Review

Rabies and rabies virus in wildlife in mainland China, 1990–2013

Lihua Wang a,b,*, Qing Tang a,b, Guodong Liang a,b

a State Key Laboratory for Infectious Disease Prevention and Control, Key Laboratory for Medical Virology, National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, 155 Changbai St., Changqing Dist., Beijing 102206, China
b Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Hangzhou, China

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SUMMARY

The number of wildlife rabies and wildlife-associated human and livestock rabies cases has increased in recent years, particularly in the southeast and northeast regions of mainland China. To better understand wildlife rabies and its role in human and livestock rabies, we reviewed what is known about wildlife rabies from the 1990s to 2013 in mainland China. In addition, the genetic diversity and phylogeny of available wildlife-originated rabies viruses (RABVs) were analyzed. Several wildlife species carry rabies including the bat, Chinese ferret badger, raccoon dog, rat, fox, and wolf. RABVs have been isolated or detected in the bat, Chinese ferret badger, raccoon dog, Apodemus, deer, and vole. Among them, the bat, Chinese ferret badger, and raccoon dog may play a role in the ecology of lyssaviruses in mainland China. All wildlife-originated RABVs were found to belong to genotype 1 RABV except for a bat-originated Ikrl virus isolated in 2012. Several substitutions were found between the glycoprotein of wildlife-originated RABVs and vaccine strains. Whether these substitutions could affect the efficacy of currently used vaccines against infections caused by these wildlife-originated RABVs needs to be investigated further. Phylogenetic analysis showed that RABVs in the bat, Chinese ferret badger, and raccoon dog were distinct from local dog-originated RABVs, and almost all collected wildlife-originated isolates were associated with older China clades II to V, suggesting the possibility of wildlife reservoirs in mainland China through the ages.

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1. Introduction

Rabies is one of the oldest diseases in recorded human history, dating back more than 4000 years.1 It occurs in over 150 countries and territories. More than 70 000 human rabies deaths occur annually, and Asia accounts for approximately 80% of the worldwide total.2 Rabies was first reported in about 556 BC and has persisted in China for more than 2500 years. Rabies has been one of the most important infectious diseases in China since the 1950s.3,4 Although comprehensive preventive measures have been taken in past decades (including dog vaccination and post-exposure prophylaxis following human exposure), rabies remains a significant public health problem in mainland China.3,5–7 Currently, China is second only to India in the number of people killed by rabies worldwide, and the epidemic area has expanded to almost the entire country. Many provinces are beginning to report their first cases in more than 10 years.3–8

The role of the domestic dog in the spread of RABVs has been established in China, and almost 95% of human cases have been associated with dog transmission.5–9 However, the number of wildlife rabies and wildlife-associated human and livestock rabies cases has increased in recent years, particularly in the southeast and northeast regions of China (Figure 1 and Table 1). The majority have occurred in the most recent 10 years. Viruses have also been isolated or detected in wildlife, including the bat, Chinese ferret badger, raccoon dog, Apodemus, deer, vole, and wolf.10–20 To better understand wildlife rabies and its role in human and livestock rabies, we reviewed what is known about wildlife rabies from the 1990s to 2013 in mainland China. Additionally, the genetic diversity and phylogeny of available wildlife-originated RABVs were analyzed.

2. Species of wildlife carrying rabies in mainland China

Any warm-blooded animal can catch rabies and pass rabies to human beings.3 Dogs are the main vectors of rabies and have played a pivotal role in human rabies in mainland China.5–9 However rabies has also been reported in wildlife and livestock
including the Chinese ferret badger, raccoon dog, bat, Apodemus, deer, vole, fox, wolf, cat, pig, yellow bull, goat, sheep, cattle, buffalo, and donkey. Cases of wildlife rabies have occurred in both rabies endemic areas (southeast) and sporadic areas (northeast) of mainland China (Figure 1, Table 1).

2.1. Chinese ferret badger

As one of the most popular wildlife animals, Chinese ferret badgers (Melogale moschata) are distributed mostly in the southeast region of China.\(^5\,11\) Since 1995, Chinese ferret badger rabies outbreaks have occurred periodically in the southeast of mainland China, including the provinces of Anhui, Jiangxi, and Zhejiang.\(^20\) RABVs were first detected in Chinese ferret badgers collected in Zhejiang Province in 2008, and have since been detected continuously in Chinese ferret badgers (alive and dead) collected in Anhui, Jiangxi, and Zhejiang provinces (Figure 1, Table 1).\(^12,19,20\) Nucleotide sequencing revealed 99.4–99.8% homology within the Chinese ferret badger isolates, and 83–89% homology to the dog RABV isolates in the nucleoprotein and glycoprotein genes in the same rabies-endemic regions.\(^12,19,20\) In addition, one study showed apparently healthy Chinese ferret badgers with a high percentage of rabies seroconversion (69.6%). Although the titration of virus neutralizing antibodies (VNA) was very low, ranging from 0 to 2.6 IU/ml, the high percentage of rabies seroconversion in Chinese ferret badgers is an interesting discovery, and could be due to abortive rabies infections in the Chinese ferret badger population.\(^20\)

2.2. Raccoon dog

In mainland China, raccoon dogs are distributed widely in the northeastern and southwestern regions of rabies-endemic areas.\(^14,21\) Two outbreaks of raccoon dog rabies have been recorded in mainland China. One occurred in the county of Qingyuan of Liaoning Province in 1982, causing more than 30 raccoon dog deaths.\(^13\) The other occurred in Inner Mongolia in 2007.\(^14\) The latter outbreak was caused by one wild raccoon dog, and 15 domestic raccoon dogs died. The rabid animals had typical clinical signs of rabies, and samples tested positive by direct fluorescence assay (DFA), reverse transcription polymerase chain reaction (RT-PCR), and mouse inoculation test (MIT). Genetic analysis of the isolated virus showed that the outbreak was caused by an arctic-like RABV.\(^14\) This was the first report of arctic-like RABV in China.

2.3. Bat

Other than carnivores, the bat is the most important natural reservoir host of RABVs known today.\(^22\) In recent years, several research groups have conducted long-term studies to investigate whether bats carry rabies in mainland China; RABV antibodies were detected in the serum of collected bats. Of the bat serum samples collected from four southern provinces (Yunnan, Guangxi, Guangdong, and Hainan) of China in 2010, 2.2% (15/685) were positive for RABV antibodies.\(^23\) However, no bat-originated lyssavirus was isolated until 2012: the first bat-originated lyssavirus (Irkut virus, IRKV-THChina12; in Murina leucogaster)
was isolated and identified in Jilin Province (northeast region of China). The nucleoprotein gene of IRKV-THChina12 shared 92.4%/98.9% (nucleotide) and 92.2%/98.8% (amino acid) identity with the two known Irkut virus isolates from Russia. The identification of IRKV-THChina12 represents the first isolation of a bat RABV in mainland China. The latter finding confirmed the existence of bat RABVs in common Chinese bat species, and we believe that additional bat RABV species will be identified in mainland China with more extensive surveillance.

### 2.4. Rat

Rabies-carrying rats have been identified in China since the 1990s. The first rat-originated lyssavirus, MRV (Mouse Rabies virus), was isolated from a vole collected in Henan Province in 1992. Phylogenetic analysis based on the whole genome showed MRV to be distinct from local dog-originated RABVs. In addition, 65 rats captured in Guangxi Province in 2000 showed 3.1% (2/65) positivity for RABV by RT-PCR. RABVs were also identified in

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14 AH, Anhui; GD, Guangdong; GX, Guangxi; HA, Henan; H, Hainan; JL, Jilin; JS, Jiangsu; JX, Jiangxi; LN, Liaoning; NM, Inner Mongolia; SC, Sichuan; XJ, Xingjiang; ZJ, Zhejiang.
15 DFA, direct fluorescence assay; RT-PCR, reverse transcription polymerase chain reaction; MIT, mouse inoculation test; FAT, fluorescent antibody test; IFAT, indirect fluorescent antibody test; FAVN, fluorescent antibody virus neutralization test; ELISA, enzyme-linked immunosorbent assay.
16 No information available.
Apodemus agrarius in Zhejiang Province in 2009. Although these viruses were distinct from local dog-originated RABVs based on phylogenetic analysis, they belonged to the genotype 1 RABVs. Rabies in rats is rather unusual, globally. However in mainland China, particularly in the rabies endemic areas, rats are widely distributed, which increases the chance of contact with rabid animals. These cases of reported rat rabies would come from contact with rabid animals.  

2.5. Rabies in other wildlife and livestock  

Rabid foxes and wolves attacking livestock or humans and causing rabies outbreaks have been reported in Inner Mongolia and Xinjiang Province, indicating that the fox and wolf carry rabies in mainland China. Cats, pigs, yellow bulls, goats, sheep, cattle, buffalo, and donkeys have also been reported to carry rabies in mainland China. Based on analysis of the epidemiology and viruses isolated or detected in these livestock, these cases were related to local dog rabies.

3. Role of wildlife in human and domestic animal rabies in mainland China

3.1. Chinese ferret badger  

Although rabies in Chinese ferret badgers has been reported in other countries, Chinese ferret badger-associated human rabies has been reported only in China. Human cases caused by rabid Chinese ferret badgers were first recorded in Huzhou, Zhejiang Province in 1994. Since then, Chinese ferret badger-associated human rabies has increased and is a public health concern in mainland China. From 1996 to 2004, more than 30 human cases were caused by Chinese ferret badger bites in Zhejiang Province. From 2004 to 2007, no human rabies cases caused by Chinese ferret badger bites were reported in these areas. In 2008, Chinese ferret badger-related human cases reemerged in Zhejiang Province: one human case was caused by infection after capture and consumption of Chinese ferret badger meat. Chinese ferret badger-associated human cases have also been reported in other provinces of China. From 2002 to 2005, seven Chinese ferret badger-associated human cases were reported in Anhui Province; in addition, from 2007 to 2008, four Chinese ferret badger-associated human cases were reported in Wuyuan, Jiangxi Province. In 2004, an independent report stated that a peasant had died of rabies after being bitten by a Chinese ferret badger in Yaan, Sichuan Province. The Chinese ferret badger-associated rabies patients have included Chinese ferret badger hunters who capture and sell Chinese ferret badgers, farmers with occasional exposure to sick Chinese ferret badgers, and residents exposed to sick Chinese ferret badgers in their yard or house. Currently, Chinese ferret badger trading and the consumption of its meat are common in the southeast areas of China, resulting in a frequent source of Chinese ferret badger bites or contact with humans. Awareness that the Chinese ferret badger is a reservoir of RABVs could help people to protect themselves, particularly those resident in the southern part of China.

3.2. Raccoon dog  

Although two raccoon dog rabies outbreaks have been recorded in mainland China since 1982, no human cases caused by a rabid raccoon dog has been reported. However, because raccoon dogs have been confirmed to carry arctic-like RABV in mainland China, raccoon dogs should not be allowed contact with domestic animals or human beings.

3.3. Bat  

Bats have played an important role in the transmission of rabies to other animals and human beings throughout the Americas and in Europe. The first bat-associated human rabies case in mainland China, reported in 2002, was that of a staff member at a television broadcasting station in Tonghua County in northeast Jilin Province. The victim suffered bat bites to the ear and died 10 days after the first manifestation of disease symptoms. In 2010, another bat-associated human rabies case was reported in Longjing City in Jilin Province. The victim suffered bat bites to the hand and died 10 days following the first manifestation of disease symptoms. Both cases developed acute progressive encephalomyelitis consistent with rabies infection, 30 and 20 days, respectively, after the bites. These results indicate that bats pose a threat to human health in mainland China.

3.4. Rat rabies  

Several human rabies cases were reported to have been caused by rats in the high-epidemic rabies areas of mainland China in the 1990s. Thereafter, rat-originated human rabies cases were rare. Considering that RABV have been detected in rats and that human rabies cases caused by rats have been reported, and taking into account the frequency of human contact with rats due to their wide distribution and high density in mainland China, we recommend that the role of rats in transmitting RABVs to humans and animals be evaluated, particularly in rat-endemic areas, even though some experts have reported that rats do not have any epidemiological role in the transmission of rabies to humans.

3.5. Other wildlife  

Wolf-associated human or animal rabies has been reported in China since the 1990s. In 1991, two wolves attacked 31 people and 127 domestic animals in Jalaite in Inner Mongolia, causing six human cases and 19 domestic animal rabies cases. Thereafter, wolf-associated human and animal rabies were reported sporadically. From 1996 to 2006, several wolf-associated human and animal rabies cases were reported in Xinjiang Province. To date, most wolf-associated cases reported in northeast China have usually been a spillover of dog rabies rather than a true cycle of wolf rabies. According to those reports, wolf cases may not be a threat to humans in other areas, including high-epidemic rabies areas in the southeast and east regions of mainland China.

Foxes are a major vector of rabies and are a RABV reservoir for sylvatic rabies in Eurasia and parts of the Americas. Wild foxes exist in the northwest, south, and northeast regions of China; additionally, foxes are bred for fur production in China. Although foxes attacking goats and causing rabies outbreaks has been reported in Inner Mongolia, fox rabies and fox-associated human and animal rabies are rare in China, probably due to the small number of animals, resulting in minimal contact with humans. According to the literature, the role of foxes in transmitting rabies infection to humans and other animals is negligible in China.

4. Genetic diversity and evolutionary characteristics of wildlife-originated RABVs and relationship to dog-originated RABVs in mainland China

4.1. Genetic diversity of the glycoprotein gene in wildlife  

Open reading frames (ORFs) of glycoprotein (G) genes of RABVs in wildlife, livestock, and domestic animals were 1575 nucleotides in length, encoding a 524-amino acid polyprotein, as reported
Figure 2. Multiple alignment of G protein amino acid residues 1–505 for wildlife-, livestock-, and dog-originated RABVs and vaccine strains used in Mainland China. Antigenic site GII (amino acid 34–42 and 198–200), GIII (amino acids 330–338), and G5 (amino acids 244–281) are underlined. Triangles indicate the N-linked glycosylation sites. Dotted lines indicate the T-cell epitopes.
previously for other RABVs in China.\cite{30,31} Comparison of RABV G genes between wildlife and domestic animals (including dogs) revealed putative amino acid sequence identities of 87.2% to 99.8%. The G gene of bat-originated IRKV-THChina12 was found to share 66.9% to 71.6% amino acid identity with other wildlife- and domestic animal-originated RABVs in China. Using the aG strand (GenBank accession number Q412744) as the reference sequence, we aligned the available G genes of wildlife-, domestic livestock-, and dog-originated lyssaviruses with human vaccine strains (CTN, Flury, and PV) and veterinary vaccine strains (SAD and ERA) in China. The highly variable regions are located in the transmembrane region (amino acids 440-461) and cytoplasmic carboxy terminal domain (amino acids 462-505) (Figure 2). Several substitutions were found in the linear epitope G5 (amino acids 253-275) of wildlife-originated lyssaviruses.\cite{52} Among the T-cell epitopes,\cite{53} amino acids 103-178, 244-291, and 336-452 were more variable in wildlife and domestic livestock-originated Chinese lyssaviruses. In addition, the bat-originated IRKV-THChina12 showed considerably lower conservation in all of these antigenic sites and epitopes. Whether these substitutions would affect the antigenic properties of these wildlife-originated RABVs, as well as the efficacy of currently used vaccines against these wildlife-originated RABV infections, should be investigated further.

4.2. Wildlife-originated RABVs are almost exclusively isolated with older lineages

The G and N gene sequences of all available lyssaviruses carried by wildlife and domestic animals (including dogs) in mainland China, together with corresponding sequences from representative lyssaviruses, were aligned and subjected to phylogenetic analysis. The G (Figure 3A) and N (Figure 3B) gene phylogenetic trees showed similar topology structure. All of the wildlife-originated lyssaviruses were grouped within the classic RABV, with the exception of the bat-originated IRKV-THChina12. The wildlife-originated lyssaviruses were distributed across five major sub-clades (designated clades I-V). As reported previously, clade I is a relatively recent lineage that is gaining dominance and is now responsible for most of the new rabies cases in mainland China.\cite{50,54,55,56} The samples in clade I were isolated almost exclusively from dogs, with almost all of the remaining samples collected from humans and domesticated animals. Only two samples were isolated from wildlife (Chinese ferret badger-originated JX09-17 and wolf-originated hubei070308). Conversely, for the older clades (clade II to clade V), a larger proportion of isolates were collected from wildlife, suggesting the existence of wildlife reservoirs in mainland China through the ages.

Figure 3. Neighbor-joining phylogenetic tree (P-distance) for (A) the G gene, and (B) the N gene of RABVs isolated from wildlife, livestock, and dogs in mainland China. G and N gene sequences of lyssaviruses isolated from wildlife, livestock, and in mainland China were downloaded from GenBank and combined with representative strains of lyssaviruses to form the dataset used in this study. Alignment of nucleotide sequences was performed using ClustalX software, version 2.1.\cite{39} Phylogenetic and evolutionary analyses were conducted using MEGA, version 3.1.\cite{16} Bootstrap analysis was performed using 1000 replications, and values greater than 70% were regarded as strong evidence for the particular phylogenetic groupings. Numbers indicate the bootstrap values from 1000 replicates. Clades I-V are indicated. Red dots indicate isolates from wildlife. Blue triangles indicate isolates from livestock. [A] G gene tree. [B] N gene tree.
4.3. The relationship between dog- and wildlife-originated lyssaviruses in mainland China

In mainland China, the dog plays a pivotal role in rabies transmission, and approximately 95% of human rabies cases are ascribed to dog bites.5-9 The phylogenetic analysis showed the isolates from dogs and dog-associated human cases to be grouped mainly within the relatively recent lineage (clade I). Only one Chinese ferret badger-originated strain and one wolf-originated strain isolated recently have been identified within the China clade I, which suggests that the incidence of wildlife rabies spillover from domestic dogs has been emerging in China recently. Other RABVs from Chinese ferret badgers, raccoon dogs, and bats have segregated into independent lineages (Figure 3) and were distinct from dog- and other domestic animal-originated isolates. The latter finding indicates that Chinese ferret badgers, raccoon dogs, and bats have formed independent rabies enzootics during long-term rabies infestation and may constitute wildlife reservoirs responsible for the independent maintenance of RABVs.

RABVs from other wildlife, domestic animals, and livestock are highly related to dog or human case isolates in rabies-endemic areas of mainland China (Figure 3). Although some subgroups are indicated by the phylogenetic tree, identities are above 90% at the amino acid level, indicating that rabies in these hosts may result from spillover from local dogs.

5. Conclusions

This review identified the following main points: (1) Several wildlife species carry rabies in mainland China. (2) Bats, Chinese ferret badgers, and raccoon dogs may serve as reservoirs for RABVs in mainland China, and could play a role in human or livestock rabies. (3) Wildlife-originated RABVs are almost exclusively isolated with older lineages (China clades II to V), suggesting the existence of wildlife reservoirs in mainland China through the ages. (4) The incidence of wildlife rabies spillover from domestic dogs has been emerging in China recently. (5) Although dog rabies elimination is of great importance in mainland China, the management of rabies in wildlife should also be strengthened. In mainland China, there is no nationwide animal surveillance system and no accurate data on wildlife population dynamics.58 More comprehensive studies on the wildlife population dynamics and wildlife rabies in mainland China, including their geographical distribution and densities are needed.

Compared to rabies in dogs, wildlife rabies control is more complex in mainland China due to the complicated ecological and biological factors associated with wildlife reservoirs, limitations in the available control methods, the broad range of public attitudes towards wildlife, poor knowledge of the role of reservoir host abundance and demography, etc. However, people in mainland China could benefit from (1) local education aimed at encouraging people to avoid contact with wildlife, especially Chinese ferret badgers, bats, and raccoon dogs; (2) being warned not to handle or feed wild mammals; (3) establishing state laws prohibiting wildlife importation, distribution, translocation, and private ownership; (4) setting up strategies for communication and cooperation between the Ministry of Health, the Ministry of Agriculture, and wildlife services from the Bureau of Forestry based on an integrated ‘One Health’ approach. In addition, enhanced surveillance, improved diagnostics, and inexpensive and potent human biologicals are also urgently needed for animal and human rabies control in mainland China to meet the goal of eliminating human rabies in South East Asia and the Western Pacific Region by 2020.

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Ethical approval: Ethical approval was not required for this review.

Conflict of interest: No conflict of interest to declare.

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