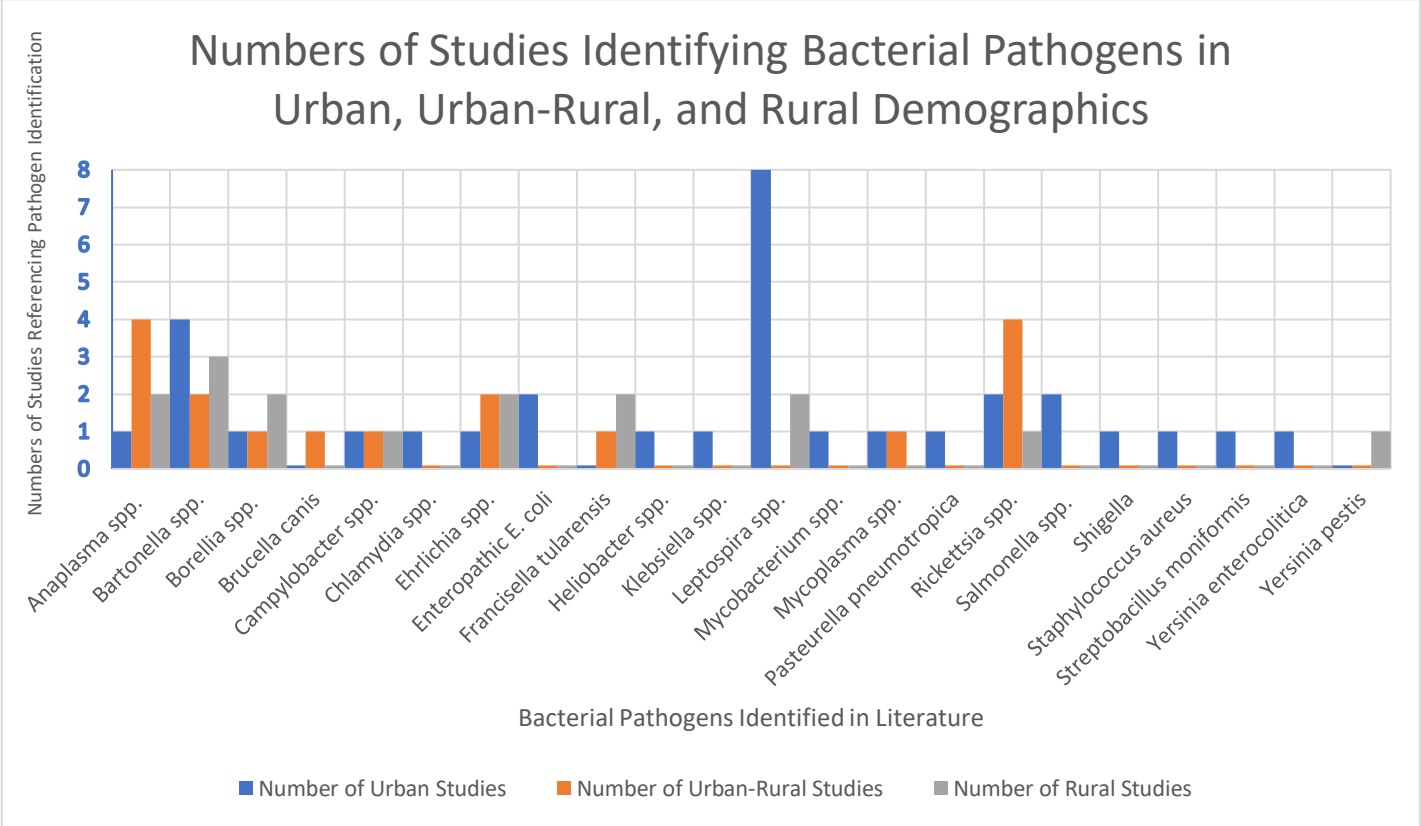


Figure 6: Numbers of Studies Identifying Protozoan Parasites in Urban, Urban-Rural, and Rural Demographics

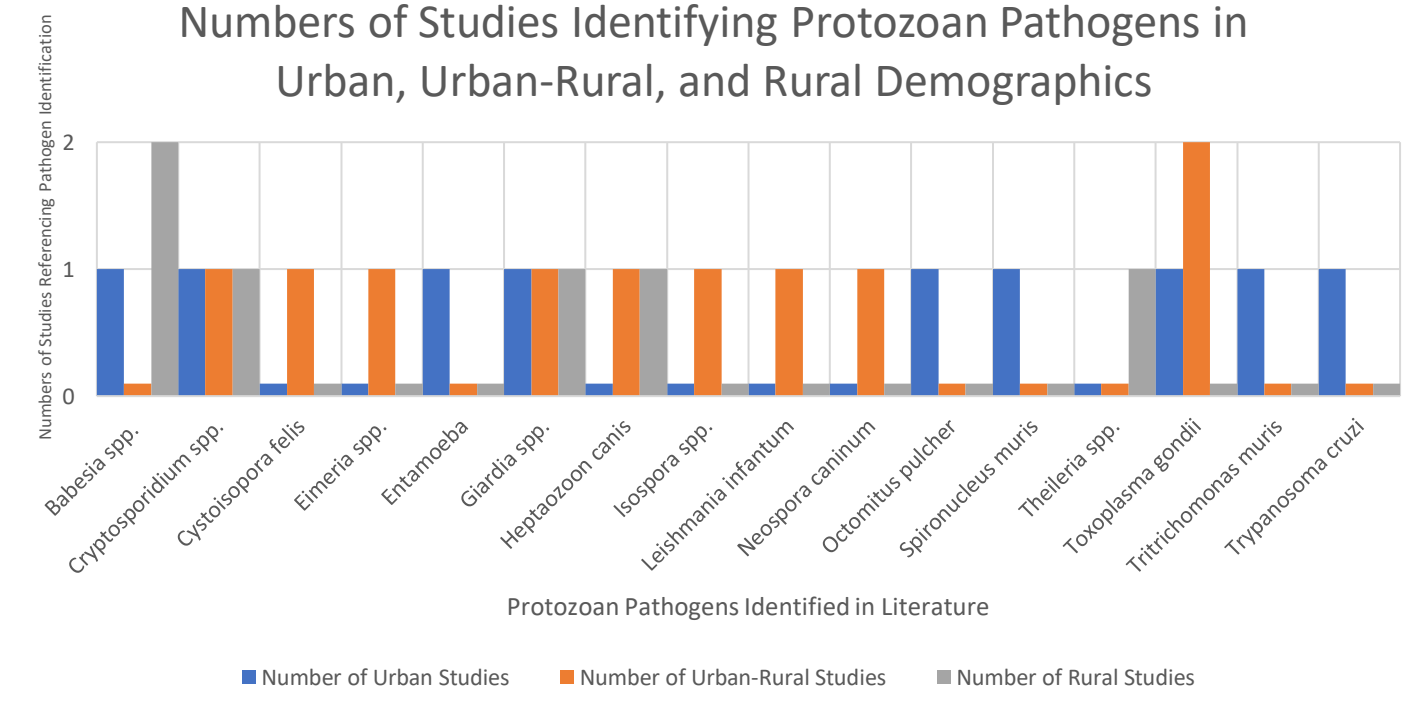


Figure 7: Numbers of Studies Identifying Viral Parasites in Urban, Urban-Rural, and Rural Demographics

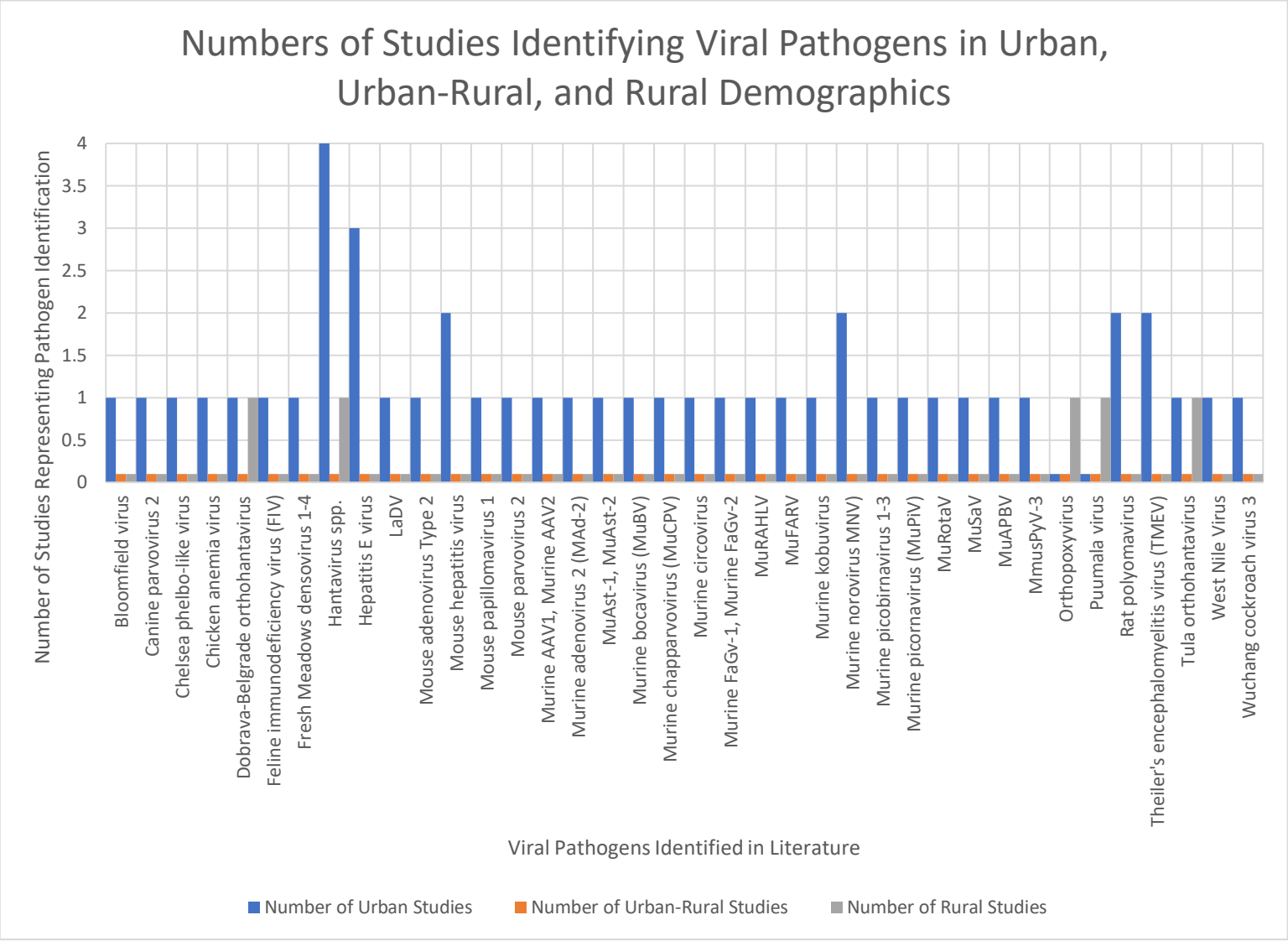
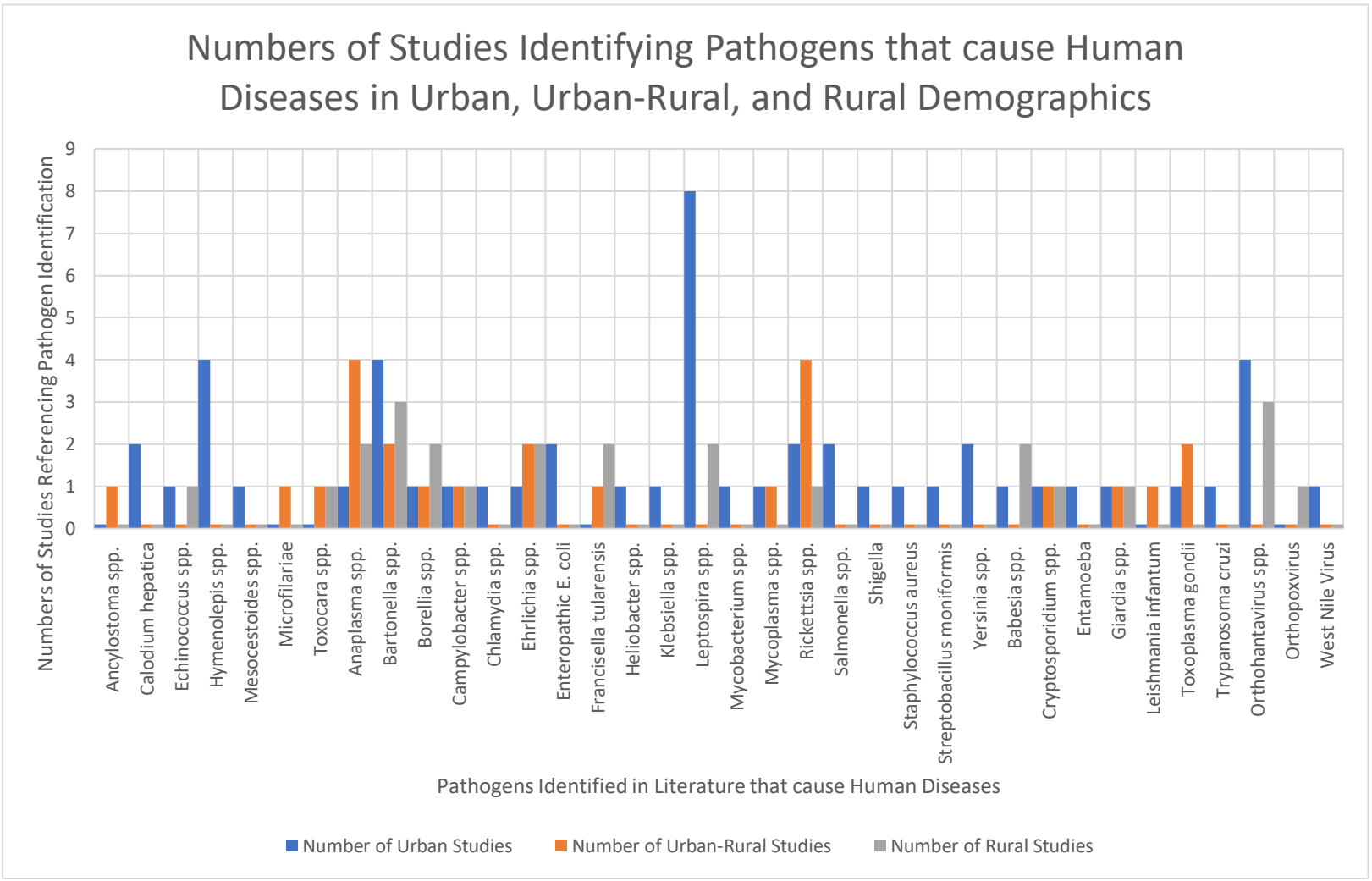


Figure 8: Numbers of Studies Identifying Pathogens that cause Human Diseases in Urban, Urban-Rural, and Rural Demographics



Figures 4-7 demonstrate the relative numbers of studies identifying specific pathogens across urban to rural scale. Figure 8 represents a truncated list of all of the pathogens detected in literature review, and specifically focuses on pathological zoonotic agents. Table 6 refers back to the carrier species of the pathogens depicted.

In Figure 4, the distribution of animal parasites is even between urban (9) and urban-rural (8) studies, with rural studies (2) being the least represented. Two animal parasites in urban environments appear in more than one study, one appearing in two studies and the other

appearing in four. Only one animal parasite in urban-rural environments appears in more than one study, appearing in two studies. Only one animal parasite is observed in studies from different demographics, appearing in both urban-rural and rural studies, once each.

In Figure 5, the distribution of bacterial pathogens is even between urban-rural (9) and rural (9) studies, with urban (19) being by far the most prevalent. Five bacterial pathogens in urban environments appear in more than one study, three appearing in two studies, one appearing in four studies, and one appearing in eight studies. Four bacterial pathogens in urban-rural environments appear in more than one study, two appearing in two studies, and two appearing in four studies. Six bacterial pathogens appear more than once in rural studies, five appearing in two studies and one appearing in 3 studies. Nine bacterial pathogens are observed in studies from different demographics, eight of which feature representations across all three demographics, one of which features urban-rural and urban identification.

In Figure 6, the distribution of protozoan pathogens is even between urban (9) and urban-rural gradient (9) studies, with rural studies (5) being the least represented. All of the protozoan pathogens, with the exception of two, are represented by one study only. The two other pathogens are each represented by two studies, one in rural, and one in urban-rural demographics. Six protozoan pathogens appear in more than one demographic; three were identified in all three demographics, one was identified in urban and rural environments, one was identified in urban-rural gradient and rural environments, and one was identified in urban and urban-rural gradient environments.

In Figure 7, the distribution of viral pathogens is highly expressed in urban (35) studies, with rural (5) and urban-rural gradient (0) being weakly represented. Six pathogens are represented more than once, will all of them being urban studies. Four pathogens were identified

in two studies, one pathogen was identified in three studies, and one pathogen was identified in four studies. Four pathogens were observed in two different demographics, exclusively in urban and rural environments.

Discussion By Pathogen Type

Animal Parasite

In total, animal parasites composed 17 out of the 106 pathogens identified in the study, or roughly 16%. If the 37 murine viruses found only in the house mouse (*Mus musculus*) were removed, then the new percentage of 17 out of 69 is roughly 25% (24.64%). 36 pathogens out of the original 106 pathogens were found to cause severe human disease. Of those 36 pathogens, 7 were animal parasites, or roughly 18% (18.42%). In this study only helminthic animal parasites were observed, 13 belonging to phylum *Nematoda* (roundworms) and class *Cestoda* (tapeworms) in phylum *Platyhelmintha* (flatworms), though the term animal parasite can include ectoparasites such as fleas and ticks as well (Nordqvist, 2018).

Roughly 1 in 4 of the pathogens discovered was an animal pathogen, with the omission of the murine viruses which are entirely asymptomatic in humans and have very minute transmission potentials, whereas they made up roughly 1 in 5 of the relevant human parasites. Animal parasites, arguably more so than bacterial, protozoan, or viral pathogens, exhibit the lowest about of genetic malleability that facilitates a host change (Amarante *et.al.* 1997). Viruses, as problematic components of their pathogenesis, undergo rapid recombination and random reassortment (Pérez-Losada *et al.* 2015). This restructuring of their genomic structure allows for the quick and pervasive shift in light of selection pressures, or in the light of resistance from host immune defences. Likewise bacterial pathogens also undergo recombination through three mechanisms; transformation, transduction, and conjugation, that allow for resistance and penetrance into new host ranges (Didelot, and Maiden, 2010). Even further, protozoans as single-

celled eukaryotes have a much simpler time evolving multiple drug resistances and evading host immune defences that larger animal parasites have (de Koning, 2017). Animal parasites are multicellular eukaryotes who are much more restrained by the costs of their complexity; a reduction in ability to recombine and adapt as fast as simpler organisms. Corresponding to this fact, animal parasites have lower levels of tissue tropism in hosts (Gazzinelli-Guimaraes, and Nutman, 2018), which is highly implicative of the findings of this study. Animal parasites should have a much steeper jump to clear when being facilitated between an animal vector and a human, thus the predominance of animal vectors being higher than what would constitute a human disease fits. Less of the animal parasites discovered across the animal subjects could reasonably make a species jump, in this case 10 of which would be unable to manifest in humans.

Animal pathogens, despite their specificity, do have marked variability categorically amongst their methods of infection. Some work through the accidental consumption of eggs by the host, some have larval stages with abrasive mouthparts to bite and burrow through the skin, and some rely on intermediate vectors to consume them in order to be subsequently consumed by a terminal host (Wakelin, 1996). They may also exhibit several life stages, each with different antigens presenting, thus affording them very strong resistance to immune defence. They are also able to negatively downregulate host immune systems, which make them pervasive and hard to eliminate natively. This feature further explains why evidence of animal parasites in sampled studies were so highly elevated; once infection was established, they are rarely expunged from the body without intervention.

Bacteria

In total, bacteria composed 24 out of 106 pathogens in the study, or roughly 23% (22.6%). If the 37 murine viruses found only in the house mouse (*Mus musculus*) were removed, then the new percentage of 24 out of 69 is roughly 35% (34.78%). 36 pathogens out of the original 106 pathogens were found to cause severe human disease. Of those 36 pathogens, 20 were bacterial pathogens, or roughly 53% (52.63%).

Roughly 1 out of 3 pathogens discovered was a bacterial pathogen, with the omission of the murine viruses which are entirely asymptomatic in humans and have very minute transmission potentials, whereas they made up roughly 1 in 2 of the relevant human parasites. Bacterial pathogens have a high potential for a number of resistances to manufactured drugs and immune responses (Vouga, and Greub, 2016; Wilson *et al.* 2002). Bacterial cells can employ extracellular polysaccharide coats, known as capsules, which serve as a major virulence factor that protect the bacterium from both host immunity and antibiotics. Bacteria prevents phagocytosis from being performed by the antibodies because of antigen shielding. As prokaryotes, bacteria is very capable of randomly mutating and surviving antibiotic attempts, which imparts resistance genes which bacteria can communicate to neighboring bacteria through horizontal gene transfer. Bacteria thrive in situations where they can invade host cells, replicate in safety of immune defences and antibiotics, and propagate, lysing and releasing to adjacent tissues while they continue their virulent spread. Because bacteria capitalize on horizontal gene transfer to give and receive randomly mutated recombinants to thrive in new environments, it

makes sense to assume that bacterial pathogens can have high levels of tissue tropism and widened host ranges. This makes sense in regards to the results of the literature review; out of 24 bacterial, 20 are able to cause proper infections in humans. A significant majority of bacteria that can infest a wide variety of animals, including non-mammalian avian subjects, demonstrates the high plasticity that bacteria can exhibit. Furthermore, because studies tested for extant pathogens in circulation or in target tissues, a high bacterial presence makes sense as they can be ubiquitous in adjacent tissues; sepsis for instance can be distributed widely across the circulatory system.

Protists

In total, protists composed 18 out of the 106 pathogens in the study, or roughly 17% (16.98%). If the 37 murine viruses found only in the house mouse (*Mus musculus*) were removed, then the new percentage of 18 out of 69 is roughly 26% (26.09%). 36 pathogens out of the original 106 pathogens were found to cause severe human disease. Of those 36 pathogens, 7 were protozoan, or roughly 18% (18.42%)

Roughly 1 in 4 of the pathogens discovered was a protozoan pathogen, with the omission of the murine viruses which are entirely asymptomatic in humans and have very minute transmission potentials. They additionally made up roughly 1 in 5 of the relevant human parasites. As protists are capable of a variety of different modifications to combat antibiotics engendered through mutations (de Koning, 2017), they are problematic pathogens to treat. Additionally, the majority of probative work done in clinical settings target viral and bacterial explanations for disease, ultimately resulting in underreporting and under funding for protozoan pathogens. Comparatively, protozoan diseases are generally less deleterious and immediately

deadly as some bacterial and viral diseases. Obvious exceptions to this statement include malaria, for example, but a multitude of protozoan diseases interact with host microbiome and cause diarrhea as a primary symptom (Burgess *et al.* 2017). This may be supportive as to the relatively higher numbers of protozoan diseases found in the literature review. An immediately or rapidly fatal pathogen is less likely to be found in average circulation unless in an outbreak. A disease that causes symptoms, but not absolutely encumbers its host, may have a strategic advantage towards distribution. Additionally, diarrhea facilitates a number of fecal-oral transmission opportunities for the pathogen.

Virus

In total, bacteria composed 46 out of 106 pathogens in the study, or roughly 43% (43.40%). If the 37 murine viruses found only in the house mouse (*Mus musculus*) were removed, then the new percentage of 9 out of 69 is roughly 13% (13.04%). The 37 murine viruses discovered were found in only a single study conducted on house mice sold in pet stores. Review of these pathogens, while capable of being transferred to humans in some cases, did not show any noteworthy human infections, nor infections attributable to any other animal except house mice. 36 pathogens out of the original 106 pathogens were found to cause severe human disease. Of those 36 pathogens, 2 were viral pathogens, or roughly 5% (5.26%)

Roughly 1 out of 8 pathogens discovered was a viral pathogen, and roughly 1 out of 20 pathogens of humans were viral pathogens. The results of the review indicate a low detection of relevant viral pathogens in the literature review, which counters knowledge of real world zoonotic diseases being highly represented by viruses (Venkatesan *et al.* 2010; Woolhouse, and

Gowtage-Sequeira, 2005). Viruses are notable for the tremendous ability to recombine and evolve rapidly to avoid detection and countenance by the innate and humoral immune system of their host. It would be expected that viruses would be highly represented across a literature review surveying zoonotic pathogens across a number of different hosts and demographics. One key difference between viruses, and prokaryotes and eukaryotes that compose the other pathogen types, is that viruses can have RNA genomes rather than DNA genomes. If studies selected for only DNA extraction and comparison, then RNA viruses may have been neglected or missed. Additionally, the studies specifically scanned for extant pathogens, meaning those currently in circulation, and not for antibodies against pathogens that could indicate previous infection. Viruses may have been cleared from the animal system when collections were taken, ignoring the potential of previous infection.

Discussion by Host Type

Rodents

As previously discussed, rodents are historically noteworthy for being causative vectors in a great number of human epidemics (Morand, Jittapalapong, and Kosoy, 2015). It is believed that mice and rats were the causative vectors for the Black Death, also known as the Bubonic Plague or the Black Plague, that lead to the deaths of 75 to 200 million, between 20-60% of Europe's entire population, across Eurasia in the span of about 20 years (Duncan, and Scott, 2005). Rodents were uniquely suited as vectors then as they are today due to two main features: duality of range, and proximity effect. Rodents are a broad order of small mammals that are globally distributed to every continent except Antarctica. Owing to this broad diversity of

landscape, rodents are also very commonly distributed across the urban-rural gradient, finding niches in natural landscapes as well as urban dwellings (Han, Schmidt, Bowden, and Drake, 2015; Meerberg, Singleton, and Kijlstra, 2009). As urban adaptors, rodents have the ability to communicate pathogens that exist from less urban reservoirs to dense metropolitan areas, such as carrying stagnant water parasites into urban apartments. This represents an opportunity for pathogens to be communicated towards areas where they may otherwise be eliminated; for example, municipal city water is treated with chlorination, ozone, or Uv disinfection (Lindsay, 2019). The proximity effect comes into action when rodents act in entering human homes and public spaces, facilitating disease communication in a novel setting.

In this literature review, six groups of rodents were identified; the House Mouse (*Mus musculus*), the Norway Rat (*Rattus norvegicus*), the Eurasian Field Mice (genus *Apodemus*), the Red-Backed Vole (genus *Myodes*), the Meadow Vole (genus *Microtus*), and the Water Vole (genus *Arvicola*). These individuals vary tremendously in demographic; the Water Vole and the Eurasian Field Mouse live in forested areas farther away from human interaction, both of whom live in either Europe or Asia. The Meadow Vole thrives in similarly described environments, but lives in North America. The House Mouse is greatly dispersed throughout North America, Europe, and Asia, with populations that are less commonly rural and wild, and more commonly closely associated with human dwellings and urban centers. Norway Rats are likewise largely dispersed throughout all continents except Antarctica, preferring to almost exclusively live in urban environments. The literature studies support observations about the demographics of all six rodent species; the house mouse and Norway rat were only observed amongst the urban studies, the Eurasian field mice, red-backed vole, and meadow vole were all found in either

urban-rural gradient or rural studies. The presence of a water vole in a single urban study is likely a result of loose definitions of urban.

In total numbers, the Norway rat held the highest number of pathogens with 18 pathogens, 13 of which were associated with human pathogens. Eurasian field mice had 17 pathogens, 9 of which were associated with human disease. House mice had 16 pathogens (53 including the 37 omitted pathogens), 8 of which were associated with human disease. Red-backed voles had 13 pathogens, 5 of which were associated with human disease. Meadow voles had 9 pathogens, 5 of which were associated with human disease. Water voles had 5 pathogens, 2 of which were associated with human disease. This trend demonstrates that by far the Norway rat, Eurasian field mice, and the house mouse demonstratively acted as both much larger pathogen carriers, but also carriers of relevant human zoonoses. As Eurasian field mice were found not just in rural studies, but across urban-rural gradient, it can be implicative that their proximity to human is in somewhere fundamental to their high carrier status. In most studies, Eurasian field mice were observed in tandem with the three genera of voles. With overlapping environments in those studies, the source of explanation for their higher pathogen yield stems from their proximal relationships to urban centers. Additionally in comparing the numbers of relevant pathogens, it is the Norway rat and house mouse that have substantially higher human zoonoses.

Carnivores

Though the term carnivore invokes images of ferocious wild animals like tigers, lions, and wolves, some of the most common carnivores that humans, especially urban humans,

interact with daily are their own pet cats and dogs. Order *Carnivora* are the branching order from which the feliforms, who give rise to our modern domestic cats (*Felis catus*) and bobcats (*Lynx rufus*), and the caniforms, who give rise to our modern domestic dogs (*Canis lupus familiaris*), arise from. These carnivores are important to the facilitation of vector-borne disease because of their predator relationships to many of the smaller animals that act as intermediate vectors. In the wild, a bobcat or any wild cat might predate upon a rodent who is facilitating a pathogen, upon which the pathogen enters a new host. For some pathogens, this relationship is essential to the life cycle of the organism, as is the case with *Toxoplasma gondii*, who requires rodents as intermediate vectors to reach their definite hosts, cats (Calero-Bernal, and Gennari, 2019). For house pets, exposure to pathogens can be just as frequent. Rodents who enter human domiciles can encounter residential pets who may predate them, or otherwise communicate pathogens with them, such as through feces and urine. For carnivore pets that are allowed outdoors, such as through walks with dogs through a park, or house cats that are allowed outside, the risk of pathogen exposure is much more elevated. Outside of homes, cats and dogs can interact with their wild or feral counterparts and, by nature of their familiarity, can be subject to pathogen transmission.

In this literature review three carnivores were identified; the bobcat (*Lynx rufus*), the domestic cat (*Felis catus*), and the domestic dog (*Canis lupus familiaris*). Bobcats are largely distributed across North America where they are described as generally unphased by human populations and existing in “urban edge” environments, which is the periphery of urban developments that still retain canopy coverage and natural prey species (Moriarty, 2018). Domestic cats and domestic dogs are termed domestic as a classification of their habitats versus

anything intraspecific; meaning that domestic animals are exclusively bound to houses and areas of human contact. Feral cats and dogs may be free roaming on a global scale, typically existing on the outskirts of human settlements. The studies in the literature review support these findings as the domestic cats and dogs were exclusively found in urban and suburban, which for the purposes of this review is considered a part of the urban-rural gradient, areas. One study (Kamani, et al. 2013) studied feral dogs who existed exclusively surrounding human areas. Bobcats who live on the periphery of human areas, were likewise found across the urban-rural gradient. Domestic cats and dogs studied were collected through urban and suburban veterinary clinics, thus likewise solidifying the trend of native populations of these carnivores.

In total numbers, domestic and feral dogs had the highest numbers of pathogens with 18 pathogens, 14 of which were relevant to human disease. Bobcats had 12 pathogens, 5 of which were relevant to human disease. Domestic cats had 11 pathogens, 9 of which were relevant to human disease. These trends demonstrate a relationship between familiarity and closeness to humans with human zoonoses carried. Both domestic cats and dogs had higher proportions of observed pathogens being linked to human zoonotic diseases, whereas the more suburban bobcat had considerably less human zoonotic pathogens. Dogs had the highest number of pathogens in total, which could be explained by differences in animal behaviors amongst the three groups. For example, dogs may be allowed to roam around public parks off leash which would bring them into contact with outside pathogens to a higher degree than house cats. Although there were no rural studies of feral cats and dogs, an assumption could be made based off of the results from the bobcat in that there may be higher levels of pathogens detected, but less of them would be human zoonotic.

Birds

Birds are substantial vectors for human relevant pathogens, as histories of West Nile virus, Lyme disease, Influenza A, and many enterpathogens such as *Salmonella* spp. attest to (Reed *et al.* 2003). Birds have features of habitat change over a year that allow for long-range disease communication in methods terrestrial vectors such as rodents could not accomplish. Birds may additionally act as literal carriers of tick diseases by carrying affected ticks nestled in their plumage as they take flight. Bird behavior can range dramatically based on residence (Miranda, 2014; Dabelsteen, and Pedersen, 1990; Jozkowicz, and Gorska-Klek, 1996). Birds in urban centers are noteworthy in their tolerance of human interaction to the point of near complete non-avoidance. Pigeons (*Columba livia*) in cities are characteristically unafraid and will scavenge human garbages, sit near places where humans eat like restaurants and cafes, and will nest in areas with some foot traffic. These situations provide ample opportunity for pathogens to be exchanged with humans, but another mechanism is also considered; fecal. Birds defecate indiscriminately on surfaces, or occasionally in flight, which is another way that humans and other animals, including those who can act as vectors, can be exposed to pathogens.

In this literature review the wood pigeon (*Columba livia*) and a collection of 32 different species of bird were surveyed. The ranges of these birds are vast and malleable based on changes in land development, though pigeons are noteworthy for their tolerances across the entirety of urban-rural gradients, even setting roost in the hearts of cities. The literature review reflects this fact as both the pigeon and the numerous birds were found in urban environments. This could suggest that birds have a preferential relationship to cities as they must provide novel food

resources and protection against larger predators, but there are too few studies investigated in this review to verify that suggestion.

In total numbers pigeons were found to host 4 pathogens, all 4 of which were relevant to human disease. The numerous birds were found to host 3 pathogens, 2 of which were relevant to human disease. Though the numbers of pathogens detected are not nearly as high as the other host types, the pathogens found in the pigeons and birds were largely relevant to human disease. As these birds were studied in chiefly urban or urban-rural gradient environments, a relationship between pathogens and their proximity to humans can be made, although there are too few studies to verify the relationship observed.

Discussion by Demographic

Urban

18 urban studies were reviewed in this literature review, spanning four of the five continents represented. 6 urban studies were conducted in North America, 3 of them in New York City, NY, 1 in California, 1 in Baltimore, MD, and 1 in Chicago, IL. 2 urban studies were conducted in South America, 1 in Columbia, and 1 in Brazil. 4 urban studies were conducted in Europe, 1 in Hamburg, Germany, 1 in Pecs, Hungary, 1 in Geneva, Switzerland, and 1 in Liverpool, United Kingdom. 4 urban studies were conducted in Asia, all 4 of which were conducted in Japan. The distribution of coverage along a continent is generally a little disparate and ignores certain portions of the landscape, though in the case of North America and Europe, a

fair amount of coverage across different landscapes is explored: for example, weather patterns in California are different than those in New York.

58 pathogens out of 106 were discovered to be unique to urban environments, meaning that only representation of these pathogens occurred in urban settings, roughly 55% (54.72%). If pathogens are considered when the murine viruses are eliminated, then the percentage of pathogens that are unique to urban environments is 21 out of 69, or roughly 30% (30.43%). If urban-rural gradient is equated with the urban studies, due to the facilitative nature between the two demographics, then 60 out of 106 pathogens are unique to non-rural (urban and urban-rural gradient) environments, roughly 57% (56.60%). If pathogens are considered when the murine viruses are eliminated, then the percentage of pathogens that are exclusively non-rural is 23 out of 69, is roughly 44% (43.50%). These percentage values do not account for the ~46% of pathogens that were observed across urban, urban-rural, and rural environments in different combinations, though they do suggest a relationship that urban environments denote more pathogenic availability. This relationship is suggested by Figures 4, 5, and 7.

Animal parasite pathogens, demonstrated by Figure 4, are highly demonstrated in urban environments within two criteria. One being that in sheer numbers of all 17 animal parasites, 9 of them were found in urban studies, all of which were also exclusive to this environment. Compared to the 8 pathogens found across an urban-rural gradient, and the 2 pathogens found in rural studies, this is highly implicative of a connection with these parasites to urban environments. The other criteria being the confirmation across multiple studies being suggestive of two pathogens being more prevalent in urban areas. *Hymenolepis* spp. and *Calodium hepatica*

are two zoonotic parasites that are associated with illness, as depicted in Table 11. *Hymenolepis* spp. is found across four different studies (Panti-May *et al*. 2017; Hayashimoto, et.al., 2015; Easterbrook, *et al.* 2007; McGarry, Higgins, White, Pounder, and Hetzel, 2014) across urban environments in Mexico, Japan, the United States of America, and the United Kingdom. Likewise *C.hepatica* is found across two different studies (Easterbrook, et.al., 2007; McGarry, Higgins, White, Pounder, and Hetzel, 2014) across urban environments in the United States of America and the United Kingdom. In all four studies that identified these two pathogens, the Norway rat (*Rattus norvegicus*) and the house mouse (*Mus musculus*) were the only surveyed carriers. The fact that these urban areas are diverse geographically, and the fact that these animals are highly associated with exclusively urban adaptive and urban exploitative lifestyles fits with the knowledge of animal parasite transmission.

Animal parasites are transmitted through a number of different mechanisms, though many capitalize on patterns of accidental ingestion or through fecal-oral communication (Wakelin, 1996). More so than rural and gradient areas, urban rodents have heightened exposure to municipal waste facilities where exposure to human waste introduces an opportunity for reverse zoonosis (Byers *et al.* 2019). Rodents have also been previously described for their zoonotic potential in urban environments by entering human spaces and communicating pathogen through proximal contact; rats and mice travel through infrastructural centers such as subways, and through private residences such as homes and apartments. Primarily fecal-oral and consumption pathways lead to new animal parasite infestation, which can be explained by rodent vectors or insect vectors such as ticks that rodents may expose humans to. Other routes of infestation include bites from larval parasites, or from consumption of undercooked meat, which

are ubiquitous risk factors across demographics, but are linked to differential rates in socioeconomic status (Koro, Anandan, and Quinlan, 2010).

Bacterial pathogens, demonstrated by Figure 5, are also highly demonstrated in urban environments in the same two criteria. One being that in sheer numbers of all 24 bacterial pathogens, 19 were found in urban environments, 7 of which were unique to urban areas. This is compared to 9 pathogens found in rural environments, only 1 of which was unique to rural areas, and to 9 pathogens found in urban-rural gradient, only 1 of which was unique to these areas. This wider range of pathogens is suggestive of an urban connection to bacterial diversity and the results detected in carrier species across the literature review. The other criteria considers the numbers of studies that confirm specific bacterial pathogens identified in a demographic. 5 bacterial pathogens in urban environments were confirmed by 2 or more studies, Enteropathic *E.coli* (Firth, *et.al.* 2014; Tanaka, Miyazawa, Watarai, and Ishiguro, 2005), *Rickettsia* spp. (Case, Chomel, Nicholson, and Foley, 2006; Easterbrook, *et.al.* 2007), and *Salmonella* spp. (Firth, *et.al.* 2014; Hamer, Lehrer, and Magle, 2012) were all confirmed in two or more urban studies, *Bartonella* spp. confirmed in four urban studies (Firth, *et.al.* 2014; Case, Chomel, Nicholson, and Foley, 2006; Easterbrook, *et.al.* 2007; Costa, *et.al.* 2014), and *Leptospira* spp. was confirmed in eight urban studies (Firth, *et.al.* 2014; Panti-May, *et.al.* 2017; Easterbrook, *et.al.* 2007; Costa, *et.al.* 2014; Koizumi, *et.al.* 2009; Agudelo-Flórez, *et.al.* 2009; Schmidt, *et.al.* 2014; Heuser, *et.al.* 2016). All five bacterial pathogens were found across multiple animal species within urban environments, including rodents, and domestic dogs and cats. Of the 19 bacterial pathogens found in urban environments, 18 of them were associated with human zoonotic disease, as depicted in Figure 8. All five bacterial pathogens with multiple identifications across studies

were significant human pathogens. By large, the numbers of bacterial pathogens detected in total suggest that they are highly capable at extending their host range, a feature which is described in literature (Wilson *et al.* 2002). Although not as disparate as the discrepancies between animal parasites in urban and other environments, urban bacterial pathogen representation is visibly more prevalent than other demographics. Of the 9 rural bacterial pathogens, only 8 are relevant to human diseases, and of the 9 urban-rural gradient bacterial pathogens, only 8 are relevant to human diseases. With both a higher range of pathogens and the higher number of relevant pathogens, it appears that urban environments have a higher volume of circulating bacterial pathogens.

A fundamental difference in how bacteria are transmitted can explain why both the prevalence is so high, as well as inform why urban centers are at an elevated risk. Bacterium can adopt free-living lifestyles where they are not beholden to an obligate host while living in circulating conditions, such as water systems, in sewage plants, or they can freely subside on non-biotic surfaces, upon which they can be introduced to human hosts (Huang *et al.* 2018). Bacteria are capable of rapid involvement with dynamic changes in host range that allow for the fluid communication across multiple vectors (Bäumler and Fang, 2013). Furthermore, once penetrance into a host has occurred, diverse strains of a bacterial pathogen evolve in response to human behavior, the most concerning of which is the evolution of antibiotic resistance. Bacteria can be spread between hosts through a number of biotic means as well, aerosolically such as through coughing or sneezing, through touch, through exchange of body fluids such as saliva, blood, and semen, and through fecal-oral transmission. Urban environments are at elevated risk for higher instances of interpersonal contact, facilitating higher bacterial saturation amongst densely packed civilizations versus those with more spread communities.

Viral pathogens, demonstrated by Figure 7, are almost exclusively represented by urban studies. As previously mentioned, 37 murine viruses were considered in Figure 7, but calculations excluding these pathogens were conducted and discussed separately. Without these pathogens only nine viral pathogens were retained for interest. Of those nine pathogens, three pathogens were relevant to human zoonotic pathogens, *Orthohantavirus* spp., *Orthopoxyvurus*, and *West Nile Virus*. Of those three pathogens, only one is highly prevalent in urban studies, *Orthohantavirus* spp., which was identified in four urban studies. The other two pathogens either had equal representation of rural and urban studies, or were exclusively reserved to rural studies. This may suggest that viruses are not as prevalent and ubiquitous to urban environments as other pathogens may have been, but an alternate explanation can be made. As previously discussed, viruses have the highest potential for rapid evolution outside of their host range to adopt and form into new epidemic host switches (Woolhouse, and Gowtage-Sequeira, 2005). With new speciation, testing for zoonotic may not be entirely indicative measure of assessing an urban or rural biosphere. If viruses make significant species jumps, as demonstrated in Table 1 showing a plurality of viral agents making successful diversification leaps, then they would speciate into new viral strains. For example, *human immunodeficiency virus (HIV)* evolved from *simian immunodeficiency virus (SIV)* in antiquity, to the point that the virus has diversified and been unable to maintain a widened host range (Sharp, and Hahn, 2010). Many of the murine viruses which have been removed from discussion, were in fact speciations of viruses that have either human or other mammal analogues (Williams, et.al., 2018). This context may also best explain why comparatively across the board, regardless of demographic, viruses were the second least

represented pathogen in terms of multiplicity of confirmatory studies, and by overall numbers once the 37 murine viruses were removed from consideration.

Rural

5 rural studies were reviewed in this literature study, spanning three of the five continents represented. Three rural studies were conducted in North America, two of them being in Canada (Himsworth *et.al.* 2010; Leighton *et.al.* 2001), and one of them being in rural Hawaii, HI, in the United States of America (Kabrane-Lazizi *et.al.*1999). Two rural studies were conducted in Europe, one being in Croatia (Tadin *et.al*. 2016), and the other being in Austria (Schmidt *et.al.* 2014). The distribution of rural studies were limited both in terms of continental coverage; both Africa and South America were not represented with rural studies, and in terms of intracontinental coverage; for instance there were no rural studies in the mainland of the United States of America.

Rural environments showed the lowest numbers of all four pathogens than either urban or urban-rural gradient studies. In context for animal parasites, only two of the 17 animal parasites found across all studies were uncovered in rural environments; both of which were a considerable zoonotic pathogen in humans. In context for bacterial pathogens, only 9 of the 24 bacterial pathogens was found in rural environments, eight of which were considerable zoonotic pathogens in humans. In context for viral pathogens, 5 of the 9 viruses when omitting the murine viruses were found in rural environments. In 2 of these cases, equal representation of the virus within rural and urban studies were found, and with another 2, the urban environment drastically identified these viruses with more concurrence. Although the lowest in numbers of distinct

protist parasites identified, it did identify three of the five relevant human zoonotic pathogens.

An explanation about geographical distribution and human avoidance provides insight as to the lower volumes of human zoonotic diseases detected in rural animals. Urbanization has provided observable changes in animal behaviors, notably with human tolerance and a decrease in predator avoidance range (Riley *et al.* 2003; Engelhardt, and Weladji, 2011). Comparatively, rural prey animals have lower thresholds to which they will allow for proximity with larger animals such as humans before they try to run away. This behavior would decrease the exposure of small animal vectors like rodents, and larger animal vectors like bobcats, in rural environments versus urban ones. Since a significant postulate of zoonotic disease is based on host-vector interaction, the results observed here may be indicative of that exact concept; with animals and humans occupying less shared space, they may exhibit less pathogen transference. Additionally, the presence of larger animals such as coyotes (*Canis latrans)*, wolves (*Canis lupus*), and bobcats (*Lynx rufus*) would act as a form of selection against vector animals that may be encumbered by their pathogen carrier status. For example, a wild mouse infested with a helminthic parasite may be subject to intestinal symptoms of dehydration, nutrient malabsorption, as well as lethargy and malaise. Such an encumbered mouse would be weakened and prone to predation by predator animals higher on the trophic scale (Sohn *et al.* 2014). Urban and urban-rural gradient animals are relatively protected from this level of predation, and often avoid predators by interacting with human domiciles.

Urban-Rural Gradient

Around 8 urban-rural gradient studies were reviewed in this literature study, spanning all five continents surveyed. Ambiguity in the constitution of an urban-rural gradient is a direct result of the non-specific nature of what constitutes variations across the urban-rural gradient. Literature has introduced an approach to describing a gradient based on the range of anthropogenic features confined in an area, such as roads and bridges, housing, municipal water, sewage, sanitation facilities, amongst many other criteria (Dahly, Adair, 2008; Hahs, and McDonnell, 2006; Suarez-Rubio, and Krenn, 2018). In this literature review 8 studies were defined as urban-rural gradient through the language represented in their respective texts, but up to 11 may be considered to have elements of an urban-rural gradient. If a study sampled both urban centers and a rural center, it may have a complicated identity for the discriminatory nature of categorization in this literature review. Furthermore, the term "suburban" is a ubiquitously used word for architects, city planners, economists, and a variety of other jobs, but has no applicable scientific definition (Forsyth, 2012). A number of studies depicted utilized this term, but made little clarification as to the degree of urbanization the area experienced. As a result, the information implied by trends in pathogen coverage is complicated, but assumptions can be made relative to urban and rural findings.

A single study of bobcats (Carver *et.al.* 2012) in an urban-rural gradient area demonstrated a great number of animal pathogens, 8 out of the 17 animal pathogens observed in this review. 7 of these pathogens were not only unique to an urban-rural gradient, but were unique to this study. As only 2 of the 8 pathogens detected were relevant to human zoonotic diseases, it could imply that the environment sampled was constructively more rural than urban.

Trends in rural diseases demonstrate that there are lower corroborating studies for particular pathogens, lower numbers of pathogen representation versus urban in total, and the pathogens discovered are generally less relevant to human zoonoses than urban pathogens. This is a similar trend discovered in animal pathogens, as well as in viral, bacterial, and protozoan pathogens. Even with the inclusion of the murine viruses, no single viral pathogen was identified within the urban-rural gradient studies. Of the bacterial pathogens, 9 out of 24 bacterial pathogens identified in urban-rural gradient studies were relevant to human zoonotic disease, the same numbers of relevant bacterial pathogens identified in rural studies. Although the overall numbers of protozoan pathogens in urban-rural studies, 9 out of 16 protozoan pathogens observed in total is directly equal to that found in urban studies, only 4 of the urban-rural gradient protozoan pathogens were relevant to human zoonotic diseases. This is in contrast to urban protozoan pathogens, of which 6 were relevant.

Ultimately these results lead to one of two conclusions. The first conclusion postulates a critique about the parameters of urban-rural gradients that have been implemented in these observed studies. The second conclusion accepts the studies at face value and examines a dichotomy between urban environments and any other environment.

Firstly, a concern about the differentiation across a gradient is an overt problem judging by how faithfully the urban-rural gradient studies adhere to the trends and numbers that the rural studies do. Studies that may have considered an area to be along the gradient may have likely overestimated the distance away from a major metropolitan area that they could observe before losing the impact of urbanization of proximate populations. It may be likely, for example, that extending just 12 miles away from the center of a city can be a drastically ecological

environment than one may consider. As studies can be unspecific with the language that constitutes a gradient, like using the term “suburban,” it could be reasonable to question the definition of an urban environment as well. A personal definition of an urban center might suggest only a highly industrialized urban areas, such as Beijing, Tokyo, or Paris, but an urban center can be defined by only the most bare components of an urbanized area (Dahly, Adair, 2008). Furthermore, an urban center can be a broad, expansive settlement with multiple demographics contained under the structure of a city; for example, New York City is arguably one of the largest metropolises. In New York City, an areas such as Times Square in Manhattan may be a quintessentially urban location, yet areas in the adjacent island of Staten Island may have pockets of less urbanized areas, such as those with woodlands, ponds, and unpaved roads. If a forest in Staten Island is considered in the same demographic along a gradient as a sewer under Times Square, then overt differences in the results might lead to an erroneous assumption about the entire New York City demographic.

Secondly, we may suppose there is a distinct difference between urban environments and every other environment. Of the urban animals surveyed, both the Norway rat and house mouse came across the plurality, if not majority of studies. Both species are understood to be urban exploiters, animals who over time have become obligate to urban environments rather than species who are urban adaptors, those who travel more freely between urban and peri-urban domains. Studies focusing on pathogen detection only in these subjects could not reveal if these pathogens exist in similar subjects in different environments, due to their obligation to urban areas. If more subjects were studied that could occupy an urban-rural gradient, then populations that are more urban versus more rural could be more directly compared to confirm any differences in pathogen reservoir status that is attributed more solely to their environment. If

there are defined distinctions in the pathogen counts/relevant human pathogen count that even slight deviation outside of a firmly urban center, then attributions could be made to the element of host-vector interaction. As previously described, urban centers bring humans and some animal vectors into proximity more so than anywhere else on the gradient. Rodents, for example, are in much more constant levels of engagement with humans within the urban structure (Cavia, Rubén Cueto, and Súarez, 2009). Other elements of urbanization, such as municipal sewers, garbage treatment facilities, and access to open area food, contribute to the ability of urban animal vectors to receive and communicate pathogens to humans. A limitation to this idea rests on that because many animals do not occupy a gradient, it is difficult to parse apart what can truly be related to environment alone.

Limitations

A number of limitations to the applicability and the scope of this literature review hinder the usage in making definite points about pathogens along an urban-rural gradient. Primarily the number of studies is a significant limitation. 31 studies in total is a brief literature review and could not be definitive of all potential avenues of further research that could be included for a more exhaustive review. 18 urban studies is likewise a very small number to glean information from, let alone the 8 representative urban-rural gradient and 5 representative rural studies. A limitation is especially pronounced in these areas as trends can be made apparent in such a small subject pool. The primary reasoning as to why so few studies were considered was based on the search criteria applied; searching for terminology such as “survey,” “urbanization,” “zoonotic/zoonoses,” “vector,” “urban(-rural) gradient,” and “pathogen(s),” there was a clear

limitation on studies that considered all of these factors together. Many studies discussed urbanization in relation to a variety of non-applicable fields, some studies discussed the urban-rural gradient in nonpathogenic contexts. To find integrative studies that combined all of these terms for usage in a literature review was challenging and suggested a lack of coverage in this relatively new area of academic investigation. With the earliest relevant study being published in 1999, and other studies of broad pathogen survey across demography not being published until the 2000's and 2010's, it is reasonable to infer that much more research in this field is not only relevant but is truly necessary to understand the interactions of pathogen exposure risk to specific subsets of the human population.

An additional area of complication was the conflict between specificity and survey. Ideally the most relevant study would have a large range of populations along an equally pronounced range in an urban-rural gradient. Wholesale pathogen screening across all four of the major pathogenic categories would allow for a much more detailed discussions of trends, and analysis of pathogen content. However, this survey approach is arguably unrealistic due to the difficulties of surveying a multitude of potential pathogens with particular genomic sequences being obligate to detect genomic evidence of bacterial or viral pathogens, advanced microscopy to detect anatomic structures of helminthic pathogens, or using specific tests for known pathogens such as western blot or enzyme-linked immunosorbent assay (ELISA). Furthermore, scientific research is most often conducted with a particular goal in mind, such as searching for prevalence of certain known human pathogens at the exclusion of potential others, to corroborate the goals of the experiment. This literature review is significantly limited by the conflict between conducting a broad survey of all circulating pathogens in a number of different hosts across a number of different environments, to searching for specific pathogens, in specific hosts, in a

specific area. The results of the studies surveyed in this literature review met somewhere in the middle of these conflicting aims.

One last limitation of this review is centered around the severe urban bias that surrounds studies in epidemiology, in ecology, and in disease. More studies observed in this literature review were centered around known urban areas versus rural areas, especially in those that conducted whole pathogen screening surveys. Furthermore, those surveys were conducted in a narrow range of urban reservoir animals, but were closer to surveys in a truer sense. This may be owing to the complexities involved with conducting unbiased pathogen survey, and the expenses and time that follow. Many, if not most, major scientific research centers are situated in urban cites across the world. In 2017, of the top ten contributors to over 82 leading scientific journals in the world, nine were hosted in major metropolitan cities including Beijing, Tokyo, Boston, Paris, and Munich (Conroy, 2018). With the bulk majority of funding and academic interest, it is a significant consideration to make that the urban environment would be of utmost relevance for a lot of scientific investigation.

Conclusion and Further Research

This literature review was helpful in confirming many beliefs about the impact of urbanization and the density of pathogen saturation that follows urban lifestyles. Though limitations ultimately obstruct the data from making clear and definitive statements, they are suggestive and confirmatory about the belief that urban centers by nature have higher pathogen expressions and more relevant zoonotic diseases in circulation. It can be stated that based on the information presented in this study that urban environments were found to host more net

pathogens, more prevalence of pathogens across different geographical cities, and to harbor more pathogens that are of immediate zoonotic pathogen concern for human disease.

To expand on this conclusion further, a more in-depth integrative study that tracks at least one urban-adaptive species across the entire urban-rural gradient should be performed. By assessing the pathogen presentation across the gradient, trends can be observed that are based on the environmental conditions and human interactions alone, a very investigatively useful connection to make that this literature review was ultimately unable to definitively reach. In addition, to really make contrasts with human involvement, some host animals that enter human domiciles should be compared with other populations of their species which does not. For instance, domestic dogs from cities and suburbs could be compared with feral dogs to observe pathogen carrier status.

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