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# *Bartonella* Bacteria in Urban Rats: A Movement From the Jungles of Southeast Asia to Metropoles Around the Globe

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Despite the widespread recognition of the risks of disease transmission associated with international trade in domestic animals and movement of exotic animals, less is known about the role of rats in carrying pathogens between continents. The genus *Bartonella*, a highly prevalent and extremely diverse group of bacteria, includes species that are excellent sentinel organisms for evaluating the transoceanic and intra-continental movement of the pathogens carried by rats of the genus *Rattus*. The patterns of spatial distribution, occurrence, and genetic diversity of *Bartonella* species infecting rats and their arthropod ectoparasites depend on the geographic locations within metropolitan areas of the Americas, Africa, Asia, and Europe. One of the points addressed in this review is a comparison of the diversity of *Bartonella* species carried by rats in their original habitats in Southeast Asia and in the cities occupied by rats recently. The invasion of *Rattus* rats into new urban territories create significant risk for human health.

Keywords: bacteria, *Bartonella*, invasive species, movement ecology, rats, *Rattus,* urban zoonoses

## INTRODUCTION

### Commensal Rats and Infectious Agents Carried by Rats in Urban Areas

People create dramatically new environments. This is especially evident in urban settings, which may favor some mammalian species that might become "synanthropic." A number of factors contribute to the public health threat presented by synanthropic animals. According to the calculations provided by McFarlane et al. (2012), human cases of zoonotic infectious diseases caused by synanthropic animals happen 15 times more frequently compared to wild animals. Urban territories may provide suitable conditions for reproduction of arthropods serving as vectors for vector-borne diseases because of some specific environmental changes, such as attenuation of the temperature range and humidity (Shochat et al., 2006; Bradley and Altizer, 2007). The environments in cities have higher land surface temperature compared to surrounding natural habitats, so-called "urban heat islands" (Grimmond, 2007). The urban heat islands represent an example of the numerous potential environmental changes caused by urbanization that can affect distribution and prevalence of zoonotic and vector-borne diseases in cities and suburban areas.

Urban development changes rodent communities dramatically. Among mammalian species adapted to life in cities, certain species of the genus *Rattus* play especially evident and important roles because of their close association with human activities (Battersby et al., 2008). Living in close proximity to human houses and having high exploratory activity, rats frequently encounter people

in cities and small towns. An extensive questionnaire conducted among residents of Baltimore, Maryland ($N = 1,363$) showed 64% of respondents seen rats on streets and alleys, 6% of residents noticed rats inside houses, and 1.2% of residents reported bites by rats (Childs et al., 1991). Microclimatic conditions in cities can affect development of the fleas found on rats (Krasnov et al., 2001) and, therefore, influence the transmission of some vector-borne bacteria. In addition, the urban environment affect availability of resources, specifically food, for rodents (Cevidanes et al., 2017), promoting higher concentration, and density of rats that in turn can facilitate density-dependent transmission of various zoonotic pathogens carried by these animals.

### *Rattus* Rats as Invasive Species

Over 60 species belong to the genus *Rattus* (Musser and Carlton, 2005). Of these, only three species, the Norway rat (*R. norvegicus*), the black (roof) rat (*R. rattus*), and the Oriental house rat (*R. tanezumi*), have dispersed around the globe and colonized urban settings in most countries, and the range of the fourth invasive species, the Pacific rat (*R. exulans*), is limited to tropical Asia-Pacific areas (Kosoy et al., 2015). Rats of the genus *Rattus* became close neighbors to humans at a very early stage of human civilization. However, during the last century, distribution of rats has dramatically expanded to new geographic regions, and the rat invasion of the cities in different countries led to dramatic challenges (Khlyap et al., 2012). Importantly, the process of rat invasion from the region of their origin to other places continues. In the past, the distribution of rats depended mainly on cart traffic and ship routes, the latter being the leading means of crossing the oceans. In the modern world, the role of railroad, truck, and airplane in transporting rats is growing (Khlyap et al., 2016).

Application of molecular tools for barcoding animal species has challenged taxonomic identification of rats. Analysis of mitochondrial DNA of rats, previously identified as *R. rattus*, demonstrated the complex of separate species within the *R. rattus*-complex (Aplin et al., 2011). A recent survey of rats belonging to this complex collected across their global range and conducted by Aplin et al. (2011) allowed discriminating several genetic lineages within the black rat complex. Their investigations demonstrated that a diversification of these lineages happened in the early Middle Pleistocene within South Asia, southern and northern Indochina, and in the region close to Himalayas. These authors also identified two other currently recognized *Rattus* species as potential derivatives of a paraphyletic *R. rattus* (Aplin et al., 2011). Interestingly, their results demonstrated that three of four phylogenetic lineages within the *R. rattus* complex happened in prehistoric times. The distribution of particular genotypes matches historically documented patterns of human dispersal and trade. Based on this analysis, Aplin et al. (2011) concluded that commensalism arose multiple times in black rats and in widely separated geographic regions. Importantly, such a regionalism may account for spreading of pathogens associated with *R. rattus* (Aplin et al., 2011). Examining multiple samples of this species from different parts of the world, Aplin et al. (2011) reported ecologically and morphologically similar lineages of rats with distinct histories

of invasion to other geographic regions. One of the lineages, designated as *R. rattus* I, has dispersed around the globe and exists alongside humans, while rats of another lineage (designated as *R. rattus* IV) have not spread beyond Bornean Malaysia, Indonesia, and the Philippines (Aplin et al., 2011; Lack et al., 2012).

### Ecology of Rats in Urban Settings

Rodents in urban environments often show specific adaptations (Khlyap et al., 2012, 2016). Sometimes it may be challenging to define urban areas using ecological perspectives, especially when suburban areas are considered. It is also important to remember that ecological conditions in urban areas vary among countries. Specifically, the distribution of rats may greatly contrast between countries in the South and Southeast Asia where *Rattus* rats occupy practically all habitats and Europe and North America where rats are commonly restricted to city limits (Khlyap et al., 2012). Himsworth et al. (2014a) demonstrated that population density of urban rats varied significantly over short distances. Populations of rats are often largest in high-density residential areas (Khlyap et al., 2016).

Some big cities are particularly favorable places for urban rats because of their aging infrastructure, high moisture, and poverty rates. Easterbrook et al. (2005) estimated an outdoor Norway rat population in residential neighborhoods of Baltimore at around 48,000 individuals. Though these rats can disperse over long distances, investigations of marked animals demonstrated that they tend to live within small individual territories, sometimes not extending beyond a single building. Genetic analysis using microsatellite markers showed that rats demonstrate strong site fidelity (Gardner-Santana et al., 2009). However, there was evidence of infrequent, long-distance movements within the city indicated by capturing some rats 2–11.5 km away from the locations assigned based on the genetic analysis (Gardner-Santana et al., 2009). Among factors influencing rat presence and abundance, Himsworth et al. (2014b) suggested building condition and specific land use. In industrialized countries, rats commonly occupy sewer system of cities (Lund, 2015).

### Pathogens and Movement Ecology of Animals

As invasive animal species rapidly become more prevalent in many parts of the world, relations between previously disconnected animal populations can promote the spread of pathogens carried by these animals (Crowl et al., 2008). On the other side of the coin, infectious agents detected in invasive animals may illustrate the "tracks" left during the spreading of their mammalian hosts. Genetic studies of animals provide irreplaceable tools for deciphering routes of invasion, but characterization of accompanying micro- and macro-parasites can provide additional support for such a goal. An assessment of risk of infectious diseases introduced by invasive animal hosts highlights importance of such information. Nevertheless, the selection of specific microbial species that can serve as markers for measuring the movement of animal hosts is not a trivial task. Clearly, the selected microorganisms should be prevalent in animal populations, but not too much so otherwise

the omnipresent infections cannot be good indicators of animal movement. Secondly, these microbial species should be highly specific to their animal hosts to reflect the long history of coevolution between animals and microbes. Finally, their genetic variability should be high enough to reflect the routes of dispersion of the animals hosting these microbial agents.

## *Bartonella* Species as Sentinel Organisms

*Bartonella* species comprise Gram-negative bacteria parasitizing mammalian erythrocytes and endothelial cells (Birtles, 2005). Infecting a wide variety of hosts, *Bartonella* may present in these animals as a subclinical and persistent bacteremia (Schülein et al., 2001). *Bartonella* species are an extremely diverse group of bacteria infecting various mammalian species, especially rodents (Kosoy et al., 2018), that also spans the symbiont-pathogen continuum (Segers et al., 2017). Moreover, these "vertebrate host-arthropod vector-bartonellae" tripartite systems appear to be globally distributed, phylogenetically complex, and provide a popular tool for ecological comparative analyses (Buffet et al., 2013; Brook et al., 2017; Kosoy et al., 2018). The rodent habitat represents an important factor for the transmission cycle of *Bartonella* in nature (Gutiérrez et al., 2015). Analyses of genetic diversity of *Bartonella* species based on sequencing approaches can be informative for comparing bacterial prevalence and diversity in rat populations across various spatial and temporal scales. However, the effect of urbanization on *Bartonella* prevalence and diversity in rat populations has never been sufficiently analyzed. The objectives of ecological studies determine the level of discrimination between compared strains or genotypes. In most situations, the investigators report discrimination of bacteria at the species level or compare sequence identity with a specific *Bartonella* type strain (Kosoy et al., 2018). In the absence of sequence data, reporting PCR-positive samples alone may overestimate bartonella prevalence in such ecological studies. Therefore, Kosoy et al. (2018) advocated that studies of prevalence of *Bartonella* should adhere to the standard of reporting only sequence-positive samples.

## METHODS

We thoroughly analyzed published literature concerning identification of *Bartonella* species in rats. For this review, we examine prevalence and diversity of *Bartonella* in rats belonging to the genus *Rattus*. Only in few instances, strictly for comparative purposes, we provided data on other mammalian species co-habiting with rats of *Rattus*. We conducted a literature search by various search engines, including PubMed, Scopus, BioOne, Medline, ScienceResearch, Google Scholar, OVID Medicine, and Web of Science. In the search, we used the following keywords: "*Bartonella* AND Rats," "*Bartonella* AND Rodents," "Bacteria AND Rattus," "Rat-Borne Diseases," "Rodent-Borne-Diseases," "Urban Bacterial Diseases," "Urban Rodents AND Pathogens," and their combinations. We analyzed data from serological, molecular, and bacteriological detection of *Bartonella* in rats. Analyzing data obtained from different

assays, we have given a priority to the results that included an identification of *Bartonella* species and genotypes.
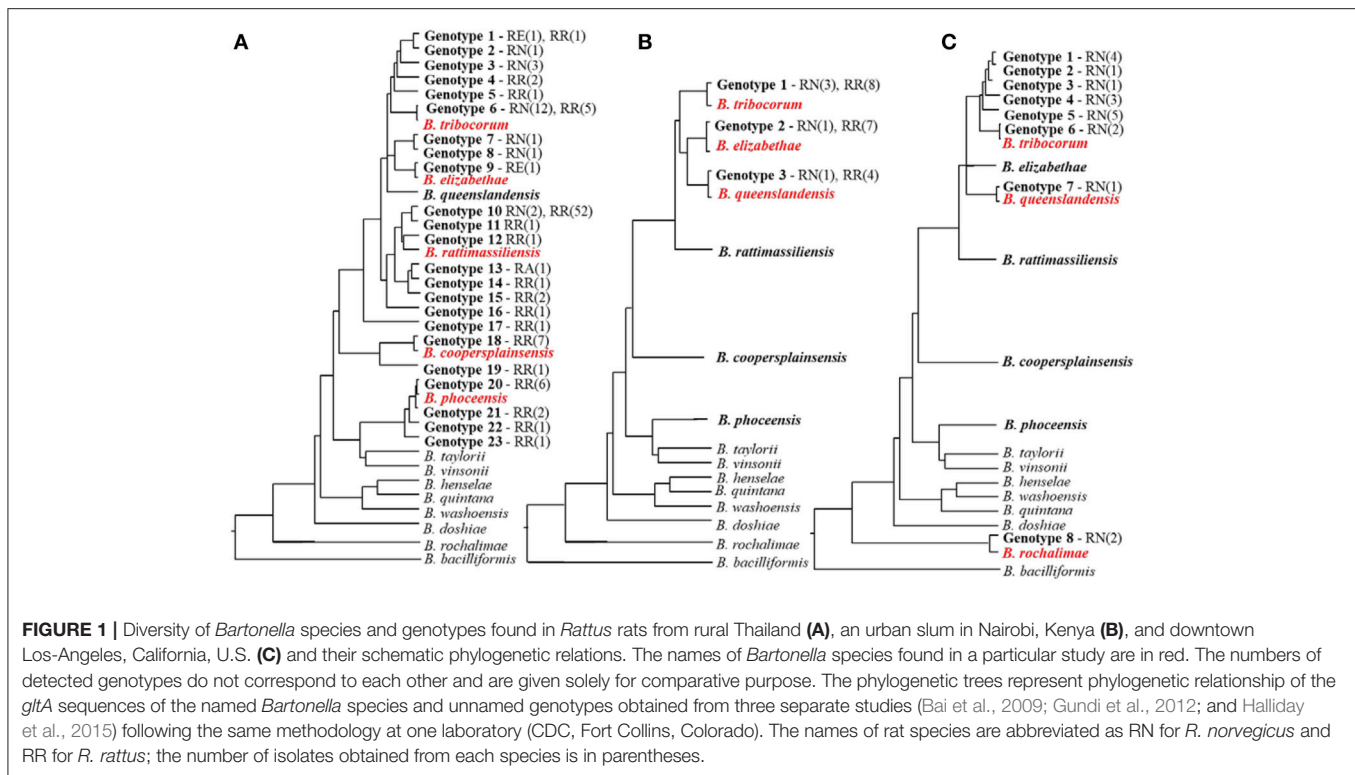
## RESULTS AND DISCUSSION

### *Rattus* Rat-Adapted *Bartonella* Species

Overall, *Bartonella* species and genotypes found in *Rattus* rats are highly specific for rodents belonging to this genus (Kosoy et al., 2012; Buffet et al., 2013). Many rat-adapted *Bartonella* species have a worldwide distribution (Buffet et al., 2013; Hayman et al., 2013). The most prevalent *Bartonella* species, such as *B. elizabethae, B. tribocorum, B. rattimassiliensis,* and *B. queenslandensis*, are phylogenetically clustered in a well-demarcated lineage (**Figure 1**). Originally, all these species were described based on the sequence distances between the species for several housekeeping gene markers (Heller et al., 1998; Gundi et al., 2004, 2009). However, the question remains how to recognize the status of strains that occupy intermediate positions between the described *Bartonella* species. This question was not unique for *Bartonella* strains found in rats. To solve this problem, Kosoy et al. (2012) proposed to use a combination of genetic markers and ecological parameters for delineation of species complexes that include closely related genospecies, named strains, and unique genotypes carried by ecologically similar mammalian hosts. Following this proposal, the *B. elizabethae* complex *sensu lato* represents a large group of species and strains associated with the Old World rats (Kosoy et al., 2012; Buffet et al., 2013). A well-characterized, but unnamed strain "Tel-Aviv" also belongs to the *B.elizabethae* species complex (Harrus et al., 2009).

In addition, three more *Bartonella* species (*B. phoceensis, B. coopersplainsensis,* and *B. rochalimae*) infect *Rattus* rats worldwide (Buffet et al., 2013). Of these three species the first two (*B. phoceensis* and *B. coopersplainsensis*) are typical for *Rattus* rats, while *B. rochalimae* is an ubiquitous bacterial species detected in a wide range of mammals, and is especially common in wild carnivores and their fleas (Bai et al., 2016). *B. phoceensis* is a bacterium originally isolated from the blood of the rats of *R. norvegicus* from the city of Marseille, France (Gundi et al., 2004). *Bartonella coopersplainsensis* was isolated from the blood of a Cape York rat (*Rattus leucopus*) in Australia (Gundi et al., 2009).

Although stressing the high level of host-specificity for *Rattus* among *B. elizabethae*-like species, we have to admit that these species can also infect other mammals, e.g., *Bandicota* rats and Asian house shrews (*Suncus murinus)* from Bangladesh and Nepal (Bai et al., 2007; Gundi et al., 2010); Brush-furred rats (*Lophuromys* sp.) from Tanzania (Gundi et al., 2012); Namaqua rock rats (*Aethomys namaquensis*) and Bushveld gerbils (*Tatera leucogaster*) from South Africa (Pretorius et al., 2004); and Cairo spiny mice (*Acomys cahirinus*) from Israel (Morick et al., 2009). The unexpectedly broad host range of *B. elizabethae*-like species might be explained by the commonality of fleas that infest various rodent species. Thus, *B. elizabethae, B. tribocorum,* and *B. queenslandensis* DNA have been detected in *Xenopsylla* fleas collected not only from *Rattus* rats, but also from gerbils, *Mus*

**FIGURE 1** | Diversity of *Bartonella* species and genotypes found in *Rattus* rats from rural Thailand **(A)**, an urban slum in Nairobi, Kenya **(B)**, and downtown Los-Angeles, California, U.S. **(C)** and their schematic phylogenetic relations. The names of *Bartonella* species found in a particular study are in red. The numbers of detected genotypes do not correspond to each other and are given solely for comparative purpose. The phylogenetic trees represent phylogenetic relationship of the *gltA* sequences of the named *Bartonella* species and unnamed genotypes obtained from three separate studies (Bai et al., 2009; Gundi et al., 2012; and Halliday et al., 2015) following the same methodology at one laboratory (CDC, Fort Collins, Colorado). The names of rat species are abbreviated as RN for *R. norvegicus* and RR for *R. rattus*; the number of isolates obtained from each species is in parentheses.

mice, and shrews worldwide (Tsai et al., 2010; Billeter et al., 2011; Bitam et al., 2012).

# BARTONELLA INFECTIONS IN URBAN POPULATIONS OF RATS

## Asia
### Bangladesh
Prevalence of *Bartonella* bacteria in *R. rattus* collected in Kamalapur, a low socioeconomic residential area of Dhaka, was 32.3% (32/99) (Bai et al., 2007). This rate was lower than that observed in two other co-habiting mammalian species: lesser bandicoot rats *Bandicota bengalensis* (63.2%) and house shrews *Suncus murinus* (42.9%). Bacteriological observations of small mammals captured in Dhaka indicated a diverse assemblage of genetic variants of *Bartonella* (Bai et al., 2007). The isolates obtained from *R. rattus* belonged to three groups, none of which aligned closely with previously described *Bartonella* species, whereas isolates obtained from lesser bandicoot rats *Bandicota bengalensis* were much closer or identical to *B. elizabethae* or *B. tribocorum*. Importantly, bartonellae isolated from two black rats captured in Dhaka were identical by the *gltA* gene to the isolates previously found in rats from Porto Santo Island, Portugal and New Orleans, Louisiana, USA. Later, multiple isolates similar to this type were found in *R. rattus* rats from Tel Aviv, Israel (Harrus et al., 2009).

### China
The first study, which demonstrated a high prevalence of *Bartonella* in *Rattus* rats in Asian cities was conducted in Yunnan

Province, the southwestern part of the mainland China (Ying et al., 2002). Culturing blood of rats from three cities (Yiliang, Baoshan, and Jianchuan) revealed 41.4% (24/58) *Bartonella*-positive animals among *R. tanezumi* subsp. *flavipectus* and 42.9% (3/7) among *R. norvegicus*. Rats in every investigated city along the coast of Fujian Province were infected by *Bartonella* species: 9.3% in Ningde, 9.5% in Fuzhou, 9.4% in Putian, 28.2% in Quanzhou, 17.4% in Xiamen, and 13.3% in Zhangzhou (Ye et al., 2009). Despite considerable heterogeneity and varying degrees of relatedness to *B. elizabethae*, all isolates from urban rats belonged to the same phylogenetic lineage. Isolates from rats from Fujian coastal regions belonged to three species: *B. elizabethae, B. queenslandensis,* and *B. tribocorum* (Ye et al., 2009).

### Indonesia
Microscopic examination of blood smears of rodents from the Greater Jakarta area revealed 6.0% (13/218) *Bartonella*-positive rodents. Of 79 *R. tanezumi,* 49 *R. norvegicus,* and one *R. exulans* captured in three study sites (Bambu Apus, Penjaringan Harbor, and Ragunan Zoo), seven *R. tanezumi* rats and one *R. norvegicus* rat were positive for *Bartonella* species (Winoto et al., 2005). Three *Bartonella* species (*B. phoceensis, B. rattimassiliensis,* and *B. elizabethae*) were found in rats (*R. tanezumi* and *R. norvegicus*) from Jakarta (Winoto et al., 2005).

### Japan
Interesting results were reported after investigation of rats collected in two cities and four suburban areas of Japan (Inoue et al., 2008). *Bartonella* isolates were obtained from *R. rattus* from suburban areas in Nakanoshima Island (2/4), Yoroshima Island (10/17), Tokunoshima Island (4/12), and Main Island (2/6). At

the same time, all *R. rattus* rats captured in cities of Yokohama ($n = 255$) and Shimoda ($n = 3$) were free of *Bartonella*. All *R. norvegicus* from the cities ($n = 85$) and suburban areas ($n = 20$) were negative for *Bartonella* (Inoue et al., 2008). Investigating *R. rattus* rats captured from several places in Japan, Inoue et al. (2008) identified *B. tribocorum, B. elizabethae, B. phoceensis,* and *B. rattimassiliensis* based on two genetic markers.

## Lao P.D.R

A molecular survey of rats was conducted in three urban areas of Laos (Angelakis et al., 2009). *Bartonella* DNA was found in 10.1% of *R. rattus* ($n = 79$) and 30.4% of *R. exulans* ($n = 23$) from Vientiane City, the largest city of Laos, which is located near its border with Thailand. Nine percent of *R. rattus* ($n = 141$) from the city of Luang Prabang in northern part of Laos were positive, as were 20.1% of *R. rattus* ($n = 159$) from a town in Luang Namtha Province near the border with Yunnan, China (Angelakis et al., 2009). Angelakis et al. (2009) identified three well-characterized *Bartonella* species (*B. phoceensis, B. elizabethae,* and *B. tribocorum*) and two additional genotypes (Lao/Nh1 and Lao/Nh2) related to *B. tribocorum*. In *R. rattus* rats, the authors found *B. phoceensis* ($n = 1$), *B. elizabethae* ($n = 2$), *B. tribocorum* ($n = 2$), and Lao/Nh2 ($n = 3$); while in *R. exulans* rats, the predominant species was *B. tribocorum* ($n = 5$) with single positive rats infected with either *B. elizabethae* or *B. phoceensis* ($n = 1$) (Angelakis et al., 2009).

## Malaysia

Urban rats were captured as part of a pest management program in Kuala Lumpur ($n = 59$) and Pulau Pinang ($n = 36$). Of the 95 bacteriologically and molecularly tested rats, 13.5% of *R. rattus* ($n = 58$) and 13.8% of *R. norvegicus* ($n = 37$) were positive for *Bartonella* (Tay et al., 2014). Five species of *Bartonella* (*B. tribocorum, B. rattimassiliensis, B. coopersplainsensis, B. elizabethae,* and *B. queenslandensis*) were identified (Tay et al., 2014).

## Nepal

*Bartonella* was detected in 39 (43.3%) of 90 *R. rattus* subsp. *brunneusculus* captured in three cities: Bhaktapur (33.3%; 12/26), Kathmandu (40.6%; 13/32), and Lalitpur (43.8%; 14/32) (Gundi et al., 2010). There were five species of *Bartonella* in *R. rattus* subsp. *brunneusculus* collected in three urban areas in Nepal, including *B. elizabethae* ($n = 5$), *B. coopersplainsensis* ($n = 3$), *B. tribocorum* (4), *B. queenslandensis* ($n = 2$), and *B. phoceensis* ($n = 1$). In addition, three genotypes were different from any described *Bartonella* species (Gundi et al., 2010).

## Singapore

A molecular survey of commensal rodents in Singapore resulted in detection of *Bartonella* DNA in 75% (3/4) of *R. norvegicus* and 34.5% (10/29) of *R. tanezumi* (Neves et al., 2018). Annandale's rats (*R. annandalei*) captured outside the urban areas were negative for *Bartonella*. The only *R. exulans* captured in a city park was also free of *Bartonella*. Characterization of *Bartonella* genotypes circulating in rat populations within Singapore has revealed five species (Neves et al., 2018). Interestingly, the composition of *Bartonella* species differed depending on the rat species. *B. coopersplainsensis, B. elizabethae, B. grahamii,* and *B. phoceensis* were found in *R. tanezumi*; whereas *B. tribocorum, B. rattimassiliensis, B. grahamii,* and *B. queenslandensis* were found in *R. norvegicus*. A smaller number of *Bartonella* species was in *R. exulans*: *B. tribocorum, B. rattimassiliensis,* and *B. phoceensis* (Neves et al., 2018).

## Taiwan

There were several studies of urban rats in Taiwan. The investigation of rodents captured in the Taichung area, including markets in the urban area, has found 52.7% of *R. norvegicus* ($n = 169$), 10% of *R. rattus* ($n = 10$), and 66.7% of *R. losea* ($n = 3$) (Hsieh et al., 2010) were positive for *Bartonella*. Among the 182 rats tested from Taichung, the city located in central Taiwan, the cultured organisms belonged to five species of *Bartonella* (Hsieh et al., 2010). Strains closely related to *B. tribocorum* and *B. elizabethae* were the most prevalent of them. In addition, *B. rattimassiliensis*, *B. grahamii*, and *B. phoceensis* were isolated from *R. norvegicus*. Several *R. norvegicus* rats were co-infected with different *Bartonella* species: 10 rats with *B. elizabethae*-like and *B. tribocorum*-like organisms and one rat with *B. phoceensis*-like and *B. tribocorum*-like organisms (Hsieh et al., 2010).

Another study in Taichung resulted in detection of *Bartonella* in 9.4% (5/53) of *R. norvegicus* and 33.3% (1/3) of *R. rattus* (Lin et al., 2008). In another study in Taiwan, the same species of *Bartonella* (*B. phoceensis, B. tribocorum, B. elizabethae,* and *B. rattimassiliensis*) were detected in rats, but, in addition, *B. queenslandensis* was also reported (Tsai et al., 2010). The *Bartonella* detected in two *R. norvegicus* rats captured on the university campus was *B. tribocorum*. As we will show later, the diversity of *Bartonella* species in rats from natural habitats can be much higher. Interestingly, Lin et al. (2008) reported isolation of strains closely related to *B. rochalimae* from *R. norvegicus* captured Taichung, Taiwan.

## Thailand

In spite of many investigations of *Bartonella* infections in rats from the fields and forest in different parts of Thailand, there were very limited efforts to investigate urban rats. There is only one report of investigation of urban rats captured in Bangkok in 2008: *Bartonella* bacteria were cultured from *R. exulans* (55.6%; $n = 9$) and *R. rattus* (67.6%; $n = 34$), and none from three *R. norvegicus* (Kim et al., 2016).

# Middle East
## Cyprus

Of 622 rats (402 *R. norvegicus* and 220 *R. rattus* subsp. *frugivorus*) collected in 51 different sites in Cyprus, 10.5% were found seropositive for *Bartonella* antibodies (Psaroulaki et al., 2010). The authors of this study used *B. henselae* antigens and, more likely, the reported antibodies were cross-reactive with other *Bartonella* species. The authors, however, claimed that the seropositivity rate significantly correlated with the presence of cat fleas, but not with the presence of rat fleas.

## Israel

*Bartonella* DNA was detected in spleen samples of 19 out of 79 (24%) *R. rattus* captured in 19 suburban sites ranged from the kibbutz Dafna in the north of Israel to the City of Beersheba in the south (Morick et al., 2009). *Bartonella* strains obtained from *R. rattus* rats captured in Tel-Aviv, Israel were characterized by sequencing multiple genetic loci (*gltA, ribC, rpoB, 16S RNA, groEL,* and the intergenic spacer region ITS) (Harrus et al., 2009). These strains were identical among themselves, and sequences of each of the analyzed genes indicated a closeness to one of the two *Bartonella* species (*B. tribocorum* and *B. elizabethae*), while being different from both of these species (Harrus et al., 2009). The characterization of these strains supports a hypothesis that it could be a separate species of *Bartonella.*

## Turkey

In a study conducted in an urban area of Zongulda in the western Black Sea Region of Turkey, only one rat out of 14 investigated, including eight *R. rattus* and six *R. norvegicus* was found to be *Bartonella*-positive (Çelebi et al., 2015). A *Bartonella* isolate obtained from *R. rattus* rats captured in Zongulda was identified as *B. coopersplainsensis* (Çelebi et al., 2015), the species which has been previously reported in Australia and Southeastern Asia (Gundi et al., 2009; Jiyipong et al., 2012).

# Africa

## Benin

A molecular survey of *Bartonella* species in rats captured inside human residences and peridomestic areas was conducted in three zones of Cotonou where half of the population of the Republic of Benin resides (Martin-Alonso et al., 2016). *Bartonella* DNA was detected in 26.3% (5/19) of *R. norvegicus* captured in the zone 1 (20.8%), whereas none of the 110 *R. rattus* captured in the three zones were found positive for *Bartonella*. Three *Bartonella* species (*B. elizabethae, B. tribocorum,* and *B. rochalimae*) were found in spleens of *R. norvegicus* rats from an urban area near Nokoue Lake in Benin (Martin-Alonso et al., 2016).

## DR Congo

In studies conducted in Djalusene, Kpandruma, Rethy, and Zaa, *R. rattus* was the only rat species captured inside houses and the domestic environment. Screening of spleen samples from the 25 captured *R. rattus* indicated the presence of *Bartonella* DNA in only one rat from Zaa (5.9%, 1/17) (Gundi et al., 2012). Out of 11 *Bartonella* sequences obtained from *R. norvegicus* rats, four were similar (96–100% homology) to the *Bartonella* strain 1-1C (GenBank EU551156), a *B. rochalimae*-like strain described from *R. norvegicus* in Taiwan. Interestingly, this strain was found only in *R. norvegicus,* not in *R. rattus,* although *Bartonella* prevalence was higher in the latter. Five sequences were similar with 97–100% homology to an uncultured *Bartonella* genotype previously detected in *R. rattus* in Nepal (Gundi et al., 2010). One sequence shared 100% homology with *B. queenslandensis,* a *Bartonella* species originally described in Australian rats (genera *Melomys* and *Rattus*) (Gundi et al., 2009). In another study conducted in Kisangani, the proportion of *Bartonella*-infected rats was significantly higher in *R. rattus* (25.0%, 5/20) than in *R.*

*norvegicus* (15.1%; 16/106) (Laudisoit et al., 2014). Two *R. rattus* and two *R. norvegicus* captured during this study in a marketplace were co-infected with *Bartonella* and *Rickettsia* species (Laudisoit et al., 2014). A strain with 100% homology with the human strain of *B. elizabethae* was reported in one of the *R. norvegicus* rats (Laudisoit et al., 2014).

## Ethiopia

Meheretu et al. (2013) reported only one rat PCR-positive for *Bartonella* among 19 *R. rattus* trapped from three localities in Tigray, the northernmost region of Ethiopia. In Aroresa, where *R. rattus* comprised 46.5% in the rodent community, none of 53 tested rats was positive. The only sequence obtained from a *R. rattus* rat from Golgolnaele, Ethiopia was different from all previously described *Bartonella* species, but clustered together with genotypes found exclusively in native rodent species (*Stenocephalemys albipes* and *Arvicanthis dembeensis*) from Ethiopia (Meheretu et al., 2013).

## Kenya

In a cross-sectional rat survey conducted in Kibera, an urban slum in Nairobi City, 24 of the 220 (11%) trapped rats were *Bartonella* culture-positive, including *R. norvegicus* (50%; 5/10) and *R. rattus* (60%; 19/32). In contrast, in the rural area Asembo on the northern shore of Lake Victoria, where *R. norvegicus* were absent, prevalence of *Bartonella* in *R. rattus* was lower (13%; 2/16) compared to Nairobi (Halliday et al., 2015). The high infection prevalence observed in *Rattus* trapped at the Kibera site is more similar to prevalence ranges observed in studies of Asian *Rattus* populations than to other African populations. The Kibera study in Nairobi, the Kenyan capital, clearly has more intensive connection with the seaport in Mombasa (in terms of rodent movement from other seaports) than the Asembo site located inland near Lake Victoria. Therefore, the high prevalence of *Bartonella*-infected rats reported from the Kibera site could relate to repeated introductions of *Rattus* species to this site (Halliday et al., 2015). Three zoonotic *Bartonella* species were identified in rats captured in Kibera slum area in Nairobi. They were *B. elizabethae* ($n = 7$), *B. tribocorum* ($n = 8$), and *B. queenslandensis* ($n = 4$) among 19 infected *R. rattus* and *B. elizabethae* ($n = 1$), *B. tribocorum* ($n = 3$), and *B. queenslandensis* ($n = 1$) among five infected *R. norvegicus* (Halliday et al., 2015).

## Madagascar

A study conducted in Central Madagascar showed that 58.9% (93/158) of *R. rattus* rats sampled in two human communities were positive for *Bartonella* (Brook et al., 2017). They found four species: *B. elizabethae* (28; 16.9%), *B. phoceensis* (40; 23.8%), *B. rattimassiliensis* (21; 12.5%), and *B. tribocorum* (1; 0.6%) (Brook et al., 2017).

## Nigeria

A study to detect *Bartonella* species in commensal rodents and their ectoparasites was conducted in town of Vom, central Nigeria. Among rats trapped there in domestic and peridomestic habitats, 36 of 121 *R. norvegicus* (29.8%), and nine of 48 *R. rattus* (18.8%) were culture-positive for *Bartonella* (Kamani et al., 2013). The prevalence of *Bartonella* DNA found in that study was

similar to the prevalence reported in rats from the Democratic Republic of Congo (Laudisoit et al., 2014). *Bartonella* strains detected in rats from Vom, a town in central Nigeria, were identical or closely related to *B. elizabethae, B. tribocorum,* and *B. grahamii* (Kamani et al., 2013). Of 36 sequences obtained from *R. norvegicus*, 26 had 98–100% similarity with *B. elizabethae* sequence. Nine of the sequences obtained from *R. norvegicus* had 97–98% similarity with *B. tribocorum* sequence, while one sequence had 98% similarity with *B. grahamii*. The *Bartonella* sequences obtained from *R. rattus* were identical to *B. elizabethae*.

### South Africa

A significant difference of *Bartonella* prevalence was observed between two rat species (24% in *R. norvegicus* vs. 5% in *R. rattus*) in South Africa (Brettschneider et al., 2012). The authors of this study proposed a mathematical model explaining that the difference between these two co-occurring rat species might be due to the observed differences in flea infestation rates between these species. Trataris et al. (2012) reported *Bartonella* infections in 13% by culturing and in 25% by PCR among rats (*R. norvegicus* and *R. rattus*) sourced from a pest control company in the Ekurhuleni Metropolitan area, the East Rand region of Gauteng, South Africa. Some isolates from the rats were similar to *B. elizabethae*, while some were relatively similar to *B. thailandensis* originally described in Asian rats (Saisongkorh et al., 2009).

### Uganda

A very low prevalence of *Bartonella* (1.3%; 3/228) was reported in *R. rattus* from villages of two districts of northwest Uganda, whereas a prevalence near 60% was in populations of local indigenous rodents (Billeter et al., 2014). The relatively low prevalence of infection may be due to the fact that *Rattus* rats were introduced into this area of the West Nile region relatively recently. Genotypes related to *B. elizabethae* were detected in three *R. rattus* rats (Billeter et al., 2014).

# Europe
## France

In contrast to numerous investigations of *Bartonella* infections in multiple sylvatic rodents in many European countries, reports of investigation of urban rats are very limited from this part of the world. Seventy-four rats (8 *R. rattus* and 66 *R. norvegicus*) were trapped in the center and suburb of the city of Marseille, France, and 20 of the *R. norvegicus*, but none of *R. rattus* were culture positive (Gundi et al., 2004). Three species of *Bartonella* were described based on characterization of the strains obtained from Norway rats from France. First, Heller et al. (1998) identified *B. tribocorum* from blood of two *R. norvegicus* rats captured near the Rhine River. Later, Gundi et al. (2004) isolated *B. rattimassiliensis* and *B. phoceensis* from rats *R. norvegicus* captured in the city of Marseille. A more recent search for *Bartonella* and various other pathogens and parasites was conducted in the urban park (Chanteraines) within Hauts-de-Seine, France (Desvars-Larrive et al., 2017). The prevalence of *Bartonella* culture-positive rats of R. norvegicus was very high (58.2%; 32/55). Surprisingly, the prevalence of *Bartonella*-DNA estimated by PCR was lower (31.4%; 27/86). The authors of this study were careful with

identification of the *Bartonella* species detected in the rats, but short sequences of the obtained *pap31* amplicons were identical to *B. henselae* sequences (Desvars-Larrive et al., 2017).

### Spain

The only other reported surveys of urban rats in Europe were from Spain: one from Andalusia and another one from the Canary Islands. *Bartonella* was isolated from two of ten *R. norvegicus* collected in a suburban area of Seville, Andalusia (Márquez et al., 2008). The ITS sequence analysis from *R. norvegicus* from Andalusia showed two genetically different variants (Márquez et al., 2008). The first genotype belonged to *B. tribocorum,* closely related to the strain KM2519 detected in *R. tanezumi* in China (GenBank EF202169). The second genotype was detected in 17 individuals and was relatively close to, but different from *B. elizabethae* (Márquez et al., 2008).

In the Canary Islands, *Bartonella* was found in *R. rattus* from two islands, Tenerife and La Palma (Abreu-Yanes et al., 2018). Overall, the prevalence of *Bartonella* in the rats of the Canary Islands was 14.3%, with variations between 13.8% inside houses and 26.7% in peridomestic habitats. The only two Norway rats from Tenerife were tested *Bartonella*-free. Fifteen *Bartonella* sequences identified in rats of *R. rattus* from the Canary Islands belonged to *B. tribocorum; B. queenslandensis* was in four rats, and *B. rochalimae* was recovered from two rats. Interestingly, two different *gltA* haplotypes similar to *B. elizabethae* were detected only in house mice (*Mus musculus*), but not in any rat (Abreu-Yanes et al., 2018).

### Portugal

A limited number of rats from Portugal (two *R. norvegicus* from Aguas de Moura and two *R. rattus* from Porto Santo Island in Madeira Archipelago) were culture-positive for *Bartonella* (Ellis et al., 1999). The strains found in Norway rats from Portugal were relatively close to *B. tribocorum* while a strain from *R. rattus* from an island of Madeira Archipelago was evidently different (Ellis et al., 1999). Interestingly, this strain from the Portuguese island was shown later to be identical to the strains described in some *R. rattus* in Dhaka, Bangladesh and in all infected black rats in Tel Aviv, Israel (Bai et al., 2007; Harrus et al., 2009).

# North America
## Canada

In Vancouver, *Bartonella* species were isolated from the blood of 25.2% (102/404) of *R. norvegicus* tested (Himsworth et al., 2015). All 102 *Bartonella* cultures isolated from *R. rattus* and *R. norvegicus* from Vancouver had identical *gltA* sequences to type strain of *B. tribocorum* (Himsworth et al., 2015).

## United States

Ellis et al. (1999) identified *Bartonella* species in 19.4% of *R. norvegicus* and 12% *R. rattus* collected from multiple U.S. cities. *Bartonella* infection in *R. norvegicus* varied significantly between investigated cities. In 3/9 localities, a statistically significant higher-than-expected prevalence of *Bartonella* infection in *R. norvegicus* was observed in Los Angeles California (56%), and New Orleans, Louisiana (56.4%). Seven of 66

(10.6%) *R. norvegicus* were culture-positive in Baltimore, Maryland. Rats of *R. rattus* were infected with *Bartonella* species in five of seven cities with a range of prevalence from 9 to 60% (Ellis et al., 1999). No positive rats of *R. norvegicus* were found in four cities: Atlanta, Georgia; Rockport, Indiana; Reno, Nevada; and New York City. Surprisingly, no *Bartonella*-positive rats were found in New York City among 87 rats cultured during the survey conducted by Ellis et al. (1999). In two other studies conducted in five sites within New York City, 33% (25/133) *R. norvegicus* were *Bartonella*-positive by PCR (Firth et al., 2014) and 23% (30/133) by culturing (Peterson et al., 2017). Ellis et al. (1999) described seven genotypes of *Bartonella* among 63 isolates obtained from *R. norvegicus*. The most frequently identified genotype (28/74) was 99% similar to *B. tribocorum*. Two of the *R. rattus* isolates from Louisiana were identical to one from an *R. norvegicus* captured in the same locality. Surprisingly, the 11 other isolates obtained from *R. rattus* captured in the United States were distinct from those from *R. norvegicus*. *Bartonella* strains detected in six of 11 *R. rattus* rats were identical to the genotype common for cotton rats (*Sigmodon hispidus*) from Georgia. One variant matched another cotton rat genotype from Georgia. Several other studies of urban rats in the U.S. and Canada have followed the study conducted by Ellis et al. (1999). Most genotypes identified in *R. norvegicus* from downtown Los Angeles, California were *B. tribocorum*: 101 of 106 (95.3%) culture-positive rats were infected with this particular species. In addition to *B. tribocorum*, three rats were infected with *B. queenslandensis* and two rats with *B. rochalimae* (Gundi et al., 2012). Testing blood of the same animals by PCR demonstrated presence of *B. rochalimae* in 37 (18.5%) rats and *B. queenslandensis* in four rats (2.0%) (Gundi et al., 2012). In Baltimore, Maryland, antibodies against *B. elizabethae* were detected in 34.1% of rats of *R. norvegicus* (Easterbrook et al., 2007).

Bartonella bacteria were cultured from blood of 43.5% (87/200) of *R. norvegicus* trapped in 16 sites in downtown Los Angeles, California, while *Bartonella* DNA was detected in 67.5% (135/200) of the same rats (Gundi et al., 2012). Another investigation of *Bartonella* that targeted populations of rats in California was conducted in the San Francisco Bay Area, where morphologically identified black rats represent two genetically distinct lineages that have been equated to *R. rattus* and *R. tanezumi* (Conroy et al., 2013). Of 50 of these black rats from six locations within Alameda county, California, eight *Bartonella*-positive rats were found in two locations within the City of Oakland nearly three miles apart. Interestingly, four rats from one location carried *B. tribocorum*, the bacterium dominant in rats in Los Angeles; whereas four *Bartonella*-positive rats from another location carried another bacterium, *B. coopersplainsensis*, originally described from *Rattus leucopus* in Australia (Gundi et al., 2009) and the most prevalent species in rats from New Zealand (Helan et al., 2018). In the U.S., this bacterium was found only in *R. rattus* from New Orleans (Peterson et al., 2017).

In New Orleans, Peterson et al. (2017) reported *Bartonella* infection by culture in 29 of 163 (17.8%) *R. norvegicus* and in five of 177 (2.8%) *R. rattus*. In Manhattan, New York City, 31 of 133 (23.3%) *R. norvegicus* rats tested were positive by PCR of spleen

and heart tissues (Peterson et al., 2017). Peterson et al. (2017) reported significant differences in Bartonella diversity among rats between New Orleans and New York. In New Orleans, these authors detected *B. coopersplanensis* in five roof rats. They did not detect *B. coopersplanensis* in Norway rats in either New Orleans or New York City. However, they found four other *Bartonella* species from New Orleans, and those fell within the clades corresponding to *B. rochalimae* (13 positive by PCR only), *B. elizabethae* (10 positive by culture), *B. tribocorum* (19 by culture), and *B. queenslandensis* (five positive by culture). Among 29 *Bartonella*-positive Norway rats from New York City (Manhattan), 26 rats carried *B. tribocorum*, while three rats were infected with *B. elizabethae* (Peterson et al., 2017). *Bartonella* sequences recovered from these rats were located in the same clades as *B. elizabethae, B. rochalimae*, and *B. tribocorum* (Firth et al., 2014), while sequences obtained via tissue cultures were located in the same clade as *B. elizabethae* and *B. tribocorum*.

# SOUTH AMERICA

## Brazil

*Bartonella* were isolated from 5 of 26 (19%) *R. norvegicus* rats from two of five slum areas of Salvador, the third most populous city in Brazil (Costa et al., 2014). Conducting a wide survey of various rodent species in different parts of Brazil, Gonçalves et al. (2016) detected *Bartonella* species in two *R. rattus* from Mato Grosso (*n* = 3) and Goias (*n* = 4), while rats of the same species from Ceará (*n* = 12), and Pará (*n* = 8) were free of *Bartonella*. Of 14 strains of *Bartonella* isolated from *R. norvegicus* from Salvador, all but one were identical to *B. queenslandensis*, the remaining strain was close to *B. tribocorum* (Costa et al., 2014).

## Peru

Analyzing *Bartonella* species in various animals inhabiting the villages in the Huaillacayan valley, Department of Ancash, Peru, Birtles et al. (1999) isolated two strains closely resembling *B. elizabethae* from rats collected in one village. This was the first reported identification of *Bartonella* species in a commensal rat from South America. Unfortunately, the authors were unable to identify the rat species. Investigating rodents in three villages in La Convencion Province of Peru for plague and *Bartonella* species, Martin-Alonso et al. (2014) tested 24 *R. rattus* from two residential areas. All 20 rats trapped in one area (Alto Ivochote) were free of *Bartonella*, whereas one of four rats captures in another area (Yoetoni) was PCR-positive for this bacterium. One sequence obtained by Martin-Alonso et al. (2014) from *R. rattus* from La Convencion Province, along with sequences obtained from two indigenous rodents species (*H. perenensis* and *Oecomys* sp.), had 98–99% sequence similarity to a genotypic variant obtained from *Oryzomis palustris* rats in the southeastern U. S. (Kosoy et al., 1997).

# Oceania
## Australia

Three novel *Bartonella* species were originally described from rats of the genus *Rattus* in Australia. Those are *B. rattaustraliani* found in rats of *R. tunneyi, R. leucopus,* and *R. conatus; B.*

*queenslandensis* found in *R. tunneyi, R. fuscipes, R. leucopus,* and *R. conatus;* and *B. coopersplainsensis* found in *R. leucopus* (Gundi et al., 2009). The last two *Bartonella* species found in Australian rats were later discovered in rats from other continents. Two *Bartonella* species were detected in spleens of *R. rattus* from the Christmas Island, Australia (Dybing et al., 2016). Of 48 positive black rats found on this island, 28 rats carried *B. phoceensis* and eight rats carried a novel *Bartonella* genotype, potentially representing a new *Bartonella* species. Christmas Island is an Australian territory in the Indian Ocean lying in close proximity (360 km) to Jakarta, Indonesia. The authors considered the possibility that this *Bartonella* species had arrived in infected rats transported over the years on ships from nearby Indonesia (Dybing et al., 2016).

### New Zealand

Using three molecular markers for identification of *Bartonella* DNA extracted from spleen samples of *R. rattus* collected in the Tongariro National Park, Helan et al. (2018) reported sequences matching *B. coopersplainsensis* and *B. henselae* from 15.4 (22/143) to 2.1% (3/143) of rats, respectively. Co-occurrence of *B. coopersplainsensis* and *B. henselae* sequences was observed in one rat. Even ff detection of prevalent *B. coopersplainsensis* was not surprising because this bacterium was described earlier in Australian rats (Gundi et al., 2009), the discovery of *B. henselae* in rats was very unexpected as this bacterium is typically found in domestic and wild cats and has never been reported previously in rats.

## DISTRIBUTION OF *BARTONELLA* IN RAT POPULATIONS WITHIN URBAN TERRITORIES

Ecological factors, including size and structure of rat populations and animal movement patterns, may determine prevalence and species diversity of *Bartonella* in rats within urban territories (Firth et al., 2014; Himsworth et al., 2015; Peterson et al., 2017). During the survey conducted by Halliday et al. (2015) in Kibera, an urban slum in Nairobi, Kenya, the proportion of infected *Rattus* overall varied from 0 to 60% by trapping zone (**Figure 2**). In three zones (A, B, and D), *Mus musculus* was the dominant species and only four *Bartonella* isolates were identified in rats (**Figure 2**). Concurrently, in two other zones, *Rattus* rats dominated in rodent populations presenting 51% in zone C and 40% in zone E. In these two zones (C and E), several species of *Bartonella* were reported (**Figure 2**; Halliday et al., 2015).

According to the investigation conducted in New Orleans, Louisiana by Peterson et al. (2017), prevalence of *Bartonella* infections ranged from 0 to 97% of rats. Most *Bartonella*-positive rats (85%) were found within a single housing block of New Orleans. All *Bartonella*-positive *R. norvegicus* rats were captured at two locations, where no roof rats were present. *Bartonella*-infected *R. rattus* were captured from five locations. Though two species of rats (*R. norvegicus* and *R. rattus*) were found in four of these five locations, no *R. norvegicus* rats were *Bartonella*-positive there. A single *Bartonella*-positive *R. rattus*

was captured at a location where *R. norvegicus* were absent. Of five trapping locations in New York City, *Bartonella*-positive *R. norvegicus* rats were reported in each of them; however, prevalence of infected rats at these locations ranged from 10 to 85% (Peterson et al., 2017).

Himsworth et al. (2015) demonstrated significant geographic clustering of *Bartonella*-positive rats within Vancouver, Canada. The prevalence of *B. tribocorum* varied significantly by city block, from 0 to 60.5%. Analyzing various ecological factors affecting prevalence of *B. tribocorum* in *R. norvegicus* rats from Vancouver, Rothenburger et al. (2018) noticed that the infection was significantly lower within city blocks with one or more low-rise apartment buildings compared to blocks with none. There was no significant association of the infection prevalence with rat abundance, suggesting a lack of density-dependent pathogen transmission. According to this analysis, the infection rate positively correlated with high minimum temperatures and the authors suggested that a baseline minimum temperature could be important for survival of fleas that serve are vectors for transmission of *B. tribocorum* among rats (Rothenburger et al., 2018).

Abreu-Yanes et al. (2018) defined environmental parameters related to the presence of *Bartonell*a DNA in rats in the Canary Islands. Specifically, their data suggest that occurrence of *Bartonella* on islands of this archipelago is influenced by biological and climatic conditions that vary among the islands. The probability of *Bartonella* infection in rodents in La Palma Island was four times higher compared to Tenerife Island and no *Bartonella*-positive rats were found in Lanzarote Island. A study carried out by Vicente and Gómez López (2012) showed that the flea *Stenoponia tripectinata* seem to have some preference for the conditions found on the four western islands, which include both Tenerife and La Palma, whereas this flea species was found in none of the 157 rodents from Lanzarote that belongs to the eastern group of islands. The results suggest that the ecological conditions on the Lanzarote Island are not suitable for the development of fleas *S. tripectinata*, while the ecological conditions on the La Palma Island (the most northwestern island of the archipelago) are more favorable for completing the life cycle of these fleas, which likely provide transmission of *Bartonella* infection between rats (Vicente and Gómez López, 2012).

Although *Bartonella* infections are prevalent in urban rat populations around the world and in many cities and prevalence of the infection can reach very high rates, we noted that rats in some cities and villages were not infected with *Bartonella* or the infection prevalence was quite low. At least, such situations were reported outside of Asia where we have not found reports of *Bartonella*-free populations of rats when a sufficient number of animals was tested. One of the first thoughts to explain the absence of *Bartonella* in some rat populations leads to representation of a kind of "island syndrome" wherein some parasites were absent or rare when a new rat population is established by invasion of a small number of individuals. In the regions where rats of the genus *Rattus* rarely occupy certain urban habitats, such as in areas of Europe and North America, populations of city rats are well-separated, in fact resembling

**FIGURE 2** | *Bartonella* species identified in *Rattus* rats from different countries worldwide.
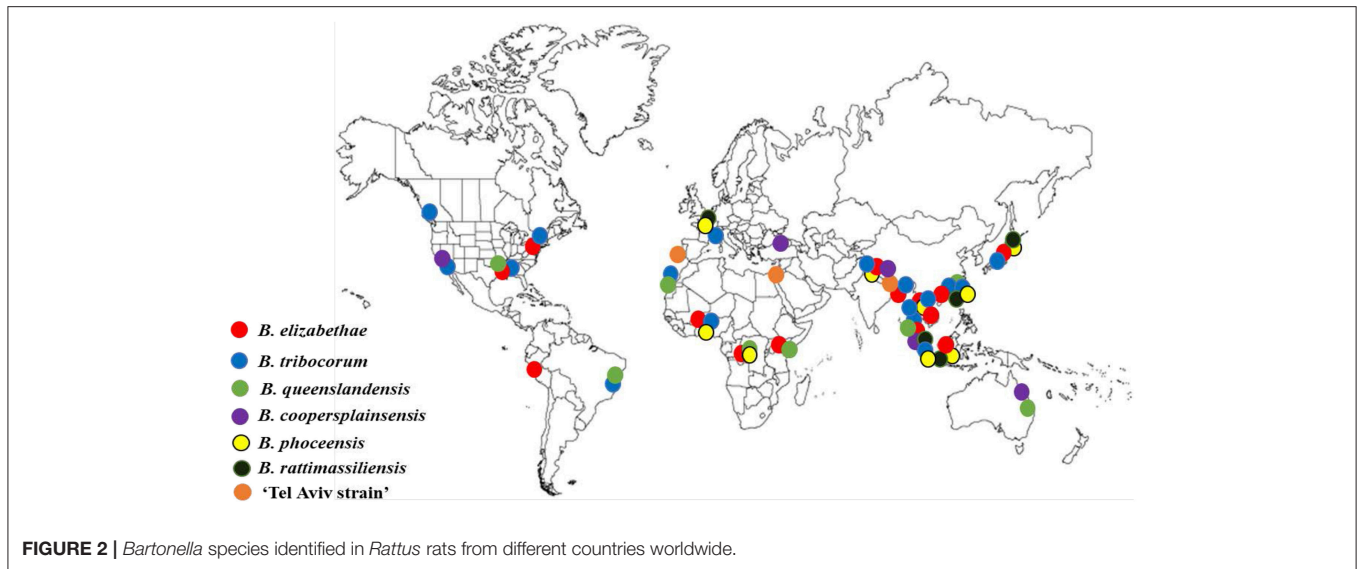
"island populations." This can explain the absence of *Bartonella* infections in rats from many big cities of the continental United States.

Noticeably, rats from the coastal cities on both Atlantic and Pacific sides (Los Angeles, Baltimore, New Orleans, New York, and Vancouver) carried *Bartonella*, while populations of rats in non-coastal cities were *Bartonella*-free (Ellis et al., 1999). In spite of a large number of rats investigated in Yokohama, Japan (255 *R. rattus* and 84 *R. norvegicus*), all tested animals were *Bartonella*-negative (Inoue et al., 2008). The rats of both *R. rattus* and *R. norvegicus* were *Bartonella*-free from some zones of the city of Cotonou, Benin (Martin-Alonso et al., 2016).

We admit that these observations are limited for supporting this statement. We can only speculate that continuous arrival of new rats through seaports is a crucially important factor for circulation of *Bartonella* among rats. Assuming an "island effect" on the formation of *Bartonella* communities in urban rat populations, we have to consider factors contributing to isolation of rat populations, such as time of establishing rat populations, distance and connectivity between continental rat populations and seaports where arrival of new rats is more likely to occur, rat population size, etc. (Papkou et al., 2016).

The "island effect" is not the only plausible explanation for the absence of *Bartonella* in rat populations within some urban areas and in some situations might not be the most important. When *Bartonella* bacteria are introduced into a new territory with invasive rats, the local conditions might not be favorable for the long-term circulation of the parasites within the newly established host population. Continuing an analogy borrowed from population genetics, a situation leads to the so-called "bottleneck effect" when bacteria are likely to be subjected to extreme changes in a host population. A critical issue is an availability of factors required for continuous transmission of *Bartonella* bacteria between rat hosts. A presence of appropriate flea species, particularly, the Oriental rat flea (*X. cheopis*) that can act as vectors, and the level of flea infestation, would be

especially important factors for survival of *Bartonella* in rats. Unfortunately, data on the distribution of fleas in urban rat populations in the U.S. are quite sparse.

The absence of *Bartonella* infections in *Rattus* rats in some Ugandan villages and overall low prevalence in invasive rats in northwestern Uganda (Billeter et al., 2014) present another interesting situation that contrasts with numerous studies demonstrating a high prevalence of bartonellae among *Rattus* rats in Asia and in many places outside of Asia, e.g., Nairobi City. The relatively low prevalence of the infection in rats in this part of Africa may relate to relatively recent introduction of *Rattus* rats into the West Nile region. This fact is in contrast to the well-established rat populations in the cities on the coastal parts of Kenya and Tanzania, which probably have existed for millennia because of the historical dispersal of humans and their cargo via ships (Aplin et al., 2011). Despite intensive investigations, only a single rat was reported on a boat moored at Rhino Camp on the west side of the Albert Nile in the late 1930s (Hopkins, 1949; Amatre et al., 2009). Despite "fairly intensive" trapping efforts at 11 sites on land in the West Nile and West Madi regions along the west side of the Albert Nile, no *R. rattus* were captured during a survey undertaken in 1937 and 1938 by Hopkins (1949). Indeed, *R. rattus* might not have become established in the West Nile until the 1950s or even the 1960s as this rat was first identified in 1958 in the Ituri District of the DR Congo, which lies across the border from the West Nile Region (Borchert et al., 2007). This is perhaps not surprising as Hopkins (1949) suggested that *R. rattus* was first introduced to Uganda in the early Twentieth Century, a date that agrees with Delany's belief that this rat species first appeared in the country around 1910 (Delany, 1975). In this part of Africa, outsiders were restricted and movement of crops was limited until 1914 when the region became a British protectorate (Borchert et al., 2007). This likely could restrict the relocation of *R. rattus* and thereby limit the introduction of *Bartonella* infected rats. The extension of the "Kenya and Uganda Railways and Harbors" to the western Uganda in 1956 or the construction of

the bridge across the Albert Nile at Pakwach in 1969 could have lead to gradual spread of *Rattus* rats to Arua near the border with DR Congo.

## THE RICHNESS OF *BARTONELLA* BACTERIAL COMMUNITIES IN ABORIGINAL RATS IN NATURAL HABITATS COMPARED TO URBAN COMMUNITIES

Provided information suggests that rat-adapted *Bartonella* species originated from Asia. The first data supporting this claim came after collection of bacteria related to *B. elizabethae* in *Rattus* rats from three districts of Yunnan province of southwestern China (Ying et al., 2002). Following this report, multiple investigations of rats in Southeast Asia (Cambodia, Laos, Thailand, and Vietnam) have also confirmed ubiquitous distribution of this infection in native rat species of the genus *Rattus* (Bai et al., 2007, 2009; Angelakis et al., 2009; Jiyipong et al., 2012). In contrast to urban rats in many countries of the world where two rat species are observed, in Asia, various species of *Rattus* occupy natural habitats from tropical lowland to mountains. For instance, the ricefield rat (*R. argentiventer*) and the Malayan field rat (*R. tiomanicus*) are common in the rice fields and plantations and the Losea rat (*R. losea*) is more typical in gardens (Kosoy et al., 2015). At the same time, only few species of rats have evidently adapted to live closely to people; specifically, *R. tanezumi* rats are common in cities, small towns, and villages.

Overall, the prevalence of *Bartonella* infections was commonly high in rats in Asia, but not higher than in urban rats in Africa or Americas. For example, Jiyipong et al. (2012) reported *Bartonella* species in 9.6% of rats in Cambodia, 11.9% in Laos, and 11.0% in Thailand, all of which are lower than the rates reported in Los Angeles, U.S. (56%) or in Nairobi, Kenya (57%). While rats of various species of *Rattus* carried *Bartonella* in natural habitats in Asia, prevalence varied between species. For example, prevalence of infected individuals has significantly varied from 3.2% in *R. exulans* to 86.4% in *R. norvegicus* in Thailand (Bai et al., 2009) or from 10% of the *R. rattus* to 66.7% of the *R. losea* in Taiwan (Hsieh et al., 2010).

The most striking difference in *Bartonella* infection between aboriginal and invasive rats was in observed diversity of the bacteria. *Bartonella* bacteria found in urban rats in Africa, Europe, and North and South Americas belonged to one or a few species or genotypes; for example, all 102 infected rats from Vancouver, Canada carried bacteria identical to each other by the *gltA*, which is a quite sensitive genetic marker (Himsworth et al., 2015). The diversity of *Bartonella* strains found in rats inhabiting natural environments in Asia was very high. Investigating rats from 17 provinces in Thailand, Bai et al. (2009) identified 23 genetic variants, which clustered with not only *B. coopersplainensis, B. elizabethae, B. phoceensis, B. rattimassiliensis,* and *B. tribocorum*, but also with numerous *Bartonella* genotypes in intermediate positions between described species or were quite different from all known species. A novel genotype of *Bartonella* with the proposed name as "Candidatus Bartonella thailandensis" was identified in

rats of *Rattus surifer* from Surin, a Thai province neighboring Cambodia (Saisongkorh et al., 2009). Klangthong et al. (2015) classified DNA sequences obtained from rats in Thailand into eight different cladograms. *Bartonella* sequences obtained from rats of several *Rattus* species from Southeast Asia represented over 40 different genetic variants and clustered into nine lineages (Jiyipong et al., 2012). All described rat-adapted *Bartonella* species were identified in rats (*R. argentiventer*, *R. tanezumi*, *R. norvegicus*, and *Bandicota indica*) from the Mekong Delta in Vietnam (Loan et al., 2015). The prevalence of *Bartonella* infection among rats trapped in farms, filed, and forest was 22.4%, much higher than the infection prevalence in rats that were purchased in city markets (8.7%). The highest prevalence was found in *R. tanezumi* (49.2%), followed by *R. norvegicus* (20.7%). No *Bartonella* was found in *R. exulans*. The species isolated from these rats were *B. rattimassiliensis*, *B. tribocorum*, *B. elisabethae, B. coopersplainensis,* and *B. queenslandensis* (corresponding to 43.8, 21.9, 18.8, 9.4, and 6.3% of 32 *Bartonella*-infected rats. Two species (*B. rattimassiliensis* and *B. coopersplainensis*) were identified in *R. tanezumi* only, while all other species of *Bartonella* were detected at least in two rat species (Loan et al., 2015). The prevalence of *Bartonella* species in rats from rural parts of Vietnam (Mekong Delta) was significantly lower than in Saigon Port, but the diversity of the species was evidently higher.

## PHYLOGENETIC RECONSTRUCTION OF GLOBAL DISSEMINATION OF *BARTONELLA* BY RATS

A comparison of *Bartonella* bacterial communities between aboriginal and invasive rats of the genus *Rattus* allows an investigation of the roles played by rats as carriers of these bacteria comparing the diversity of *Bartonella* genotypes in rats between Southeast Asia where presumably original diversification happened and other parts of the world where only two rat species were relatively recently introduced. Hayman et al. (2013) analyzed variations of one genetic locus (the *gltA* as the most widely used molecular marker for differentiation of *Bartonella* species) of 191 strains of rat-associated bartonellae from 17 countries. The phylogeographic analysis supported the hypotheses that *Bartonella* species likely originated in Southeast Asia. The analysis has also highlighted the role of *R. rattus* in disseminating *Bartonella* bacteria to other continents. Black rats have invaded most countries of the world with main introductions that happened through several commensalism events (Aplin et al., 2011). Furthermore, the phylogenetic analysis conducted by Hayman et al. (2013) demonstrated that diversification of species belonging to the *B. elizabethae* species complex occurred in Southeast Asia before some of the species belonging to this complex were transmitted to other geographic regions. Importantly, their analysis suggests that there were multiple disseminations of these bacteria within Asia and numerous introductions from Asia to other parts of the world. This conclusion is based on identification of several

major clades of *Bartonella* strains of Southeast Asian origin that dispersed globally.

Specifically, *Bartonella* strains obtained from rats of the genus *Rattus* from different continents and countries were grouped into six major clades that presumably originated in Southeast Asia. Of those, one clade (A) is distributed globally with strains found in most regions, but not in Central Africa. Likely, *R. norvegicus* play the leading role in distributing *Bartonella* species belonging to this clade. The analysis also suggests that the process of bacterial dispersal in this species clade is still continuous. Strains belonging to another clade (B) were detected only in Asia and Western Europe. The strains belonging to the third clade (C) dispersed to countries of Africa, North and South America. Strains grouped into the D are found in Africa and North America, besides Asia. Clade E has limited geographic spread, with only a Eurasian distribution. Finally, the strains combined into the clade F are distributed across Pacific and were detected in East Asia, Australia, and western part of North America (Hayman et al., 2013).

## *BARTONELLA* DNA IN RAT ECTOPARASITES

Multiple field observations and limited experimental studies support the major role of rat fleas in transmission of bartonellae among rats. Gutiérrez et al. (2015) highlighted the importance of the level of the flea's host specificity, flea exchange between rodents, and flea abundance for success of transmission of *Bartonella* bacteria. The host specificity of some flea species, e.g., *X. cheopis*, may influence the acquisition or the restriction of specific *Bartonella* species and strains to rats. There are many reports of the presence of *Bartonella* DNA in ectoparasites collected from *Rattus* rats. *Bartonella* DNA was detected in 59.1% of 193 *Xenopsylla cheopis* fleas collected from 62 *Rattus* rats (*R. exulans, R. norvegicus,* and *R. rattus*) captured in Khon Kaen, the northeastern province of Thailand. Sequence analysis of DNA present in rat fleas from this area demonstrated the presence of *Bartonella* species similar to *B. elizabethae, B. rattimassiliensis, B. rochalimae,* and *B. tribocorum* (Billeter et al., 2013). Another study in Thailand targeting rats and their ectoparasites in villages from all regions of the country indicated that the prevalence of *Bartonella* DNA varied substantially depending on ectoparasite species (Klangthong et al., 2015). Of the multiple arthropods screened during this study, the highest prevalence of *Bartonella* DNA was in louse (*Polyplax* and *Hoplopleura,* 57.1%) and flea (*X. cheopis,* 25.8%) pools. Only few positive samples were found in pools of mites (*Leptotrombidium* and *Ascoschoengastia,* prevalence 1.7%) and ticks (*Haemaphysalis* species, prevalence 3.5%). Most identified sequences found in arthropods have been found in rats and belong to the *B. elizabethae* species complex. Eight sequences of *B. tribocorum* were detected from six flea pools. One genotype identified as *B. queenslandensis* (99.6% identity) was found in a flea pool. One flea pool was positive for *Bartonella* with genotype being not reported in rats, but still closely related to *B. tribocorum* (96.8 % identity). Some identified *Bartonella* sequences from tick and louse pools shared close

similarity with *B. coopersplainsensis*. Interestingly, *B. phoceensis* DNA was detected solely from ectoparasites (louse, mite, and tick pools) (Klangthong et al., 2015). Fleas obtained from rats in Taiwan harbored DNA of several *Bartonella* species (Tsai et al., 2010). *Bartonella* DNA detected in eight lice (*Polyplax*) obtained from five *Bartonella*-positive *R. norvegicus* from Taiwan was identified as *B. phoceensis*. The authors noticed that fleas collected from adult rats (77.1%) more likely *Bartonella*-positive than fleas collected from juvenile rats (42.3%).

Laudisoit et al. (2014) reported a high prevalence of *Bartonella* DNA in rat fleas from Kisangani, D. R. Congo. *Bartonella* genotypes detected pools of fleas *X. cheopis*, ticks *R. sanguineus*, and mites *Haemolaelaps* from Nigeria were identical or similar *B. elizabethae* (97–100% similarity), but a genotype found in a flea *Ctenophthalmus* pool was *B. tribocorum* (97% similarity) (Kamani et al., 2013). Nine of 12 genetic variants detected in rat fleas in Uganda belonged to the *B. elizabethae* species complex (Bai et al., 2017). In Madagascar, *B. elizabethae* was found in fleas of *Synopsyllus fonquerniei* and *X. cheopis,* while *B. phoceensis* and *B. rattimassiliensis* were found in sucking lice of the genus *Polyplax* (Brook et al., 2017).

In New York City, *Bartonella* DNA recovered from Oriental rat fleas collected from Norway rats belonged to three *Bartonella* species. The most common sequences clustered with *B. tribocorum*, while sequences related to *B. elizabethae* and *B. rochalimae* were less common in fleas (Frye et al., 2015). There are more reports of *Bartonella* DNA detected in rat blood. The main message that we can deliver from these studies is that the range of *Bartonella* genotypes found in ectoparasites, especially in fleas matches very much the spectrum of bacterial species found in rats. This contrasts with some observations made during investigations of sylvatic rodent communities when a considerable discordance between genotypes of *Bartonella* obtained from several 'rodent host-ectoparasite' pairs was reported (Abbot et al., 2007). A recent experimental study conducted by McKee et al. (2018) supported vector capacity of Oriental rat fleas (*X. cheopis*) for transmission of a rat-adapted *Bartonella* species. Specifically, this experiment demonstrated acquisition of *B. elizabethae* by experimentally exposed rat fleas and excretion of *Bartonella* DNA in flea feces over several days (McKee et al., 2018).

## RAT-ASSOCIATED BARTONELLOSIS IN HUMANS

Pathogens carried by Norway and black rats can lead to significant morbidity and mortality in people around the world (Himsworth et al., 2013). The first species of rat-associated *Bartonella* proven to be a human pathogen was *B. elizabethae* (at that time described as *Rochalimaea elizabethae*) (Daly et al., 1993). This bacterium was isolated from blood of a 31-year old male patient with endocarditis admitted to the Saint Elizabeth Hospital in Massachusetts, U.S. The patient had no history of exposure to cats or other pets or intravenous drug use. A source of the infection remained mysterious until Ellis et al. (1999) found relatively similar bacteria in rats from the U.S. Ying et al. (2002)

reported a variety of similar bacteria in rats in Southern China and, finally, an identical bacterium was found to be prevalent in rats from Vietnam (Loan et al., 2015). Later, an identical bacterium was identified in a febrile patient in Bangladesh (Faruque et al., 2017).

The strains identical or closely similar to rat-adapted *Bartonella* species, including *B. elizabethae, B. tribocorum,* and *B. rattimassiliensis* were identified in blood clots from eight febrile patients from two Thai provinces, Chiang Rai and Khon Kaen (Kosoy et al., 2010). These genotypes represented more than one-half of the *Bartonella* genotypes identified in human patients with fever of unknown etiology enrolled into this study. Importantly, some genotypes identified in rats from Los Angeles showed 98.8% similarity to the isolate obtained from a Thai patient (GenBank accession number GQ225706) (Gundi et al., 2012). Moreover, the strain of *B. tribocorum* identified in a Thai patient was identical to a *Bartonella* sequence detected in *X. cheopis* fleas collected from *R. norvegicus* rats in Los Angeles, California (Billeter et al., 2011). More recently, a strain of *B. tribocorum* was cultured with a bacteremia level of 60 colonies per 1ml from the blood of a 64-year old male patient with complaints of fatigue, muscle pain, and headache in France (Vayssier-Taussat et al., 2016).

Another species of *Bartonella (B. rochalimae),* though not specific for rats, was found in *Rattus* rats and their fleas from Asia and America (Billeter et al., 2011; Gundi et al., 2012). This bacterium was originally described as a human pathogen when it apparently caused fever and splenomegaly in a U.S. patient who became ill after traveling to Peru (Eremeeva et al., 2007). This bacterium was found in dogs and many wild mammalian species (foxes, rats, shrews, gerbils, and raccoons), suggesting that multiple reservoirs may be involved in its maintenance (Bai et al., 2016).

From our standpoint, the most intriguing and convincing case was reported from Tbilisi, the capital of the country of Georgia, where an 18-year old woman was admitted to hospital with a 2-week history of malaise, fever, and severe lymphadenopathy (Kandelaki et al., 2016). The patient lived in a residential area within Tbilisi and had not recently traveled outside the city. Based on lymphadenopathy and some other clinical manifestations, clinicians suspected cat scratch disease (CSD) although the patient denied any contact with cats. The clinical specimens were sent to the laboratory and results proved that indeed the bacterium found in samples from the patient belonged to the genus *Bartonella*. However, analyses that are more precise demonstrated that the strain was not *B. henselae*, the agent of CSD, but belonged to the *B. elizabethae* species complex. Thorough phylogenetic analysis involving seven molecular targets demonstrated that the bacterium had a divergence of 3.4% from *B. elizabethae* and 5.6% from *B. tribocorum*. Most importantly, this strain was identical to the Tel Aviv strain of *Bartonella*, which is prevalent and the only strain identified among *R. rattus* rats captured in Tel Aviv, Israel (Harrus et al., 2009).

The results of several serological surveys supported a potential exposure of people to rat-adapted *Bartonella* species. A survey of 630 drug users conducted in Baltimore, Maryland, reported seroprevalence of antibodies to rat-specific *B. elizabethae* (33%),

3-fold higher than prevalence to the cat-specific *B. henselae* (11%) or louse-transmitted *B. quintana* (10%) (Comer et al., 1996). A similar survey conducted in Central and East Harlem in New York City showed an even higher prevalence of seroreactivity to *B. elizabethae* (46%) compared to antibody positivity observed to *B. henselae* (10%) and *B. quintana* (2%) (Comer et al., 2001). A study of homeless people in Stockholm, Sweden reported high seroprevalence (52%) to *B. elizabethae* (Ehrenborg et al., 2008). McVea et al. (2018) reported exposure to rat-associated *Bartonella* species among intravenous drug users in an impoverished neighborhood of Vancouver, Canada. A retrospective serological survey of archived specimens indicated that *Bartonella* antibodies are prevalent among febrile patients in the Kathmandu Valley of Nepal (Myint et al., 2011). When 11 cases with high titers were compared to eight different *Bartonella* antigens, the highest titers (ranged from 1:256 to 1:2,048) reported in three patients were against the antigen of *B. elizabethae*.

## THE MOVEMENT OF *BARTONELLA* BY RATS FROM SOUTHEAST ASIA TO URBAN CENTERS IN OTHER PARTS OF THE WORLD

A high diversity of *Bartonella* species and strains on the one side and association of specific *Bartonella* species with mammalian hosts on the other, in our case with rats of the genus *Rattus*, provide an opportunity for reconstructing the movement of these bacteria from the jungles of Southeast Asia to cities on all continents except for Antarctica. The studies of *Bartonella* strains associated with the rats of genera *Rattus* and *Bandicota* demonstrated that these bacteria cluster into a separate phylogenetic lineage (Heller et al., 1998; Ellis et al., 1999; Ying et al., 2002; Castle et al., 2004; Gundi et al., 2004, 2009). These *Bartonella* species likely originated in Southeast Asia and subsequently dispersed from Asia with *Rattus* rats because of human activity. Later these bacteria became common and widespread in urban and peridomestic environments around the world (Childs et al., 1999; Ellis et al., 1999).

We have to distinguish roles played by rats as hosts of *Bartonella* within the lands where they had originally diversified from rats that have been translocated in recent human history. Data supporting the hypothesis of the Old World origin of *Rattus* rat-associated *Bartonella* species include the widespread occurrence of genetically related isolates of *Bartonella* species in *R. norvegicus* from Portugal, the United States, and South America (Buffet et al., 2013). On the other hand, there is an evident difference between the *Bartonella* isolates obtained from rats and from indigenous rodents of America (Ellis et al., 1999). The first evidence *Bartonella* genotypes from Southeastern Asia being related to *B. elizabethae* came from identification of the high diversity of *Bartonella* in *R. tanezumi* rats in several cities of southern China and in lesser bandicoot rats (*Bandicota bengalensis*) and black rats (*R. rattus*) in Dhaka, Bangladesh (Ying et al., 2002; Bai et al., 2007). A few of the multitude of genotypes

found in these rats were identical to sequences of cultures from *Rattus* rats found in France, Portugal, and the United States.

We propose to consider a "source-sink" ecological model developed in the field of population ecology of animals and plants (Pulliam, 1988) for comprehending the differences described earlier in this article. According to the original scheme, rat populations distributed across source habitats within the native range in Asia ("source") are self-sustaining; while the rat populations introduced to other continents ("sink") can be maintained continuously only by immigration of rats from natural habitats. Assuming the role of aboriginal rat populations as "sources" and the role of commensal rats in the continents where rats were introduced relatively recently as "sinks," we can propose one more component for inclusion into this conceptual model. The assemblage of *Bartonella* strains in rats inhabiting big cities in Asia is commonly less diverse compared to populations of rats in native habitats and rural areas within the range of natural origin, but more diverse than in cities of other continents. These communities represent intermediate positions in the "source-sink" model. For example, the number of rat species in Bangkok, Ho Chi Minh City, Yangon, and others is restricted to only two commensal rat species common to urban areas in Africa, Americas, and Europe; but have a reduced diversity compared to communities observed in the forests or fields in Southeast Asia outside cities. The reduced number of rats in big Asian cities can explain the intermediate rate of *Bartonella* circulated within these rat populations. For example, the diversity of *Bartonella* species observed in rats from Dhaka, Bangladesh (Bai et al., 2007) was higher than in rats from cities in Americas and Europe (Gundi et al., 2012), but lower than in natural and agricultural settings in Thailand (Bai et al., 2009). Although all described *Rattus* rat-associated species of *Bartonella* have a worldwide distribution, the diversity of *Bartonella* genotypes in rats from natural habitats of southeastern Asia is much higher compared to a number of strains reported in all cities of the world outside Asia.

In a number of studies, *Bartonella* infection prevalence was higher in *R. norvegicus* compared to *R. rattus* (Ellis et al., 1999; Hsieh et al., 2010; Martin-Alonso et al., 2016). In some situations, this difference can be explained by the load of ectoparasites carried by these rats, but likely this is not the sole explanation. Brettschneider et al. (2012) noticed a similar effect and argued that more detailed biological research on *Bartonella* infections is needed to explain such observations. Based on comparative phylogeography of invasive rats in the United States, Lack et al. (2013) came to conclusion that rats of *R. norvegicus* may contribute to a greater diversity of pathogens from various international sources and spread them across the U.S. compared to *R. rattus*. Their premise is based the data suggesting that gene flow among populations was higher for the Norway rats compared to *R. rattus* (Lack et al., 2013). In addition, their analyses support their hypothesis that *R. norvegicus* rats invade both Atlantic and Pacific coasts of the U.S. and likely from different points of their origin (Lack et al., 2013). A comparison of *Bartonella* observed in both *R. norvegicus* and *R. rattus* in the US cities (Ellis et al., 1999) and phylogenetic analysis of *Bartonella* isolates conducted by Hayman et al. (2013) support this supposition.

## CONCLUSIONS

*Bartonella* species, being a highly prevalent and extremely diverse group of bacteria, are excellent sentinel organisms for evaluating the transoceanic and intra-continental movement of the pathogens by rats of the genus *Rattus*. The analyses described in this article confirmed the role of human-mediated distribution of invasive rat species in dissemination of rat-adapted parasites. Intensive collections and characterization of the *Bartonella* strains recovered from *Rattus* rats allowed the demonstration of the global dissemination of such strains from Asia to Africa, Australia, Europe, and finally to the Americas. Phylogenetic analyses of rat-adapted strains represent an interesting model for investigating pathogen-host coevolution. The interesting question remains how introduction of specialized parasites introduced via invasive rodent hosts can alter parasite community dynamics. Finally, the accumulation of reports of human cases associated with rat-borne *Bartonella* species has increased concern about public health consequences of the global distribution of these bacteria and their introduction to urban centers.

## AUTHOR CONTRIBUTIONS

MK and YB contributed conception and design of the study, organized the database, wrote the manuscript.

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