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Review

A review of the prevalence of emerging Bartonellosis in humans and animals in China

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The genus *Bartonella* is comprised of 20 species and subspecies, in which 10 species are responsible for human infections. The identification of the causative agent of cat-scratch disease, bacillary angiomatosis, urban trench fever, and Carrion's disease has raised the emerging medical importance of *Bartonella* spp. This article provides an overview of bartonellosis with emphasis on its prevalence in China.

Key words: *Bartonella*, cat-scratch disease, wild animal, prevalence.

INTRODUCTION

Bartonella is a small, fastidious, intracellular Gram-negative bacteria that has been identified recently in a wide range of domestic and wild mammals. The genus *Bartonella* has expanded in the recent 15 years from the single *Bartonella bacilliformis* to at least 20 recognized species and subspecies, in which at least 10 of these species and subspecies are known or suspected to be pathogenic for humans (Guptill, 2010). As the improvement on its diagnosis continues, knowledge of the spectrum of clinical diseases resulting from *Bartonella* infection is expanding. Three *Bartonella* species, *B. bacilliformis* (Carrion's disease), *B. henselae* (cat-scratch disease), and *B. quintana* (trench fever), have been well elucidated as primary pathogens of human bartonellosis. In China, this infection lacks recognition especially in clinicians. Some well known bartonellosis, like cat-scratch disease, bacillary angiomatosis, infective endocarditis had not been clinically associated with *Bartonella* infection. However, recent epidemiological studies confirmed the high prevalence of *Bartonella* infection in animals and humans in China. In the present minireview, we focuse on the investigations of bartonellosis in China that published in Chinese and English journals. This literature review is expected to add some new information to the research community.

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PREVALENCE OF BARTONELLOSIS IN RODENTS

The first investigation on bartonellosis was reported in Yunnan province, China (Bai, 2002). From 1999 to 2007, the mentioned research group collected 913 rodent samples from 19 cities and counties in Yunnan, China (Yang et al., 2008; Ying et al., 2002). After bacteria isolation and polymerase chain reaction (PCR) confirmation, 27.5% (251/913) of the rodents belonging to 9 species were found to be infected with *Bartonella* spp., with the highest infectious rate in *Apodemus chevrieri* (Figure 1). A partial fragment of the citrate synthase (gltA) of all isolates was sequenced and 32 genetic variants were confirmed. Phylogenetic analysis based on the partial gltA gene established that 32 variants branched into the clade of *Apodemus elizabethae*, *Apodemus tribocorum*, *Apodemus grahamii*, *Apodemus washoensis Apodemus taylrii*, and *Apodemus phoceensis*. Notably, 4 strains clustered together into a clade that is distinct from other known rodent *Bartonella* spp., and was named *Apodemus yunnannensi*. Here, the phylogenetic tree was reconstructed by incorporating the corresponding gltA sequence of all 20 known species, which elucidated the findings in the said study. Moreover, phylogenetic analysis showed that the *Bartonella* spp. infected in rodents was relative host-specific (Figure 2) in China since majority of the isolates from *Apodemus, Rattus*, and *Eothenomys* clustered within distinct groups. In Fujian province, rodent-associated *Bartonella* spp. was also detected in 20.55% (15/73) of *Suncus mnurinu* and

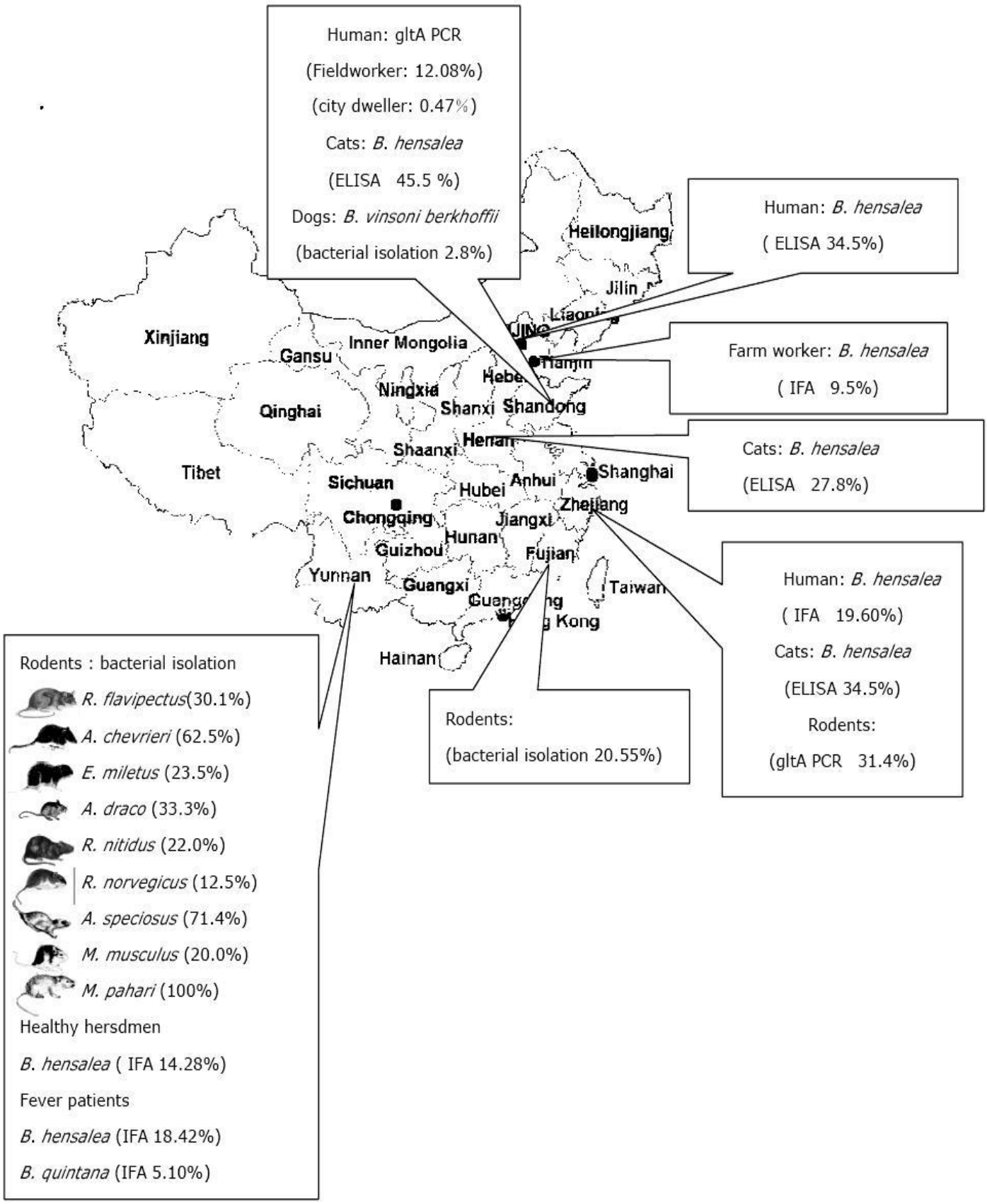

Figure 1. Overview of the prevalence of Bartonellosis in China based on a literature review. Detection method and tested *Bartonella* species were provided.

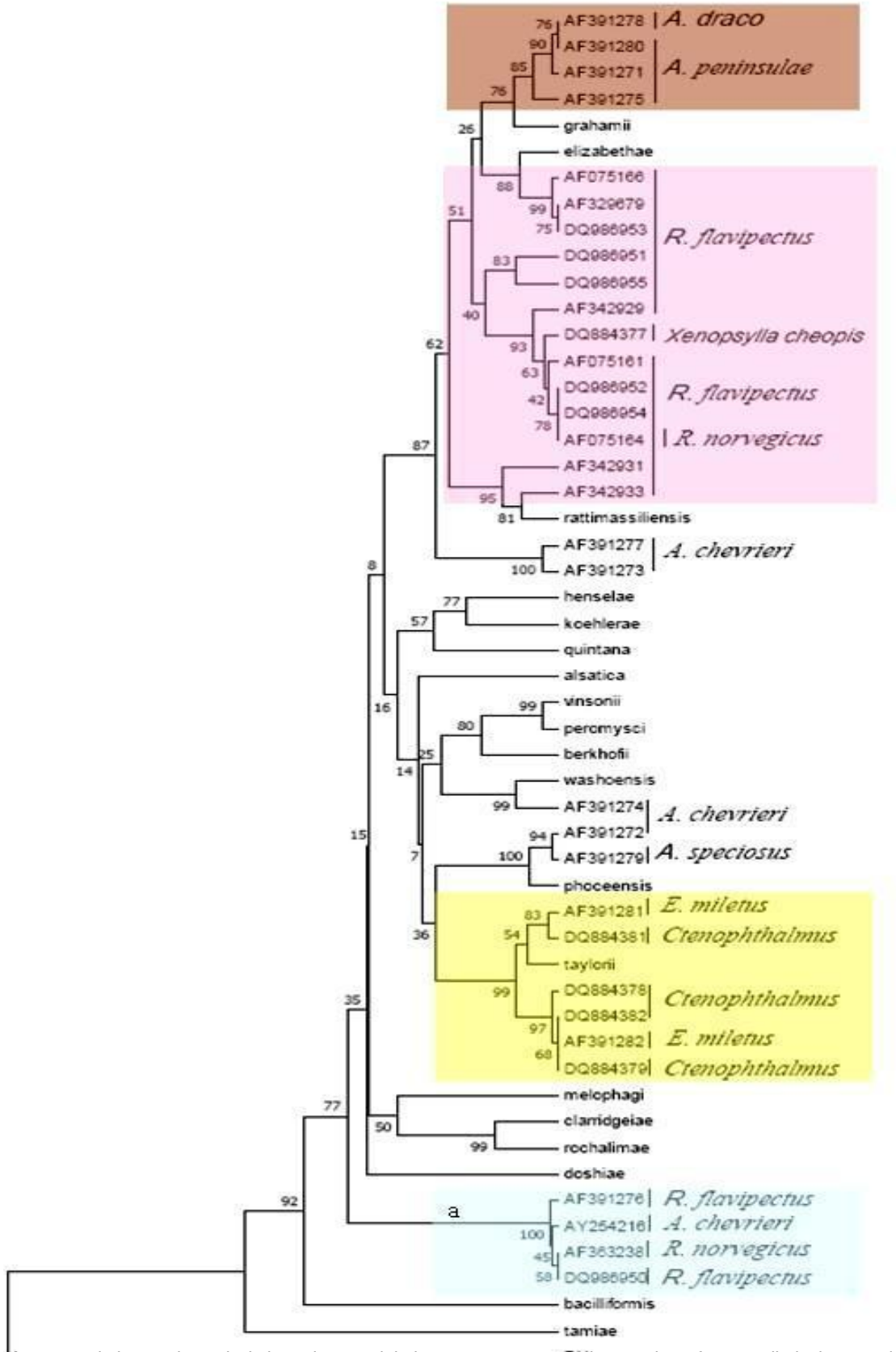

Figure 2. Phylogenetic analysis based on partial gltA sequence. Accession number of Bartonella isolates and nomenclature of rodent and tick species were provided. BU represented the *Brucella abortus* that was selected as the outer group in this phylogenetic tree. The distance indicated by the scale bar is equivalent to the base substitution/10 nucleotides.

8.97% (7/78) of *Rattus norvegicus* (Ye et al., 2006; 2009). Statistical analysis showed infection is more prevalent in tropical zones ($P < 0.001$). Rodent isolates from Fujian province were mainly clustered in three species (*Apodemus elizabethae*, *Apodemus qeenslandensis* and *Apodemus tribocorum*). In Zhejiang province, Eastern China, 31.4% (134/427) of the rodents, consisting of 9 species (*Apodemus agrarius*, *Rattus losea*, *Rattus norvegicus*, *Eothenomys melanogaster*, *Niviventer confucianus*, *Suncus murinus*, *Microtus fortis*, *Rattus flavipectus*, and *Apodemus speciosus*), were positive for *Bartonella* infection by gltA-based PCR detection. Analysis of sequence homology indicated that the rodent isolates were related to *Apodemus rattimassiliensis* and *Apodemus grahami* (Liu et al., 2010; Sun et al., 2010a).

PREVALENCE OF BARTONELLOSIS IN HUMANS

Seroprevalence of *Bartonella* infection in humans was also investigated in the Yunnan province by indirect immunofluorescent assay (IFA) (Yang et al., 2007). Patients with fever of unknown origin (288) and 91 health herdsmen were investigated for the evidence of *Apodemus henselae* and *Apodemus quintana* infections. Results showed 14.28% (13/91) of the herdsmen were positive for *Apodemus henselae* infection while 18.42 and 5.10% of the patients with fever were positive for *B. henselae* and *B. quintana*, respectively ($P > 0.05$). In Northern China, the investigation on *Bartonella* infection in humans showed a big discrepancy in different cities. In the Shengli area, Shandong province, people working in the field (12.08%, 29/240) were confirmed to be a susceptible population for *Bartonella* infection as compared with city dwellers (0.47%, 2/210) (Yang, 2008). In the city of Beijing, the capital of China, a high seroprevalence of *B. henselae* infection was recorded (34.5%, 123/357) using a homemade ELISA kit (Yang et al., 2007b). Statistical analysis confirmed that the infection was not related with the dog and cat exposure. Interestingly, seroprevalence in populations of age < 18 was lowest (21.4%, 3/14) while old people (age > 40) were the most susceptible (37.5%, 21/56), $P < 0.05$. However, low seroprevalence was reported in Tianjin (130 kilometers away from Beijing). Only 9.5% (21/220) of the farm workers were confirmed to be positive for *B. henselae* infection using IFA (Zhang et al., 2008). This discrepancy may be caused by the difference in the detection method used or the participants recruited. In Zhejiang province, *B. henselae* antibodies were detected in 19.60% (109/556) of the human subjects (IFA). Additionally, factors of age and gender were not involved in the infection. However, dog biting was found to be a risk factor of *B. henselae* infection, which is not in accordance with the study performed in Beijing. The authors explained that exposure to dogs may also be more likely similar to the exposure to cats. Moreover, dogs, which served as the host for *Ctenocephalides felis*, will enhance the possibility of vector-borne infection (Sun et al., 2010b).

PREVALENCE OF BARTONELLOSIS IN CATS AND DOGS

B. henselae prevalence in cats was investigated in Northern China. Using the ELISA, 27.8% (78/281) of the cats in the Henan province and 45.5% (15/33) of the cats in the Shandong province showed to be sero-positive (Yang et al., 2007a). However, no genetic information was available from those studies to explore the association of cat isolates and human isolates. Cats in Zhejiang province were also screened for the seroprevalence of *B. henselae* infection (ELISA). Results confirmed that 34.5% of the cats (20/58) were positive (Fu et al., 2008). In Shandong province, 2 dog-associated bartonella isolates were confirmed from 71 dog blood samples. Phylogenetic analysis based on sequence of 16S rRNA, gltA and 16S-23S rRNA ITS showed the 2 isolates belong to the species of *B. vinsoni berkhoffii* (9).

PREVALENCE OF BARTONELLOSIS IN OTHER ANIMALS

Bartonella spp. have been isolated from many other species of domestic and wild animals, including coyotes, horse, deer, cattle, foxes, lions, rabbits, sea turtles, beluga, and porpoises (Breitschwerdt and Kordick, 2000; Maggi et al., 2005, 2008; Jones et al., 2008; Valentine et al., 2007). Although, *Bartonella* infection in these animals was not investigated in China, infection was confirmed in macaques by IFA (36% positive) and bacteria culture (5% positive). Phylogenetic analysis showed those isolates from macaques were *Bartonella quintana* (Huang, 2010). Also in that study, 70 blood samples from rabbits were collected for detection. As a result, no positive sample was confirmed.

Bartonella is one of the most neglected zoonotic pathogen. In China, *Bartonella* infection has not been clinically associated with human diseases since few cases of confirmed human bartonellosis were reported. However, recent studies had confirmed that *Bartonella* infection is prevalent in humans, cats, rodents, and dogs in certain areas of China. Further serological surveys and molecular epidemiological studies are needed to confirm the mode of infection, vector involvement, source of bartonellosis infection, and evaluation of its public health burden in China.

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