The Novel H7N9 Influenza A Virus: Its Present Impact and Indeterminate Future

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Rats, Cities, People, and Pathogens: A Systematic Review and Narrative Synthesis of Literature Regarding the Ecology of Rat-Associated Zoonoses in Urban Centers

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Abstract

Urban Norway and black rats (*Rattus norvegicus* and *Rattus rattus*) are the source of a number of pathogens responsible for significant human morbidity and mortality in cities around the world. These pathogens include zoonotic bacteria (*Leptospira interrogans*, *Yersina pestis*, *Rickettsia typhi*, *Bartonella* spp., *Streptobacillus moniliformis*), viruses (Seoul hantavirus), and parasites (*Angiostrongylus cantonensis*). A more complete understanding of the ecology of these pathogens in people and rats is critical for determining the public health risks associated with urban rats and for developing strategies to monitor and mitigate those risks. Although the ecology of rat-associated zoonoses is complex, due to the multiple ways in which rats, people, pathogens, vectors, and the environment may interact, common determinants of human disease can still be identified. This review summarizes the ecology of zoonoses associated with urban rats with a view to identifying similarities, critical differences, and avenues for further study.

Key Words: Black rat—Ecology—Norway rat—*Rattus norvegicus*—*Rattus rattus*—Urban—Zoonotic disease.

Introduction

Rats (*Rattus* spp.) are a source of a number of zoonotic pathogens responsible for significant human morbidity and mortality. The urban environment is particularly problematic with regard to rat-associated health risks because cities provide an optimal habitat for rats, leading to close contact between rats and people and, potentially, zoonotic disease transmission. Given the unprecedented rates of global urbanization (United Nations 2012), it is important to develop a thorough and modern understanding of rat-associated zoonoses (RAZ) in urban centers. This understanding is essential for: (1) Accurately gauging the presence, magnitude, and nature of rat-associated health threats in cities around the world; (2) monitoring and mitigating the risk of rat-associated zoonotic disease emergence now and in the future; (3) increasing awareness among health-care professionals regarding the presence of and risk-factors associated with RAZ to reduce under diagnosis and misdiagnosis of these diseases; and (4) developing informed and effective rat control strategies, and other public health measures, to reduce and prevent rat-to-human disease transmission.

The objective of this review is to summarize, evaluate, compare, and contrast the peer-reviewed and published literature regarding the ecology of RAZ in Norway rats (*Rattus norvegicus*), black rats (*Rattus rattus*), and people living in urban centers, with a view to synthesizing what is already known, and identifying knowledge gaps to address in the future.

Methods

Databases used included: Medline, Embase, Web of Science, BIOSIS Previews, and Zoological Record Plus. Text word searches (including "wildcards" to capture term variations, *e.g.*, zoono*) were conducted using keywords pertaining to rats (rat, rats, Rattus rattus, Rattus norvegicus, Norway rat*, brown rat*, black rat*, roof rat*), rat-associated zoonoses (zoono*, zoonotic disease, leptospir*, Weil's disease, hanta*, hantavirus, Seoul hantavirus, Seoul virus, hemorrhagic fever with renal syndrome, plague, Yersin*, Rickettsia, typhus, murine typhus, Streptobacillus monilliformis, rat bite fever, Haverhill fever, Bartonell*, Salmonell*, Campylobacter*, E. coli, hepatitis E virus), and the urban environment (urban,

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city, cities, metropol*). Groups of key words were combined using Boolean operators. Medline and Embase were also searched using Medical Subject Headings (rats, zoonoses, urban health, urban populations, and cities). Papers in languages other than English were excluded. The literature search was conducted between December, 2011, and February, 2012, and identified a total of 704 papers for initial consideration.

To ensure that the review was focused on the most up-to-date research, all papers published prior to 1990 were excluded ($n = 209$). Remaining papers ($n = 495$) were organized according to the amount of information they contributed regarding the ecology of zoonotic pathogens associated with Norway and black rats. Papers with significant ecologic content (*e.g.*, reviews, observational studies, modeling studies, large case series, etc.) were retained ($n = 213$) and all other papers (*e.g.*, case studies, studies with low sample size, studies focused exclusively on pathogenesis, pathogen genetics, treatment methodology, etc.) were excluded ($n = 282$). For this step, papers were screened by 2 reviewers (C.G. Himsworth and K.L. Parsons), and decisions (inclusion vs. exclusion) were arrived at by consensus. Finally, papers not focused on Norway and black rats in urban centers (*e.g.*, studies with a primarily rural focus, studies focused on other rodent species, etc.) were excluded ($n = 71$). Additional sources ($n = 19$) were added through citation searching and to fill specific information gaps. A total of 161 papers were reviewed in detail.

Data from these papers were extracted and synthesized based on the methodology for narrative synthesis described by Arai et al. (2007). The goal of narrative synthesis is to identify themes common across research regarding a particular subject that then can be used to identify commonalities and critical differences among included papers.

Results and Discussion

Overview of rat-associated zoonoses

Bacterial zoonoses. *Leptospira interrogans*, a Gram-negative spirochete bacterium, is considered to be the most widespread zoonotic pathogen in the world (Evangelista and Coburn 2010) (Table 1). Different strains (serovars) are adapted to different mammalian hosts (Bharti et al. 2003, Guerra 2009, Ko et al 2009), and although almost any animal can be a *Leptospira* spp. carrier, rats are the most common source of human infection, particularly in urban environments (Ko et al. 1999, Guerra 2009, Ko et al. 2009, Evangelista and Coburn 2010). The serovars most commonly associated with rats are Icterohemorrhagiae and Copenhageni (Ko et al. 2009).

In the animal reservoir, *Leptospira* spp. colonize the kidneys and are shed in the urine (Guerra 2009, Ko et al. 2009). People may become infected through direct contact with rat urine or indirectly through contact with contaminated soil or water (Bharti et al. 2003, Guerra 2009, Meerburg et al. 2009, Evangelista and Coburn. 2010). Leptospirosis (*i.e.*, infection with *Leptospira* spp.) most commonly causes an undifferentiated febrile illness (Bharti et al. 2003), but may progress to Weil's disease, a syndrome characterized by jaundice, hemorrhage, and renal failure (Bharti et al. 2003, Ko et al. 2009, Meerburg et al. 2009) with a mortality rate of 5–15% (Ko et al. 1999, Yanagihara et al. 2007, Meerburg et al. 2009). *Leptospira* spp. are also associated with a pulmonary hemorrhage syndrome (Bharti et al. 2003, Ko et al. 2009) that has a mortality rate of up to 50% (Ko et al. 2009). Some studies have suggested that rat-associated serovars may be more pathogenic to humans compared with serovars from other animal hosts (Bishara et al. 2002), whereas others have found this not be the case (Perrocheau and Perolat 1997).

Although *Leptospira* spp. are ubiquitous in rat populations (Bharti et al. 2003, Guerra 2009, Ko et al. 2009, Meerburg et al. 2009), human disease is most common in the tropics (Bharti et al. 2003), particularly in Southeast Asia, Oceania, the Indian subcontinent, the Caribbean, and Latin America (Evangelista and Coburn 2010).

Yersinia pestis, a Gram-negative bacillus (Perry and Fetherston 1997, Zietz and Dunkelberg 2004), is the etiologic agent of the plague. Norway and black rats are the most common source of the pathogen in cities (Chanteau et al. 1998), and the bacterium is spread between rats, and from rats to people, via fleas (Perry and Fetherston 1997). *Xenopsylla cheopis* (the oriental rat flea) is the classic vector in urban centers (Perry and Fetherston 1997, Chanteau et al. 1998, Meerburg et al. 2009, Monecke et al. 2009), although several flea species, particularly those in the genus *Xenopsylla*, can be competent vectors (Perry and Fetherston 1997, Zimba et al. 2011). While feeding on an infected rat, fleas ingest the bacteria, which subsequently proliferate and form a blockage in the digestive tract (Perry and Fetherston 1997, Monecke et al. 2009). This blockage prevents blood meals from entering the stomach, resulting in starvation, which causes fleas to bite repeatedly and regurgitate bacteria into subsequent hosts (Perry and Fetherston 1997, Monecke et al. 2009).

When an infected flea bites a human, the bacteria spread to local lymph nodes and replicate, causing them to swell and create the characteristic bubo (Perry and Fetherston 1997, Zietz and Dunkelberg 2004), from which bubonic plague gets its name. This is followed by systemic spread of the bacteria, with replication in the internal organs (Perry and Fetherston 1997). Clinically, bubonic plague is characterized by headache, chills, fever, and malaise, which may progress to sepsis and death (Zietz and Dunkelberg 2004). Mortality rates may reach 20% in developing countries where access to health care is minimal (Chanteau et al. 2000). Although the bubonic form of plague is most common, the pneumonic form (associated with person-to-person aerosol transmission) may occur during the height of an outbreak (Chanteau et al. 2000, Keeling and Gilligan 2000a).

Although rats are an important reservoir for human infection (Boisier et al. 1997, Perry and Fetherston 1997, Chanteau et al. 1998, Rahelinirina et al. 2010), plague is lethal to rats themselves; therefore, they are not thought to maintain *Y. pestis* in nature (Perry and Fetherston 1997). Some researchers have suggested that more resistant rodent species (*e.g.*, mice and voles) are required to form enzootic foci, and that it is the transmission of plague from these enzootic hosts to susceptible rat populations that results in explosive outbreaks and human infection (Perry and Fetherston 1997). Persistence of plague in a particular location depends upon the presence of suitable maintenance hosts, as well as a climate conducive to flea activity and bacterial replication (Perry and Fetherston 1997), which may be the reason why the distribution of plague is limited compared to other RAZ. The most significant foci of enzootic plague are located in Africa, Southeast Asia, and South America (Perry and Fetherston 1997). These countries

Table 1. Summary of the Main Zoonotic Pathogens Associated with Norway and Black Rats (*Rattus norvegicus* and *Rattus rattus*) in Urban Centers

Zoonotic organism	*Associated disease in rats*	*Associated disease in people*	*Method of transmission between rats*	*Method of transmission from rats to people*	*Distribution*
Leptospira interrogans	None	Febrile illness, Weil's disease (jaundice and renal failure), pulmonary hemorrhage	Direct or indirect contact with urine	Direct or indirect contact with rat urine	Worldwide
Yersinia pestis	Septicemia (often fatal)	Bubonic plague (febrile illness, lymphadenitis, sepsis)	Fleas	Fleas	Primarily Asia, Africa, and South America
Rickettsia typhi	None	Febrile illness, rash	Fleas	Fleas	Worldwide
Bartonella spp.	None	Febrile illness, endocarditis, neuroretinitis	Fleas	Fleas	Worldwide
Streptobacillus moniliformis	None	Haverhill fever and rat bite fever (febrile illness, rash, polyarthritis, pharyngitis, sepsis)	Close contact	Direct contact with rats or ingestion of food contaminated by rats	Worldwide
Seoul hantavirus	None	Febrile illness, hemorrhagic fever with renal syndrome (hemorrhage, shock, renal failure)	Contact with urine, feces, or saliva, intraspecific aggression	Direct or indirect contact with rat urine, feces, or saliva	Worldwide (human disease primarily in Asia)
Angiostrongylus cantonensis	Granulomatous pneumonia	Febrile illness, eosinophilic meningitis, ocular angiostrongyliasis	Indirect; consumption of mollusk intermediate host.	Indirect; consumption of intermediate host, contaminated vegetation, or paratenic host	Primarily South East Asia, South Pacific, Australia, and the Caribbean; occasionally found elsewhere

also have the highest incidence of human infection (Perry and Fetherston 1997).

Rickettsia typhi is a Gram-negative obligate intracellular bacterium of white blood cells (Civen and Ngo 2008). It is believed to be present in rat populations worldwide (Azad et al. 1997, Civen and Ngo 2008) and is transmitted among rats, and from rats to people, by fleas, particularly *X. cheopis* (Civen and Ngo 2008, Meerburg et al. 2009). After the flea feeds on an infected rat, *R. typhi* multiplies in the flea's intestinal tract and is shed in the feces (Civen and Ngo 2008). Infection occurs when flea feces are inoculated into the skin through the fleabite or via scratching (Civen and Ngo 2008). Unlike *Y. pestis*, *R. typhi* does not adversely affect the flea and may even be transmitted vertically from the infected flea to its offspring (Azad et al. 1997).

R. typhi causes murine typhus in people, which is generally a self-limiting disease (Azad et al. 1997, Civen and Ngo 2008) characterized by fever, headache, lethargy, myalgia, arthralgia, nausea, vomiting, and a characteristic skin rash (Gray et al. 2007, Civen and Ngo 2008). Mortality is approximately 1% and 4%, with and without appropriate antimicrobial therapy, respectively (Azad et al. 1997, Civen and Ngo 2008).

Bartonella spp. are a Gram-negative red blood cell-associated coccobacillus (Boulouis et al. 2005, Saisongkorh et al. 2009). This rapidly expanding genus currently has 30 characterized species, with more being discovered with each study (Breitschwerdt and Kordick 2000, Saisongkorh et al. 2009). A number of mammalian species can serve as reservoirs, and different species of the bacterium appear to be adapted to different hosts. Norway and black rats can be infected with several related species, including *B. elizabethae*, *B. trobocorum*, *B. rochalimae*, *B. phocensis*, and *B. rattimassiliensis* (Billeter et al. 2011), and simultaneous infection with multiple species is not uncommon (Ellis et al. 1999, Inoue et al. 2008).

Rat populations worldwide are thought to be infected with *Bartonella* spp. (Boulouis et al. 2005, Saisongkorh et al. 2009); however, the degree to which rats are a source of infection for people is not known (Meerburg et al. 2009). Thus far, there have been a limited number of published cases of human disease attributed to rat-associated *Bartonella* spp. (Boulouis

et al. 2005), including cases of endocarditis and neuroretinitis associated with *B. elizabethae*, and febrile illness attributed to *B. rochalimae* (Breitschwerdt and Kordick 2000, Saisongkorh et al. 2009). Not much is known about the source of these human infections (Boulouis et al. 2005).

It is suspected that *Bartonella* spp. are transmitted among rats and from rats to people by arthropod vectors, particularly fleas (Breitschwerdt and Kordick 2000, Saisongkorh et al. 2009, Tsai et al. 2011). Rat-associated *Bartonella* spp. have also been identified in lice, mites, and ticks (Reeves et al. 2006, Reeves et al. 2007 Tsai et al. 2011); however, the role of these vectors in *Bartonella* spp. ecology remains to be determined. Some studies have also suggested that *Bartonella* spp. may be transmitted vertically from infected rodents to their offspring (Breitschwerdt and Kordick 2000).

Streptobacillus moniliformis, a pleomorphic Gram-negative bacillus (Elliott 2007, Gaastra et al. 2009), is part of the normal flora of the rat oropharynx, and is thought to be present in rat populations worldwide (Elliott 2007, Gaastra et al. 2009, Meerburg et al. 2009). *S. moniliformis* can be transmitted to people through the bite of an infected rat, which causes the aptly named rat bite fever, and through ingestion of food contaminated by rats, which causes Haverhill fever (Gaastra et al. 2009, Meerburg et al. 2009). Infection with *S. moniliformis* in people manifests as fever, headache, chills, vomiting, skin rash, and polyarthritis, although pharyngitis and vomiting may be more pronounced with Haverhill fever (Elliott 2007, Gaastra et al. 2009, Meerburg et al. 2009). If left untreated, *S. moniliformis* infection can progress to septicemia and the mortality rate is 7–13% (Elliott. 2007, Gaastra et al. 2009, Meerburg et al. 2009).

Other bacteria. Rats are capable of carrying and shedding *Escherichia coli* (Burriel et al. 2008, Guenther et al. 2010, Nkogwe et al. 2011), *Salmonella* spp. (Yokoyama et al. 2007, Nkogwe et al. 2011), and *Campylobacter* spp. (Nkogwe et al. 2011), all of which are important causes of gastrointestinal disease in people. Additionally, studies have shown that rats are frequently colonized by antibiotic-resistant strains of these bacteria (Yokoyama et al. 2007, Burriel et al. 2008, Guenther et al. 2010, Nkogwe et al. 2011), although the public health significance of these findings remains unknown. Rats are also competent hosts for several *Borrelia* spp., and may contribute the ecology of urban Lyme disease, particularly in Eurasia (Matuschka et al. 1996, Richter et al. 1999, Richter et al. 2011).

Viral zoonoses. Seoul hantavirus (SEOV) is an RNA virus of the genus *Hantavirus*, Family Bunyaviridae (Kariwa et al. 2007, Meerburg et al. 2009). Rats are the primary reservoir for SEOV (Meerburg et al. 2009), which is shed in the urine, saliva, and feces (Hinson et al. 2004). The virus is spread among rats through environmental contamination, social contact, and intraspecific aggression (*e.g.*, biting) (Kariwa et al. 1998). In male Norway laboratory rats, infection with SEOV actually increased aggressive behavior, thus facilitating virus transmission (Klein et al. 2004). Transmission of the virus from rats to people is thought to result from aerosolization and inhalation of rat excreta, although exposure via contaminated food or fomites is possible (Kariwa et al. 2007).

Seoul hantavirus is one of several rodent-associated hantaviruses that cause hemorrhagic fever with renal syndrome (HFRS) (LeDuc et al. 1992). Approximately 20% of all HFRS cases are thought to be due to SEOV infection, whereas 70% are due to Hantaan virus, for which the striped field mouse (*Apodemus agrarius*) is the reservoir, and the remaining 10% are due to other hantaviruses (Kariwa et al. 2007). In some areas, however (*e.g.*, Huludao, China), SEOV is the most common cause of HFRS (Guan et al. 2009).

HFRS is characterized by fever, myalgia, and headache, progressing to multisystemic hemorrhage and renal failure (LeDuc et al. 1992, Arikawa et al. 2001, Kariwa et al. 2007). The mortality rate for HFRS is 5–10% (Kariwa et al. 2007), and survivors may develop chronic renal impairment upon recovery from the acute phase (LeDuc et al. 1992). Infection with SEOV may also lead to hepatic dysfunction not observed with other hantavirus species (LeDuc et al. 1992, Kariwa et al. 1998, Arikawa et al. 2001).

Although SEOV is thought to have a worldwide distribution in rat populations (Arikawa et al. 2001, Kariwa et al. 2007, Meerburg et al. 2009), HFRS is largely limited to Asian countries, including China, Russia, and Korea (Arikawa et al. 2001, Kariwa et al. 2007). That being said, human exposure to SEOV (as evidenced by seropositivity) has been documented in countries outside of Asia (Yanagihara 1990) and, in the United States, seropositivity has been associated with proteinuria and hypertensive renal disease (LeDuc et al. 1992, Glass et al. 1993, Glass et al. 1994).

Other viruses. Hepatitis E virus (HEV) is a recently recognized viral zoonosis (Meng 2011) and a common cause of acute hepatitis in people (Hyams 2002). Although pigs are thought to be the primary reservoir (Meng 2011), studies have shown that rats may also be HEV carriers (Kabrane-Lazizi et al. 1999, Favorov et al. 2000, Meng 2011). New research, however, has shown that HEV in rats is only partially related to that found in humans and pigs (Meng 2011, Purcell et al. 2011). Additionally, rat HEV does not appear to be transmissible to nonhuman primates, and human HEV does not appear to be transmissible to rats (Purcell et al. 2011), suggesting that rat HEV is not zoonotic.

Rats are increasingly being investigated as a source of emerging viruses. For example, one researcher suggested that the severe acute respiratory syndrome (SARS) virus may have been spread by black rats during a 2003 outbreak in a Hong Kong apartment complex (Ng 2003).

Parasitic zoonoses *Angiostrongylus cantonensis*

Norway and black rats are the main reservoirs for this parasitic nematode, the adults of which reside in the pulmonary arteries (Wang et al. 2008, Wang et al. 2012). Eggs are passed in the feces and develop to an infectious stage in a molluscan intermediate host (Wang et al. 2008). Humans can become infected by consuming the intermediate host, a paratenic host (*e.g.*, an amphibian or crustacean that consumed the intermediate host), or vegetation contaminated by molluscan mucus (Wang et al. 2008). Once ingested by a person, the larvae migrate to the central nervous system or eyes where they cause eosinophilic meningitis or ocular angiostrongyliasis (Wang et al. 2008, Wang et al. 2012). The parasite is primarily found in Southeast Asia, the South Pacific, Australia, and the Caribbean, although endemic foci can also be found in Africa, the United States, and South America, and cases may occur sporadically in other areas

(e.g., Europe) (Wang et al. 2008, Simoes et al. 2011, Wang et al. 2012).

Other zoonotic parasites. Rats are the reservoir for the zoonotic tapeworms *Hymenolepis* spp. and *Rodentolepis* spp., which reside in their intestinal tract (Easterbrook et al. 2007a, Milazzo et al. 2010, Hancke et al. 2011). Larval stages can be transmitted among rats, from rats to humans, and, occasionally, among humans, via the feces or through consumption of an arthropod intermediate host (Centers for Disease Control and Prevention 2012b). In people, the parasite may develop in the intestine and cause enteritis (Marangi et al. 2003, Maggi et al. 2005). Rats are also a reservoir for *Capillaria* spp., a nematode that infects the rat liver (Ceruti et al. 2001, Easterbrook et al. 2007a, Milazzo et al. 2010). Eggs are released into the environment upon the death of the rat, or through the feces of a predator that consumes an infected rat (Centers for Disease Control and Prevention 2012a). Infection in humans is usually asymptomatic but can result in hepatitis (Centers for Disease Control and Prevention 2012a).

Although not a direct source of infection for people, rats are an intermediate host for *Toxoplasma* spp. and can serve as a source of infection for cats and other animals, which, in turn, are a source of infection for people (Webster 1994, Frenkel et al. 1995, Vujanic et al. 2011). Rats are also being investigated as a potential reservoir for zoonotic *Cryptosporidium* spp., a gastrointestinal parasite of people (Kimura et al. 2007).

Common epidemiologic themes for the above zoonoses

The changing face of rat-associated zoonoses. The frequency and distribution of RAZ has changed over time in association with changes in human populations. In particular, increasing urbanization and urban poverty have resulted in the emergence, or re-emergence, of RAZ in urban centers. For example, although leptospirosis has long been considered a primarily rural or occupational disease, the incidence of urban leptospirosis is increasing (Ko et al. 1999, Evangelista and Coburn 2010, Socolovschi et al. 2011). Similarly, the incidence of SEOV HFRS in Chinese cities is increasing, and this increase has been attributed to urban population growth, in combination with concomitant increases in urban rat populations and rat-human contact (Guan et al. 2009). Additionally, several African cities, particularly in Madagascar, have experienced a re-emergence of urban plague since the 1980s (Chanteau et al. 2000, Migliani et al. 2006).

Interestingly, some zoonoses that have historically been associated with urban centers are now moving farther afield. In the United States, for example, murine typhus, although still present in many urban centers (Silpapojakul et al. 1993, Azad et al. 1997, Comer et al. 2001, Gikas et al. 2002), is shifting to a suburban focus involving cat fleas and opossums (Azad et al. 1997, Civen and Ngo 2008). In New Zealand, *R. typhi* infection in people is most strongly associated with exposure to rats at rural holiday homes (Gray et al. 2007).

The role of climate, season, and weather in rat-associated zoonoses. Climate, season, and weather play strong roles in the ecology of many RAZ by influencing human exposure to zoonotic organisms and through their effect on the biology and ecology of rats, vectors, and pathogens. In the case of *Leptospira* spp., heavy precipitation and flooding facilitate dispersal of leptospires in the environment, increasing human contact with the bacterium (Evangelista and Coburn 2010). Leptospirosis is, thus, most common in tropical areas with high annual rainfall (Yanagihara et al. 2007), and the incidence of disease is highest in the wet season (Venkataraman and Nedunchelliyan 1992, Ko et al. 1999). As well, studies of urban leptospirosis have shown that cases are associated with proximity to water bodies and flood plains (Barcellos and Sabroza 2001, Bhardwaj et al. 2008, Reis et al. 2008, Tassinari et al. 2008, Guerra 2009, Evangelista and Coburn 2010, Martins Soares et al. 2010), and that people suffering from the disease report increased contact with flood water compared to those not affected (Ko et al. 1999).

The incidence of SEOV HFRS in China is highest in April and lowest in September (Guan et al. 2009), which is thought to reflect seasonal differences in rat abundance and rat-human contact (Guan et al. 2009). Annual temporal variation in plague transmission, on the other hand, is most likely a result of seasonal changes in flea population dynamics (Boisier et al. 1997, Boisier et al. 2002, Migliani et al. 2006). Similarly, murine typhus cases occur predominantly during warm weather, which promotes high flea populations (Civen and Ngo 2008).

Y. pestis, itself, requires sufficient ambient heat to activate genes that cause it to block the flea gut and trigger the chain of events required for transmission (Migliani et al. 2006). Should the temperature be too hot (i.e., >28°C), however, fleas can clear the blockage and will not transmit the bacterium (Perry and Fetherston 1997). This may be one of the reasons why plague epidemics tend to subside at high temperatures (Perry and Fetherston 1997).

What remains to be determined is the potential impact of climate change, particularly since the incidence and distribution of other rodent-associated zoonotic diseases, such as Lyme disease, are changing rapidly in association with changing climate (Mills et al. 2010, Leighton et al. 2012). Climate change could influence the ecology of RAZ in a variety of ways, for example by precipitating changes in pathogen distribution, vector abundance, transmission pathways, and pathogen prevalence/load in rats and vectors (Mills et al. 2010).

Ecology of zoonoses in rat populations. An understanding of the 'behavior' of zoonotic pathogens in rat population is crucial for identifying which rats or rat populations pose the greatest health risk for people. For example, for an individual rat, the probability of infection with *Leptospira* spp., SEOV, and hepatitis E virus, increases with age (Bharti et al. 2003, Vanasco et al. 2003, Krojgaard et al. 2009, Johnson et al. 2010), likely because of increased opportunity for exposure. For SEOV, in particular, infection and viral shedding is most common in old, large male rats (Cueto et al. 2008), because intraspecific aggression appears to play important role in virus transmission (Yanagihara 1990). At a population level, pathogen prevalence may decrease at the height of juvenile recruitment, which is the time when the greatest number of young, uninfected rats leave the nest and enter the population (Liu et al. 2010). Overall, the above suggests that well-established, mature, and stable rat populations may pose the greatest health risk to people.

That being said, the impact of externally imposed changes in rat population dynamics (*e.g.*, large-scale poisoning or trapping campaigns) on the ecology of RAZ is unclear. For other infectious diseases in wild populations, control methods based on culling animals may actually cause an increase in disease prevalence by disrupting normal population ecology and thereby enhancing disease transmission (Bolzoni et al. 2007). Anthropogenic changes in rat populations may have similar unintended effects. For example, previous plague epidemics have revealed that large rat die-offs consistently precede human casualties (Chanteau et al. 1998, Keeling and Gilligan 2000a, Boisier et al. 2002, Monecke et al. 2009). This is a result of the fact that *X. cheopis* (the primary plague vector) prefers to feed on rats but will feed on humans (thus transmitting the disease) when the rat population collapses (Monecke et al. 2009). Thus, culling of rats during a plague outbreak may actually increase the incidence of disease in people by removing the rat flea's preferred host (Keeling and Gilligan 2000b, Monecke et al. 2009).

The geographic distribution of rat-associated zoonoses. The prevalence of many zoonotic pathogens in rat populations is highly variable among cities. Studies of *Leptospira* spp. in Norway rats (using culture) have shown that the prevalence of infection was 80% in Salvador, Brazil (Calderwood et al. 2008), 17% in Tokyo, Japan (Koizumi et al. 2009), 21% in Medellin, Columbia (Agudelo-Florez et al. 2009), and 96% in Buenos Aires, Argentina (Scialfa et al. 2010). Similarly, the prevalence of *Barontella* spp. infection in black rats (using culture and/or PCR) was 43% in Nepal (Gundi et al. 2010), 24% in Israel (Morick et al. 2009), and 32.3% in Bangladesh (Bai et al. 2007). There is also marked variation in prevalence of infection among cities in the same country (Liu et al. 2010), and even among different locations within a city (Taylor et al. 2008, Krojgaard et al. 2009, Koizumi et al. 2009). For example, a study of *Leptospira* spp. in Copenhagen, Denmark, showed that, despite robust rat populations in all locations sampled, 1 location had no positive animals, whereas the prevalence in other locations ranged from 48% to 89% (Krojgaard et al. 2009). In Buenos Aires, Argentina, the prevalence of SEOV seropositive rats ranged from 0% to 26.1% at different sites within the city (Cueto et al. 2008). Variation in pathogen prevalence, even over a short geographic distance, suggests that site-specific prevalence of zoonoses in rat populations may be more relevant from a public health standpoint than aggregated city- or country-wide measures.

The reasons for this heterogeneity in pathogen prevalence are unclear but could be attributable to limited rat home ranges, with disease transmission occurring primarily among family groups (Traweger et al. 2006). Alternatively, features of the physical microenvironment in which rats reside may affect pathogen prevalence through their effect on rat, vector, or pathogen ecology (Traweger and Slotta-Bachmayr 2005). Finally, it is possible that some of these differences may be artifactual (*i.e.*, due to variation study methodologies).

This latter point is particularly problematic when comparing studies documenting zoonotic pathogen exposure in people. For example, the prevalence of SEOV exposure (as evidenced by seropositivity) in the United States varies from 34% to 74% in Baltimore, to 31% to 41% in New Orleans, to 5% to 9% in Houston, to 0% to 3% in San Francisco (Yanagihara 1990). However, marked variation in the demographic under consideration hinders study comparability and identification of the precise reasons behind this variation.

Risk factors for infection and disease in people. Although many of the reasons behind geographic variations in the prevalence of RAZ remain unclear, it is possible to identify risk factors for exposure to these pathogens in people. Among the most important of these risk factors is country of origin. Both epidemic and endemic rat-associated zoonotic diseases are more common in developing versus industrialized nations (Evangelista and Coburn 2010). This may be partially due to the climate in developing countries, which tends to be warmer and wetter, and thus more conducive to the transmission of RAZ (Yanagihara et al. 2007). Perhaps the stronger determinant, however, is high rates of urban poverty in these areas (Ko et al. 1999, Johnson et al. 2004, Ko et al. 2009). For example, during an outbreak of leptospirosis in Salvador, Brazil, people residing in urban slums were 4 times more likely to get leptospirosis compared to non-slum dwellers (Ko et al. 1999). Additionally, people living in poor, densely populated areas of Madagascar are more likely to get bubonic plague compared to the general population (Boisier et al. 2002). These findings are hardly surprising given that impoverished urban populations experience inadequate housing, infrastructure, and sanitation, which promote rat infestations, enable close contact between rats and people, and facilitate pathogen transmission (Boisier et al. 1997). Additionally, impoverished populations often have limited access to medical care, hindering zoonotic disease diagnosis and treatment (Chanteau et al. 2000, Meerburg et al. 2009).

Paradoxically, in Peru, populations with the highest rate of exposure to *Leptospira* spp. had comparatively lower rates of disease, suggesting that prior exposure to the bacterium leads to protective immunity (Johnson et al. 2004). Barcellos et al. (2001) suggest this as the reason why people residing in the highest risk areas for *Leptospira* spp. infection in Rio de Janeiro, Brazil, were actually less likely to develop clinical leptospirosis during an outbreak.

Even within developed countries, the urban poor may be at an increased risk for exposure to and infection with RAZ because of declining infrastructure (*i.e.*, urban decay), poor standards of living, inadequate hygiene, intravenous drug use, homelessness, and immunosuppression (*e.g.*, HIV/AIDS) (Comer et al. 2001). For example, Childs et al. (1992) found that 16% of people from an inner city population in Baltimore, MD, had been exposed to *Leptospira* spp. and that seropositivity was associated with low income and African American ancestry. Additionally, there have been several cases of clinical leptospirosis in homeless people from Baltimore, all of which were associated with exposure to rats in alleyways (Vinetz et al. 1996). However, 2 studies of SEOV exposure in Baltimore intravenous drug users showed that the prevalence of antibody against the virus was low (<1%) and not significantly different from that found in people visiting the emergency room or a sexually transmitted disease clinic (who were assumed to be at lower risk of exposure) (Childs et al. 1991, Khabbaz et al. 1994).

Although impoverished populations may be at increased risk, people have the potential to acquire RAZ regardless of their socioeconomic status. For example, a study in Tokyo, Japan, identified at least 13 cases of autochthonous Weil's

disease in nonimpoverished individuals between 2002 and 2008 (Koizumi et al. 2009).

Finally, it is important to note that it is the home (vs. work or social) environment that appears to play the most important role in determining an individual's risk of exposure to RAZ (Bishara et al. 2002, Jansen et al. 2005). For example, studies have shown that seeing rats around the household, particularly groups of rats, is an independent risk factor for *Leptospira* spp. exposure and infection (Ko et al. 1999, Sarkar et al. 2002, Bhardwaj et al. 2008, Reis et al. 2008).

One question yet to be addressed is whether immunosupression could significantly affect the risk of RAZ. Given the variety of conditions that can lead to immuosupression, from HIV/AIDS to medical intervention for cancer and rheumatologic disease, the degree to which these conditions influence the risk of RAZ in urban populations warrants further study.

Burden of disease in people. Although RAZ represent a diverse group of organisms, their clinical manifestations are strikingly similar and frequently nonspecific (Boisier et al. 1997, Perrocheau and Perolat 1997, Bharti et al. 2003, Gray et al. 2007, Civen and Ngo 2008, Guerra 2009, Evangelista and Coburn 2010). This lack of clinical specificity, in combination with lack of awareness among health care practitioners, can lead to high rates of misdiagnosis and underdiagnosis (Silpapojakul et al. 1993, Vinetz et al. 1996, Bharti et al. 2003, Yanagihara et al. 2007, Guerra. 2009), particularly in developed countries where these diseases are less common (Silpapojakul et al. 1993, Vinetz et al. 1996, Bharti et al. 2003). A lack of access to reliable diagnostic tests in many laboratories may further hinder the detection of RAZ (Chanteau et al. 2000, Elliott 2007, Gaastra et al. 2009). Finally, in many cases, the patients themselves are unaware of rat or vector exposure, which means that a detailed history may not be helpful in making the diagnosis. For example, many people with murine typhus do not recall being bitten by fleas (Silpapojakul et al. 1993, Gray et al. 2007, Civen and Ngo 2008), and a significant proportion of those with so-called rat bite fever do not recall having contact with a rat (Elliott 2007, Gaastra et al. 2009).

Under-diagnosis and misdiagnosis are problematic and may lead to delayed or inappropriate treatment, causing increased mortality from otherwise survivable diseases (Ko et al. 1999, Chanteau et al. 2000) and chronic debilitating illness in otherwise healthy working-age individuals (Ko et al. 1999, Yanagihara et al. 2007, Martins Soares et al. 2010). Under-diagnosis and misdiagnosis can also lead to underreporting of RAZ, making it difficult to estimate or deal with the health burden associated with these diseases. Underreporting can also be a result of different infectious disease reporting systems. For example, leptospirosis was eliminated from the list of nationally notifiable diseases in the United States in 1995 (Vinetz et al. 1996, Katz et al. 2002), whereas Germany implemented a mandatory reporting system for infectious diseases, including leptospirosis, in 2001(Jansen et al. 2005).

Effect of zoonotic organisms in rats. Despite the range of clinical manifestations associated with RAZ in people, with the exception of *Y. pestis* (Perry and Fetherston 1997), all of the aforementioned pathogens cause asymptomatic infections in rats (Easterbrook et al. 2007a, Tucunduva de Faria et al. 2007, Guerra 2009, Ko et al. 2009). Indeed, not only do infected rats appear clinically normal, so close is the adaptation between many of these zoonotic pathogens and their hosts that infection may not even result in tissue pathology or elicit a functional immune response. For example, studies have found that there are no significant differences in the microscopic appearance of tissues from rats with and without renal *Leptospira* spp. infection (Tucunduva de Faria et al. 2007), and

Table 2. Conclusions from a Review of the Literature Regarding the Ecology of Zoonotic Pathogens Associated with Norway Rats and Black Rats (*Rattus norvegicus* and *Rattus rattus*) in Urban Centers

Knowledge gained from previous study of rat-associated zoonoses	• The ecology of rat-associated zoonoses is changing in association with global urbanization and urban poverty. • Climate, season, and weather influence the ecology of rat-associated zoonoses through their effects on the distribution of and interactions among rats, vectors, and zoonotic pathogens, which ultimately influence human exposure to zoonotic pathogens. • The ecology of zoonotic pathogens in rat populations influences the risk of zoonotic pathogen transmission from rats and people. • The distribution and prevalence of rat-associated zoonoses is heterogeneous, even over a short geographic distance. • Developing nations and impoverished populations within developing and developed nations are at highest risk for rat-associated diseases. • With the exception of plague, infection with zoonotic organisms does not cause clinical illness in rats, and immune responses to zoonotic organisms in rats may be variable or absent.
Remaining knowledge gaps	• What is the impact of climate change on the ecology of rat-associated zoonoses in urban centers? • How do rodent control methods impact the ecology of rat-associated zoonoses? Can epidemiologic information regarding rat-associated zoonoses be use to create targeted rat control measures geared to prevent zoonotic pathogen transmission, specifically? • What is the true prevalence and distribution of rat-associated zoonoses in rats and people? Why does the prevalence of exposure to and infection with rat-associated zoonoses in rats and people vary among geographic locations? Is it possible to identify features of the physical microenvironment that promote or decrease pathogen transmission? • How does immunosupression affect the risk of rat-associated zoonoses in people? • What is the true health burden caused by rat-associated zoonotic disease in people?

many rats infected with *Leptospira* spp. or *Bartonella* spp. have no detectible antibody response to the pathogen (Breitschwerdt and Kordick 2000, Calderwood et al. 2008, Agudelo-Florez et al. 2009, Aviat et al. 2009, Villanueva et al. 2010). Similarly, rats infected with SEOV can remain persistently infected even in the face of neutralizing antibody (Kariwa et al. 2007). Indeed Easterbrook et al. (2007b) showed that SEOV can actually modify the rat immune system to maintain infection and viral shedding. In the case of *Streptobacillus moniliformis*, the bacterium is considered to be part of the normal flora of the rat oropharynx (Elliott 2007, Gaastra et al. 2009).

One implication of inconsistent immune responses in rats is that, for those wishing to study RAZ in their rodent hosts, the choice of diagnostic test is critical to the validity and meaning of research findings. For example, given that many rats infected with *Leptospira* spp. do not mount an antibody response (Calderwood et al. 2008, Agudelo-Florez et al. 2009, Aviat et al. 2009, Villanueva et al. 2010), the use of serology could underestimate the prevalence of infection. Additionally, studies have shown that many rats have *Leptospira* spp. antibody against serovars that are nonhomologous to those with which they are infected and/or serovars known to be maintained in another, non-rat species (Calderwood et al. 2008, Agudelo-Florez et al. 2009, Krojgaard et al. 2009, Villanueva et al. 2010), suggesting that serostatus may be completely unrelated to infection status. In contrast, for SEOV, there appears to be good concordance between serology and pathogen presence (by PCR or culture) (Jiang et al. 2008).

Conclusions

Overall, it is clear that urban Norway and black rats can pose a significant health risk to people through the transmission of zoonotic diseases and that this risk is likely to increase with increased urbanization and urban poverty (*e.g.*, because of increased habitat available for urban rats and increased contact between rats and disadvantaged people). It is also clear the ecology of RAZ is difficult to understand because it is based on the complex interactions of a number of factors, including rats, people, pathogens, vectors, and the urban environment. Although the literature to date has provided a solid foundation for our knowledge of RAZ, there are a number of gaps that require further consideration (Table 2). Only by developing a complete and comprehensive understanding of urban-rat-associated zoonoses will we be able to accurately estimate the health risks posed by urban rats, and develop informed and effective strategies to monitor and mitigate those risks.

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