Aboriginal and Invasive Rats of Genus *Rattus* as Hosts of Infectious Agents

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Abstract

From the perspective of ecology of zoonotic pathogens, the role of the Old World rats of the genus *Rattus* is exceptional. The review analyzes specific characteristics of rats that contribute to their important role in hosting pathogens, such as host–pathogen relations and rates of rat-borne infections, taxonomy, ecology, and essential factors. Specifically the review addresses recent taxonomic revisions within the genus *Rattus* that resulted from applications of new genetic tools in understanding relationships between the Old World rats and the infectious agents that they carry. Among the numerous species within the genus *Rattus*, only three species—the Norway rat (*R. norvegicus*), the black or roof rat (*R. rattus*), and the Asian black rat (*R. tanezumi*)—have colonized urban ecosystems globally for a historically long period of time. The fourth invasive species, *R. exulans*, is limited to tropical Asia–Pacific areas. One of the points highlighted in this review is the necessity to discriminate the roles played by rats as pathogen reservoirs within the land of their original diversification and in regions where only one or few rat species were introduced during the recent human history.

Key Words: *Rattus*—Old World rats—Rat-borne infections—Ecology—Taxonomic revisions.

Introduction

FROM THE PERSPECTIVE OF ECOLOGY of zoonotic pathogens, the position of the Old World rats of the genus *Rattus* is exceptional. Identification of rats and rat fleas as reservoirs and vectors of bubonic plague a little more than a century ago opened a new era in understanding of epidemiological significance of rats and other rodents in transmission of infectious agents and made apparent the importance of rat-borne diseases to public health around the globe. During the century following the discovery of zoonotic nature of plague, the number of human diseases found to be associated with rats has continued to increase as has our understanding that the presence of rats in human environment can have serious implications for public and veterinary health. In addition to being reservoirs for zoonotic diseases, rats historically present threats to food supplies and are also seen as pests because of their destructive behaviors that can cause economic losses and lead to structural damages.

Understanding of specific characteristics of rats that contribute to their important role in hosting pathogens, such as host–pathogen relations and the true rate of rat-borne infections, taxonomy, and rat ecological and other risk factors are essential and need to be assessed further. What makes rats so important carriers of diverse pathogens? Is it the diversity of rat species, their genetic variability, complex behaviors, ability to travel and to adapt to human environment, or other factors? The short answer is that none of these factors separately can provide even an approximate picture of such complex relations between rats and the diverse pathogens associated with this group of rodents. In spite of numerous investigations of rats as carriers and/or reservoirs (the terms are commonly misused), attempts to interpret such observations in relation to disease transmission are very rare. Among recent review publications addressing this question, we can highlight papers by Gratz (2006), Battersby et al. (2008), Meerburg et al. (2009), Aplin et al. (2011), Khlyap et al. (2012), and Himsworth et al. (2013b).

The fact that commensal rats (or synanthropic rats—the terms intensively discussed by Khlyap et al. 2012) are invasive species in the most parts of the world is well known to zoologists, but very often is ignored by specialists within public health agencies of many countries (Childs et al. 1999). This fact means that the approaches used to evaluate a role of

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rats as pathogen reservoirs within the land of their origin should differ considerably from those employed in regions where only one or a few rat species were introduced during recent human history. Mentioning the introduction of rats to new regions beyond the land where they existed from the earliest times, it is important to keep in mind that this is a very dynamic and continuous process. Recent taxonomic revisions within the genus *Rattus*, which resulted from applications of new genetic tools (Robins et al. 2007, Galan et al. 2012), represent another challenge in understanding relationships between the Old World rats and the infectious agents that they carry.

This review does not pretend to answer all the questions why rats of genus *Rattus* are so special in transmission of infectious diseases. We intend to fill certain gaps in evaluating the natural history of rat–pathogen systems and specifically to describe some aspects of rat phylogenetics, ecology, and biogeography (including human-mediated colonization history) as they may relate to several zoonotic pathogens. More importantly, the objective of this review is to stimulate collaborations between zoologists, ecologists, microbiologists, and epidemiologists when dealing with rats, which as a group presents an evident and growing epidemiological significance that cannot be ignored.

Materials and Methods

This work is based on the analysis of published literature using various databases, including, but not limited to, Medline, PubMed, OVID, Bio One, Web of Science, BIOSIS Zoological Records, Scopus 264, Research Gate, Global Health, and Google Scholar. The key words for the search included rats, rodents, small mammals, *Rattus*, urban animals, invasive species, rodent-borne diseases, zoonoses, rat pathogens, plague, tularemia, rickettsia, bartonella, leptospirosis, hantaviruses, and many others. Selected publications were organized into the main categories, such as rat-borne diseases (52), urban zoonoses (12), rats in Asia (49), *Rattus* taxonomy (32), rat biology (42), rats as invasive animals (38), and other categories related to more general aspects of rodent-borne diseases and rodents. For the citation section, we selected review publications primarily because of the extensive literature on some aspects of the problem and the need to provide as broad coverage as possible within the limited space available for this article. Although most cited publications are written in English, we have included some related references in French and Russian.

Results and Discussion

Taxonomy

There are 66 recognized species within the genus *Rattus* (Musser and Carlton 2005). From the standpoint of its systematics, the genus *Rattus* is one of the more complex and rapidly changing mammalian genera (Aplin et al. 2003). Musser and Carlton (2005) classified current species of *Rattus* into seven systematic groups: (1) The *norvegicus* group with the Norway rat *R. norvegicus* and a few related species; (2) the *exulans* group containing only the species the Pacific rat, *R. exulans*; (3) the *rattus* group with the black rat *R. rattus* and a large number of closely related species; (4) the native Australian group *fuscipes*; (5) the native New Guinean group *leucopus*; (6) the native Sulawesian group *xanthurus*; and (7) a seventh assemblage containing unaffiliated species

for which phylogenetic affinities are uncertain. The phylogeny based on analysis of whole mitochondrial genomes suggested an early divergence within *Rattus* that happened around 3.5 million years ago and led to the separation of the Australo-Papuan lineages from the Asian and Island Southeast Asian lineages (Robins et al. 2008).

Association of aboriginal Rattus *species with natural habitats and human settlements*

Species of *Rattus* occupy diverse habitats within the area of their original diversification. In Southeast Asia, the natural habitats range from tropical lowland to mountains. Discussing the distribution of rats in Thailand, Lekagul and McNeely (1977, from Nowak 1999) noticed that six of 12 species tend to avoid human settlements and live primarily in natural habitats. For instance, *R. argentiventer* is common in rice fields, *R. losea* (and its sibling species *R. sakeratensis*) is more common in gardens, although it can be found in rice fields as well, and *R. tiomanicus*, which is found in gardens, plantations, and scrubs. Importantly, several rat species have clearly adapted to human-created environments. For example, *R. tanezumi* occupy towns, villages, farms, although they are also abundant in natural habitats. *R. nitidus* and *R. exulans* are found mostly in houses within villages. *R. norvegicus* are common in urban ecosystems and especially numerous in big cities (Herbreteau et al. 2012, Ivanova et al. 2012). According to Musser and Carlton (2005), *R. exulans, R. nitidus*, and *R. norvegicus* cannot be found in primary forest in the Philippines and Sulawesi, being fully associated with human environment, whereas many indigenous species of *Rattus* are restricted to in the remnants of primary forest that still survive in these countries.

Invasive species of the Rattus *genus*

Among the numerous species within the genus *Rattus*, only three species—the Norway or brown rat (*R. norvegicus*), the black or roof rat (*R. rattus*), and the Asian black rat (*R. tanezumi*)—have colonized urban ecosystems globally for a historically long period of time (Bobrov et al. 2008, Aplin et al. 2011, Khlyap et al. 2012). The forth invasive species *R. exulans* is limited to tropical Asia-Pacific areas. Application of the term ''invasive species'' versus ''native species'' reflects the fact that black and Norway rats are characterized as historically introduced species, cosmopolitan in their distribution, and alien by their introduction to places where they did not inhabit previously, and mostly living inside houses or using other man-made features. These species are distributed throughout the world, principally through occasional introductions, and the extent of their range is determined mainly by ground traffic and ship navigation (Khlyap et al 2012). The latter was a leading factor for crossing ocean barriers (Kucheruk and Lapschov 1994).

Geographic origin and dispersal of Norway rats

Norway rats, despite their common name, are believed to have originated from the plains in Heilongjiang Province of northern China (Nowak 1999). In China, fossils of *R. norvegicus*, dated to Holocene and late Pleistocene, were found in cave deposits from the Sichuan-Guizhou region (Zheng 1993, cited by Wilson and Reeder 2005). The question of

when Norway rats became commensal with humans remains disputed, but it is clear that they have spread and established their presence along routes of human migration and currently are present almost everywhere humans live. Although the general perception is that Norway rats colonized Europe during the 18th century, a discovery of numerous remains of those rats in an archaeological site in Tuscany, Italy, dated to the 14th century AD (Clark et al. 1989) provides a possibility of the establishment of small populations in western Europe well before that. Paris was colonized shortly after 1750 (Vigne and Villié 1995) and European part of Russia by the 17th century (Bobrov et al. 2008, Khlyap et al. 2012).

Norway rats reached North America between 1750 and 1775 (Nowak 1999). The first appearance of rats in Alaska was not recorded, but the rats became established there soon after the arrival of Europeans (Rausch 1969). Further invasion of Norway rats in northern Eurasia continued during the 18th to 20th century. The rats reached the coast of the Sea of Okhotsk and Chukotka or dry regions of Central Asia (Uzbekistan and Kazakhstan) during the last decades of 20th century. At present, almost all of European Russia is populated by Norway rats, but significant parts of western and eastern Siberia have remained rat free (Bobrov et al. 2008, Khlyap and Warshavsky 2010).

Within North America, Norway rats occur from northern Alaska along the Pacific coast and across temperate latitudes to the Atlantic Ocean. Following its introduction, this species colonized many cities throughout the entire United States. The northern Rocky Mountain States were the last section of this country to be colonized by these rats. Studies in five states (Colorado, Idaho, Montana, Utah, and Wyoming) conducted from 1947 through 1955 showed rats present in all of these states (Harmston and Wright 1960). A recent study conducted in many US localities revealed that at least four invasions, each of which were distinct in space and/or time, have occurred to establish the current distribution of the Norway rat in the United States (Lack et al. 2013). In the US cities, Norway rats are mostly restricted to man-made environments within urban ecosystems, especially at the more northern latitudes. In the warmer southern regions of the United States, Norway rats can live away from human populations, occupying grassland and marshy rural areas (Glass et al. 1989).

We still lack a worldwide phylogeographic study that captures the global picture of the invasion pathways followed during the spread of Norway rats. Lack et al. (2013) have detected high frequencies of long-distance dispersal between distant localities, as well as high gene flow among established populations, which suggests high frequencies of novel introductions and good assimilation of newcomers into established populations. The important message from an epidemiological standpoint is that Norway rat populations are highly connected, potentially promoting a high rate of spread of rat-borne zoonotic pathogens and parasites across large continental areas.

Geographic origin and dispersal of black (roof) and Asian black rats

Similar to the Norway rats, the origins of the black rats are hotly debated. Nowak (1999) indicated that this species probably originated in the Malaysian region, whereas Musser and Carlton (2005) stated that these rats are native to the Indian Peninsula, from which they were introduced world-wide. The results from a recent investigation conducted by Aplin and his collaborators from many countries suggested multiple geographic origins of black rats and closely related forms (Aplin et al. 2011). These authors found a strong phylogeographic pattern with well-differentiated lineages of black rats native to South Asia, the Himalayan region, southern Indochina, and northern Indochina to East Asia. This diversification probably happened in the early Middle Pleistocene. Whether these lineages represent separate species is still unclear. Among the four mitochondrial lineages, two karyotypic forms have been described as separate species, the black rat *R. rattus* and the Asian black rat *R. tanezumi*. However hybridization and gene flow occur locally between these lineages, both in their area of origin (Pagès et al. 2013) and in introduced areas (Lack et al. 2013). The two karyotype forms have been introduced in many places of the world, in certain cases in the same places, such as has occurred in South Africa (Bastos et al. 2011) and California (Lack et al. 2013). Finally, one of the important conclusions from these recent studies conducted by Aplin et al. (2011) and others is that commensalism arose multiple times and in different populations of black rats.

According to Musser and Carleton (2005), the black rat began to expand out of its original area in the Indian Peninsula about 10,000 years ago. They appeared on the eastern coast of the Black Sea prior to or during the Neolithic Age. The earliest evidence of a long distance invasion of *R. rattus* was reported from the Levant and dated to 1500 BC (Ervynck 2002). The next stage of this ancient invasion was reported throughout the Roman Empire, reaching England as early as the 1st century (Engels 1999). At that time, the black rats were confined to trading routes and ports (Audouin-Rouzeau and Vigne 1994). Since that time and as a result of later invasion events, this species has been introduced to all continents through human overseas travel.

In the 5th century black rats spread through river trading routes until they reached the Baltic Sea, including the Finland Gulf and, in the 10th to 12th centuries, the European part of Russia, including Moscow (Bobrov et al. 2008). Black rats probably reached East Africa and western Indian oceanic islands during the 10th century, when the Indian Ocean was the site of a vast trading network, connecting societies between China and the Mediterranean (Tollenaere et al. 2010). Independently, black rats reached West Africa during the 15th century along with the first Portuguese seafarers, but did not further colonize inland until the 18th and 19th centuries as a result of the development of commercial transport along large rivers and roads in the region (Konečný et al. 2013). Black rats also succeeded in occupying the Asian part of Russia by the end of the 19th century. From the late 1960s to the 1980s, these rats settled in the central part of European Russia (Bobrov et al. 2008, Khlyap and Warshavsky 2010).

Black rats are now most often found in large numbers in coastal areas because of the way this species is spread via sea ships (Kucheruk and Lapschov 1994), although large populations occupy inland areas in tropical countries as in west and south Africa (Bastos et al. 2011, Konečný et al. 2013). Being a better climber than Norway rats, they often live in high places and can be found in the top floors of buildings or in attics. Black rats can often inhabit sea ships and therefore are common within sea ports. In a Pacific seaport of Russia, black rats were found in 10.6% of ships coming from India,

6.8% of ships from Singapore, and 3.3% of ships from Vietnam (Belyev et al. 1975).

A study in Senegal, western Africa, revealed very complex invasion pathways largely influenced by human trade routes and characterized by long-distance dispersal, multiple introductions from different source populations, and genetic admixture of newcomers originating from different source populations (Konečný et al. 2013). By contrast, black rat populations in the United States were founded by only one (or a few related) lineages or geographic sources, and microsatellite analyses suggest that dispersal is spatially restricted, with a relatively low frequency of long-distance dispersal (Lack et al. 2013). Importantly, rats of both *R. rattus* and *R. tanezumi* lineages were identified in the San Francisco Bay region in California (Conroy et al. 2013). *R. tanezumi* rats are founded in southeastern Asia, the Malay Archipelago, and in the west of New Guinea, northward to eastern China and Japan. Single records of *R. tanezumi* were reported from the western shores of South and North America and from South Africa (Aplin et al. 2011).

All of these studies indicated that black rats display very complex pathways of invasion, mostly human mediated and largely influenced by the history of trade routes. During the last century, however, the number and range of black rats have been reduced across most of the globe. They are primarily confined to warmer areas, having been largely driven out by Norway rats in cooler regions and in urban ecosystems.

Dispersal of Pacific rats

Polynesian (or Pacific) rats *R. exulans* may also be able to be dispersed via ships, but the area of their colonization is mostly limited to Pacific islands. This species originated in Southeast Asia, but has invaded Fiji and most Polynesian islands, including New Zealand, Easter Island, and Hawaii. Occupying new island territories, *R. exulans* maintain the ability to easily adapt to different habitats from grasslands to forests developed in Southeast Asia. These rats cannot swim over long distances but were able to reach islands with human migrations across the Pacific (Musser and Carlton 2005). Pacific rat dispersal was used to model the history of Polynesian settlement, as this animal traveled with ancestral Polynesians as they dispersed throughout the Pacific (Matisoo-Smith et al. 2004). Archaeological records of the Polynesian rats, outside its presumed original distribution, dated its presence from around 4000 BP in East Timor, 3000 BP in west Polynesia to 1000 BP in south Polynesia. However, new invasions from insular Southeast Asia have recently occurred with populations of Pacific rats established in Taiwan and the Ryukyu Islands of Japan (Kuo et al. 2011). Therefore, new invasion threats exist for all of the Pacific areas, including South Japan islands, Australia, New Zealand, New Caledonia, and French Polynesia. There are also concerns about the invasion of the northern part of the Indochinese region because *R. exulans* is currently absent from small villages in north Laos, although present in large cities such as Luang Prabang (Promkerd et al. 2008).

Zoonoses associated with rats of genus Rattus within their natural range

In Asian countries where most *Rattus* species originated, rats continue to present a huge threat to human health,

causing significant morbidity and mortality. Historically, plague caused by the Gram-negative bacterium *Yersinia pestis* attracted particular attention among specialists and the general public. The picture of plague distribution in the world has significantly changed during the last 30–40 years. Before the 1970s, more than 90% of the total world incidence of human plague was reported from southeastern Asia (Velimirovic 1972), but at present only a few plague foci are still active in this region and the occurrence of human plague is much lower in comparison with certain eastern and central African countries, where the disease now predominates. Although this disease has become much less prevalent, plague still causes fear and even mass hysteria, as demonstrated during a 1994 pneumonic plague outbreak in India (Gage and Kosoy 2005). Myanmar last reported plague to the World Health Organization (WHO) in 1994, Laos in 1996, Vietnam in 2002, and Indonesia in 2008 (World Health Organization 2010). This does not mean that *Y. pestis* no longer circulates in rat populations or plague cases among people and animals cannot reoccur in this region, and to some degree it undoubtedly reflects the passive surveillance of plague in rodents and humans in this part of the world. Another explanation, although speculative, relates to the potentially better adaptation *Y. pestis* strains have to native rodent populations or possibly to other components of the parasitic system that allow it to survive in a cryptic form.

In the Indian subcontinent, the commensal species shown to be important reservoirs of plague include *R. rattus, R. norvegicus,* and *Bandicota bengalensis.* Despite many reports of finding dead rats in India, only few rats of the *R. rattus* species were confirmed as serologically plague-positive during recent years that could be also taken as evidence that the relevant rat populations have remained highly susceptible to plague rather than a lack of involvement of these animals in local plague cycles. Plague is endemic over the large territory of Myanmar, but the most recent data were obtained in the 1970s. The highest rates for serological positivity in Rangoon (Yangon) were observed in *B. bengalensis* (15.4%), *R. norvegicus* (11.1%), and *R. rattus* (7.6%) (Brooks et al. 1977). In Indonesia, plague activity was reported in the Boyolali area of central Java in the late 1970s with the detection of *Y. pestis* in two rat species, *R. rattus diardii* and *R. exulans ephippium* (Kusharyono et al. 1980).

Many more reports of plague activity exist in Vietnam, involving primarily *R. rattus* and *R. norvegicus,* along with the bandicoot rat (*B. bengalensis*) and the shrew (*Suncus murinus*) (Suntsov et al. 1997). There are diverse plague foci in China as well, but for our review it is important to note specifically the focus in Yunnan (southwestern province of China), where *Y. pestis* infects primarily the commensal rat *R. tanezumi flavipectus* (identified as *R. flavipectus* in the old Chinese literature). Analysis of *Y. pestis* strains isolated from rats of Yunnan showed that strains isolated from geographically distinct foci were genetically divergent (Zhang et al. 2009). Although Yunnan is considered the site of origin for the third plague pandemic, such diversification of *Y. pestis* to local conditions was not reported from regions with introduced plague (Gage and Kosoy 2005).

Bacteria belonging to the genus *Bartonella* represent another group of pathogens hosted by many rat species and presumably transmitted by rat fleas. Several studies of *Bartonella* species and genotypes detected in *Rattus* rats

demonstrated that most of them are clustered into a defined phylogenetic lineage that can be subdivided further into a number of subclusters (Kosoy et al. 2012). The first evidence that *Bartonella* strains belonging to this lineage in fact originated from Asia was provided by a discovery of the diversity of such bacteria in rats in southwestern China (Ying et al. 2002). Following investigations of rodents from Thailand, Laos, Cambodia, Taiwan, and Vietnam revealed high prevalence of bacteria belonging to the genus *Bartonella* in many rats species (Bai et al. 2009; Hsieh et al. 2010; Jiyipong et al. 2012; Hoang at al., current issue). The proportion of culture-positive samples has greatly varied by rat species from 3.2% in *R. exulans* to 86.4% in *R. norvegicus* (Bai et al. 2009). Genera of *Bartonella* and *Brucella* are sister taxa, thus it also is interesting to note that new *Brucella* species were isolated from native rats *R. fuscipes* captured in North Queensland, Australia (Tiller et al. 2010).

Rats are well known to be one of the most important reservoirs and sources of transmission for leptospirosis. People usually become infected with these spirochetes through exposure to water contaminated by the urine of infected animals, mainly rats. During a survey of leptospiral antibodies conducted among samples collected from 1164 rodents from the northeastern, northern, central, and southern regions of Thailand it was found that the following rats were seropositive: *R. exulans* (6.9%), *R. rattus* (5.0%), and *R. norvegicus* (2.6%) (Wangroongsarb et al. 2002). The predominant serovars of *Leptospira* in *R. exulans* and *R. norvegicus* in this study were *pyrogenes*, whereas those of *R. rattus* were *sejroe*. Another serological investigation of rodents in Thailand resulted in the detection of Leptospira antibodies to serovars *pyrogenes* (39.1%), *sejroe* (19.1%), *bataviae* (10.0%), *pomona* (6.4%), *autumnalis* (5.5%), *copenhageni* (3.6%), and *javanica* (3.6%) (Kositanont et al. 2003). The seropositivity rates by animal species were 7.9% in *R. norvegicus*, 6.8% in *R. exulans*, and 4.7% in *R. rattus*. An investigation of rodents for *Leptospira* species conducted in two localities of Cambodia demonstrated that prevalence of leptospirosis in rodents was higher in low-slope locations, corresponding to rain-fed paddy fields, especially in the rainy season (Ivanova et al. 2012). Rats of *R. exulans* inhabiting households showed significantly lower levels of infections, whereas rodents living in and near forests showed higher levels of infection. A survey conducted in the Philippines reported that 92% of rat serum samples were positive for anti-leptospira antibodies (Villanueva et al. 2010). The authors of this study observed that the rats obtained in Manila were mostly *R. norvegicus*, whereas those obtained in Laguna were mostly *R. tanezumi*.

Salmonella species were reported in *Rattus* rats in Southeast Asia. Among 600 rats of the species *R. argentiventer* captured in rice fields of five provinces in the Mekong delta, Vietnam, 116 (19.3%) were *Salmonella* positive (Phan et al. 2005). Among the 116 *Salmonella* isolates reported, nine serotypes were identified, with the most common being *S. london, S. weltevreden,* and *S. derby*. In Ipoh, Malaysia, two of eight bacteriologically examined *R. rattus* rats were found to be positive (Joseph et al. 1984).

The presence of *Orientia tsutsugamushi*, the agent of scrub typhus, was reported in 10 of 22 species of small mammals investigated in eight provinces of Thailand (Coleman et al. 2003). Prevalence of the infection among rodents varied from 1% in Nonthaburi to 18% in Chiangrai. The highest rates of infection were observed in *R. bukit* (25%), *R. rattus* (23%), and *R. argentiventer* (22%), whereas only two of 146 (1%) *R. exulans* were found positive. A study conducted by Lerdthusnee et al. (2008) suggested that areas of greatest risk for scrub typhus occur in the ecotones of scrub areas where rats of the *R. rattus* complex are abundant. The newly invaded localities of Taiwan demonstrated the potential contribution of *R. exulans* to the spread of *O. tsutsugamushi* (Kuo et al. 2011).

Results from a recent investigation of rodent-borne diseases in Thailand conducted by Herbreteau et al. (2012) suggest that rats of some species (*e.g.*, *R. andamanensis, R. argentiventer,* and *R. norvegicus*) harbored more pathogens than was expected on the basis of regression predictive models. This investigation also stressed that caution should be taken in nonflooded lands and forests, whereas surveys focused primarily on paddy rice fields and households.

Zoonoses associated with invasive Rattus rats

The invasion of rats into urban ecosystems and their establishment in these sites can have significant implications for human health. Nowak (1999) noted that over the last 10 centuries, rat-borne diseases may have taken more human lives than all of the wars ever fought. The best-known example of the introduction of new zoonotic disease by rats is plague pandemics. In the mid-14th century, one-third of the human population in Europe perished from plague, and black rats are widely blamed as the main source of this pandemic, although their contribution was likely to be minimal in the British Isles and northern Europe where these rats were rare or absent at the time and transmission more likely occurred through the bites of infectious human fleas rather than rat fleas (Ell 1980). The third and last pandemic of plague started in China and spread around the world aboard rat-infested ships at the beginning of 20th century.

As a particular example of pandemic spread of plague by rats and its subsequent introduction and establishment, plague first was imported into San Francisco and several other US seaports in 1899 (Gage and Kosoy 2005). At that time, the level of infestation of ocean-going ships with rats was very high. From 1925 to 1927, 50% of ships entering the port of New York were rat infested (Caten and Kartman 1968). During investigations of the plague epidemic in San Francisco in 1907, >1% of collected rats were infected with *Y. pestis* (Caten and Kartman 1968).

Since the last pandemic, plague's geographic range has expanded greatly, posing new threats in previously unaffected regions, including the western United States, portions of South America, southern Africa, and Madagascar (Gage and Kosoy 2005). It is important to note that all strains of *Y. pestis* in the continents where it was introduced during the third pandemic belong to the Orientalis biotype, which is specific to *Rattus* rats in Asia. Not surprisingly these strains are less diverse than those found in Asia because they arose from a limited number of strains that arrived with rats on ships (Gage and Kosoy 2005).

Acknowledging the low diversity of *Y. pestis* strains circulating in rat populations outside South and Southeast Asia, it would be important to list some findings of other *Yersinia* species in rats that have not been reported within the natural range of *Rattus* rats. A survey of Norway rats in several cities

of the country of Georgia resulted in culturing of 17 strains of *Yersinia pseudotuberculosis* (Nersesov et al. 1997). A strain of *Y. pseudotuberculosis* was isolated from a Norway rat from Fuchu region in Japan (Iinuma et al. 1992). Both *Y. pseudotuberculosis* and *Y. enterocolitica* strains were isolated from Norway and black rats in Czech Republic (Aldová et al. 1977).

Bacteria related to *Bartonella elizabethae* emerged from Asia with *Rattus* rats due to human activity before becoming common and widespread in urban and rural environments around the world (Childs et al. 1999, Ellis et al. 1999). Isolates from *R. norvegicus* in New Orleans and Baltimore were identical to one of the strains obtained from *R. tanezumi flavopictus* captured in Yunnan, China (Ying et al. 2002). In another study, Bai et al. (2007) provided clear evidence that *Bartonella* genotypes identified at high prevalence among *B. bengalensis* and *R. rattus* in Dhaka, Bangladesh, were identical to sequences of cultures from *Rattus* rats in France, Portugal, and the United States. All *Bartonella* strains identified in black rats captured in Tel Aviv, Israel were identical to the strain found previously in *R. rattus* in Dhaka, Bangladesh (Harrus et al. 2009).

The *Bartonella* isolates from *R. norvegicus* in New Orleans, Los Angeles, Baltimore (all United States), and Peru, and from *R. rattus* from Portugal are phylogenetically close to strains from Bangladesh, Indonesia, southern China, Thailand, and Vietnam (Kosoy et al. 2012). Interestingly, not all *Rattus* rat populations within US cities carry bartonellae. Although populations of *Rattus* rats are highly infected with *Bartonella* strains in Atlanta, Baltimore, New Orleans, Oakland, and Los Angeles, all examined rats were *Bartonella*-free in Denver, Chicago, Los Vegas, New York, and Phoenix (Ellis et al. 1999, Kosoy, unpublished). We can only speculate about factors regulating the invasion of *Bartonella* infection into some cities. The two most reasonable explanations relate to: (1) The "founder effect," when a small population of rats relocated to a new location was not infected or when bacterial population was not large enough to maintain its circulation, and (2) the presence of an appropriate flea vector, such as *Xenopsylla cheopis*, the oriental rat flea, the distribution of which is probably determined by climatic factors in some rat populations in the United States.

A genetic analysis of *Bartonella* strains obtained from rats from 17 countries has demonstrated that this bacterial complex evolved and diversified in Southeast Asia before being disseminated by *R. rattus* and *R. norvegicus* to other parts of the globe. This analysis also suggested that there have been numerous dispersal events within Asia and introductions from Asia to other regions, with the apparent global dispersal of six major clades containing Southeast Asian isolates (Hayman et al. 2013). These results are in interesting concordance with the conclusion made by Aplin et al. (2011) that commensalism in black rats arose multiple times.

Leptospiral infections are common in *Rattus* rats from many parts of the world and the level of prevalence of this infection in rats can be very high (Gratz 2006). Among the examples, we can list observations indicating that *Leptospira* was found in 45% of Norway rats in the Ripa Grande–San Michele Port in Rome, Italy (Pezzella et al. 2004) and in 16.9% of brain tissues and 27.1% of kidney tissues of Norway rats collected along the Black Sea coast of Turkey (Sunbul et al. 2001). Two surveys conducted to identify *Leptospira interrogans* in Norway rats from an urban slum in Salvador, Brazil revealed a very high prevalence of the infection; *Leptospira* was isolated from kidneys or urine in >80% of rats (de Faria et al. 2008, Costa at al. 2014). A recent investigation of ecology of *L. interrogans* in Norway rats in an inner-city neighborhood of Vancouver, Canada, demonstrated that the prevalence of this infection varied remarkably (from 0% to 66.7%) between city blocks (Himsworth et al. 2013b).

Rattus rats are thought to be competent hosts for several *Borrelia* species and may contribute the ecology of urban Lyme disease foci, particularly in Eurasia. Rats apparently introduced borreliosis on the island of Madeira, Portugal, with up to 50% of tick-infested *R. rattus* being infected with *Borrelia* spirochetes (Matuschka et al. 1996). Another example of possible introduction of tick-borne borreliosis by rats was observed on Monhegan Island in Maine, although prevalence of the infection on this island was not reported (Smith et al. 1993). This phenomenon was not observed or considered within the Asian range of the distribution of rats.

Rat bite fever is another bacterial zoonosis for which two bacterial species carried by rats have been identified: *Streptobacillus moniliformis* and *Spirillum minus* (Elliott 2007, Gaastra et al. 2009, Meerburg et al. 2009, Himsworth et al. 2013a). Reports of *Salmonella* infection in rats are more frequently reported outside Southeast Asia, with most positive rats being found around farms. Among 35 rats of *R. norvegicus* trapped in four egg-producing poultry farms in Germany, five strains of *S. gallinarum* and one strain of *Salmonella* subgroup II were isolated from the intestinal content of six rats (Badi et al. 1992). *Salmonella* infection was detected in 8% of Norway rats from the West Midlands, UK (Hilton et al. 2002), and 12 different *Salmonella* species were found in the intestine of 56 rats of both *R. rattus* and *R. norvegicus* in Cyprus (Antoniou et al. 2010).

An investigation of chicken layer farms in eastern Japan demonstrated an involvement of *R. rattus* rats in the epidemiology of *Salmonella* in these areas (Lapuz et al. 2008). A total of 113 (13.3%) and 158 (18.6%) out of 851 rats examined were positive for *S. enteritidis* and *S. infantis*, respectively (Lapuz et al. 2008). *S. enterica typhimurium* was isolated from the intestinal contents of *R. rattus* and *R. norvegicus* rats captured in Yokohama City, Japan (Yokoyama et al. 2007). A recent experimental study of transmission and maintenance of *Salmonella* contamination cycles in naturally infected black rats from farms in Japan indicated that wild roof rats could persistently carry *Salmonella* and contaminate commercial poultry facilities through intermittent fecal shedding (Umali et al. 2012). The examination of fecal samples from 204 rats trapped across Trinidad found four rats (2.0%) positive for *Salmonella* species by isolation (Nkogwe et al. 2011).

Rickettsia typhi is present in rat populations worldwide and is transmitted among rats and from rats to people by fleas, particularly *X. cheopis* (Civen and Ngo 2008, Himsworth et al. 2013b). In rat fleas collected from *R. norvegicus* in Los Angeles, California, DNA of two rickettsial species (*R. typhi* and *R. felis*) were detected (Abramowicz et al. 2011). *R. felis* was also identified in cat fleas (*Ctenocephalides felis*) parasitizing rats in Cyprus (Psaroulaki et al. 2006).

Rats are the primary reservoir for Seoul hantavirus, one of several rodent-associated hantaviruses that cause

hemorrhagic fever with renal syndrome in people. Unlike other hantaviruses, Seoul hantavirus has been found to have a worldwide geographic range, stretching from Asia to Africa, Europe, and both Americas (Childs et al. 1987, Childs et al. 1991, Arikawa et al. 2001, Kariwa et al. 2007). Genetic analysis of 136 strains of Seoul viruses shown that all non-Chinese strains and most of the Chinese variants fell into one phylogroup (A), whereas the Chinese strains originating from mountainous areas were clustered into three other distinct groups (Lin et al. 2012). The authors of this study estimated that this worldwide-distributed phylogroup in fact has arisen only within the last several centuries and all non-Chinese variants appeared to be directly originated from China. Remarkably, the authors proposed that their data support the notion that Norway rats originated in China and then migrated to Europe and subsequently to the Americas in the 18th century (Lin et al. 2012). Another analysis revealed that the Seoul virus strain found in Norway rats captured in Belgium was related most closely to strains from France, Indonesia, Japan, Singapore, Cambodia (those associated with *R. norvegicus*), and Vietnam (Plyusnina et al. 2012).

Recent studies have shown that rats can carry hepatitis E virus (HEV) worldwide (Lack et al. 2012). Antibodies against HEV were found in *R. norvegicus* and *R. rattus* rats across the United States (Kabrane-Lazizi et al. 1999, Favorov et al. 2000, Purcell et al. 2011). In Japan, HEV is reported in 32% of Norway rats and 13% of black rats (Hirano et al. 2003). A broad-spectrum RT-PCR resulted in the detection of a novel HEV in feces from Norway rats from Germany (Johne et al. 2012).

Discussion

Understanding the dissemination of potential pathogens and the role of specific rat hosts in the dissemination process is crucial if control measures are to be implemented to mitigate the introduction of new infections into new environments and hosts (Hayman et al. 2013). One of the points highlighted in this review is the necessity to discriminate the roles played by rats as pathogen reservoirs within the land of their original diversification and in regions where only one or few rat species were introduced during the recent human history. While rat populations distributed within the native range in Asia are self-sustaining, the rat populations introduced to other continents depend on continuous immigration of rats from established natural habitats. Host–pathogen systems established within aboriginal populations of rats can serve as an origin of many rat-borne pathogen, which can be introduced to new regions and continents.

Populations of rats established in big metropolitan areas within the range of natural origin and diversification of the genus *Rattus* represent another element that requires specific attention. Rat communities in cities such as Bangkok, Ho Chi Minh City, Yangon, and others might not restricted to only two commensal species of rats, but at the same time the composition of such communities can be expected to have a reduced number of species compared to rat communities observed in fields or natural habitats. The reduced rat community composition can further determine the diversity of infectious agents maintained within rat populations in large Asian cities. A similar situation was observed during an investigation of *Bartonella* infections in rats from Dhaka,

Bangladesh (Bai et al. 2007), with the diversity of *Bartonella* species much higher than in American and European cities (Gundi et al. 2012), but much lower than was observed in natural and agricultural settings in Thailand (Bai et al. 2009). Such communities can play a role in the selection of certain microbial species and strains that could be further distributed by rats to other continents. Multiple geographic origins of commensalism of black rats, as demonstrated by Aplin et al. (2011), is likely to have implications for the distribution and dispersal of rat-borne pathogens. These findings indicate that rats originating from different geographic regions are likely to have acquired distinctive suites of pathogens, leading to a higher than average pathogen diversity among rats of this taxonomic group.

As contact increases between rats and humans, the risks that humans will be exposed to rat-associated disease agents also is likely to increase. Rats can play another indirect role in increasing human disease risks by providing the vectors of these diseases with infectious blood meals, as well as the blood meals required to complete their development and reproduction successfully. It can be expected that human risks of exposure to rat-associated pathogens transmitted by vectors will increase as vector populations also increase, particularly when the vector populations undergoing expansion occur in areas heavily used by humans.

Urban development clearly creates dramatic changes in rodent communities. Typically, as the level of urbanization increases, so will the intensity of changes in the rat communities living within a city's limits. Commonalities found between the geographic areas analyzed include a dominance of Norway rats, which have historically colonized urban ecosystems on a global basis. Some differences in rat ecology among Africa, Europe, and Americas can be explained partially by the fact that black and Norway rats were introduced into the New World much later than to Africa, northern Asia, and Europe. Various aspects of the biology of rats, such as their enormous reproductive potential, feeding behavior, and adaptations to city environment, contribute to the failure of many rat control programs, but also demonstrate the necessity of investigating many aspects of the biology and ecology of these animals to identify factors affecting prevalence and diversity of rat pathogens.

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