Li et al. Zoonoses (2024) 4:7
DOI 10.15212/ZOONOSES-2023-0038

ORIGINAL ARTICLE

Epidemiological Characteristics of Human Rabies in Urban and Suburban Districts in Shanghai, 2006–2021

Zhi Li[1], Jiayu Hu[1], Zhuoying Huang[1], Xiang Guo[1], Jia Ren[1], Jing Qiu[1], Xiaoying Ma[1], Han Yan[1], Fang Huang[1] and Xiaodong Sun[1,*]

***Corresponding author:**
E-mail: sunxiaodong@scdc.sh.cn (XS)

[1]Institute of Immunization, Shanghai Municipal Center for Disease Control and Prevention, Shanghai 200336, China

Received: September 3 2023
Revised: November 21 2023
Accepted: December 22 2023
Published Online: January 12 2024

Abstract

Objective: Rabies is a vaccine-preventable, viral zoonotic disease caused by a lyssavirus. This study was aimed at analyzing the epidemiological characteristics of human rabies in Shanghai to provide valuable information to support accurate prevention and control.

Methods: Individual-level data on human rabies and dog bites/attacks in Shanghai were collected from 2006 to 2021. Demographic characteristics, spatial and seasonal patterns, and correlations were analyzed to explore the epidemiological profiles. Infection risk was predicted with a Bayesian aggression model.

Results: A total of 43 human rabies cases were registered in Shanghai in 2006–2021; the annual average incidence rate was 0.01/100000. Males and residents at ages of 10 to 19 years and over 50 years had an elevated risk of rabies. All cases were reported in suburban districts and peaked in July. The body parts most frequently injured by dogs were the hands (48.84%). The fatality rate was 100%. Most cases (86.05%) were not treated after exposure. A total of 310 dog bites/attacks were reported and significantly correlated with the number of cases (P=0.010). The predicted risk of human rabies was higher in suburban than urban areas.

Conclusion: The incidence of human rabies in Shanghai was relatively low; nevertheless, risk still existed, particularly in suburban areas.

Key words: Human rabies, Epidemiology, Surveillance, One health, Prediction

INTRODUCTION

Rabies is a vaccine-preventable, viral, zoonotic disease caused by lyssavirus, which leads to progressive and fatal inflammation of the brain and spinal cord; rabies kills most individuals who do not receive post-exposure prophylaxis (PEP) after infection [1,2]. A total of 59,000 human deaths have been estimated to occur annually in more than 150 countries, mainly in Africa and Asia; moreover, 40% of cases are in children under 15 years of age, predominantly in poor rural populations [3].

Human rabies remains a serious public health problem in China [4], where rabies ranks among the top five infectious diseases in terms of reported mortality. Dogs are the major source of human rabies [5]. In recent decades, the number of human rabies cases has fluctuated.

Two epidemic peaks occurred in 1981 and 2007, with 7,037 and 3,300 cases, respectively [5,6]. In recent years, the government issued the National Medium and Long-Term Animal Epidemic Prevention Planning (2012–2020) and the National Animal Rabies Prevention and Control Plan (2017–2020), which have highlighted strategies for rabies control and prevention [7,8]. Meanwhile, China adopted "One Health" strategies for rabies control in rural areas, to promote exchange across disciplines, data sharing, and coordination of anti-rabies efforts [9,10]. In 2004, the real-time Notifiable Infectious Disease Reporting System was established in China, thus facilitating complete and timely reporting of infectious disease cases including human rabies [11-13]. The number of human rabies cases continually decreased and reached its lowest level in 2020; 202 cases have occurred since 2007 [14].

Historically, human rabies cases have been reported in all provinces, predominantly in the eastern and southern regions of the country [15]. Currently, cases occur primarily in the southern and central regions, and are gradually spreading through the north [5]. As a neglected disease, human rabies predominantly affects already marginalized, poor and vulnerable populations, for which effective vaccines and immunoglobulin therapies are often not readily available or accessible [16]. Human rabies poses a high risk of transmission and disease burden in rural areas, but has been less of a concern in urban and suburban areas. In this study, the epidemiological characteristics of human rabies in Shanghai from 2006 to 2021 were analyzed, to provide information to aid in accurate prevention and control, particularly in urban and suburban areas.

MATERIALS AND METHODS

Study sites

Shanghai, one of the four municipalities, is the largest city in the country, and serves as a global financial hub located on China's central coast. The land area of Shanghai comprises 6,340.5 km^2, which is divided into 16 county-level districts (Fig 1): seven (Huangpu, Xuhui, Jingan, Changning, Putuo, Hongkou and Yangpu districts) urban and nine (Minghang, Baoshan, Fengxian, Jiading, Songjiang, Qingpu, Jinshan, Chongming and Pudong new districts) suburban.

Data collection

Confirmed or clinical cases with individual data collected through the Notifiable Infectious Disease Reporting System between January 1, 2016, and December 31, 2021, were reviewed. The data included demographic information, residence type, case classification, date of onset, and date of death, if applicable. In addition, the number of dog bites/attacks involving one dog biting multiple people

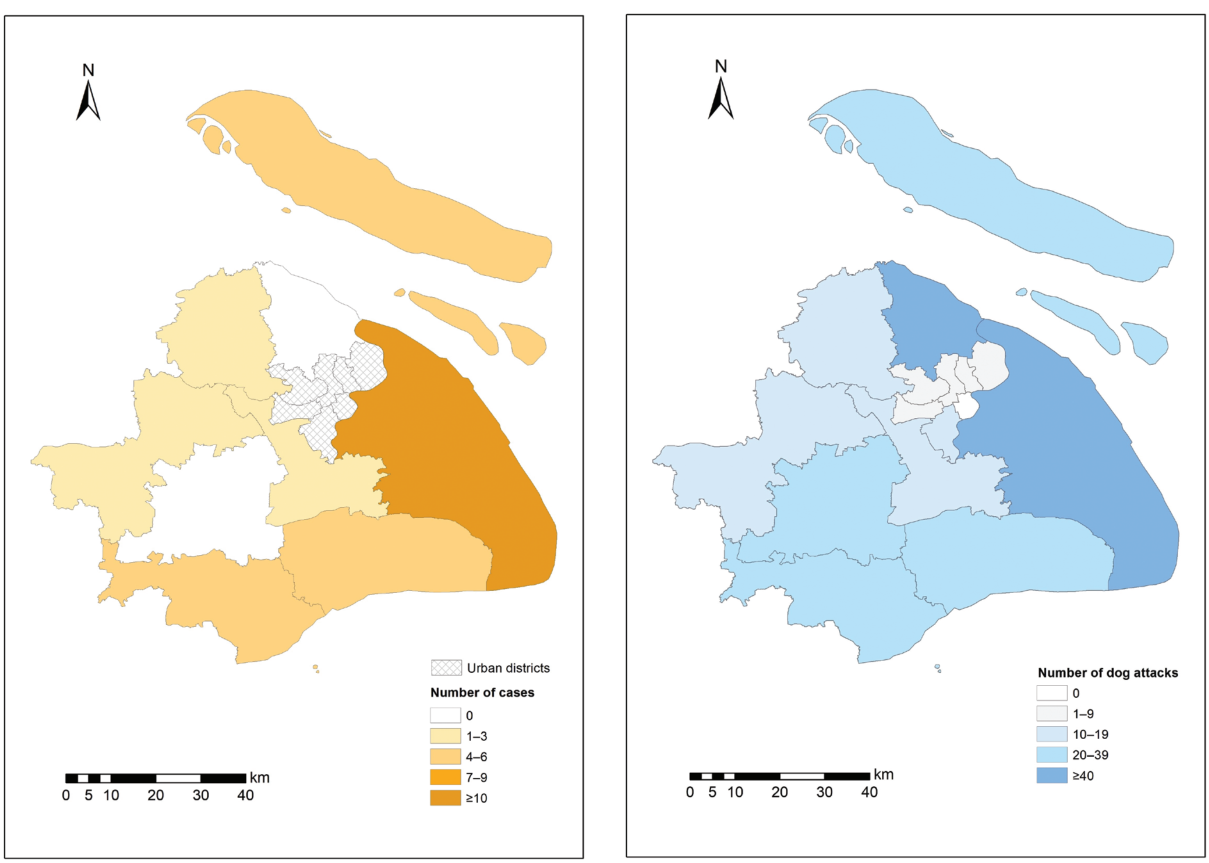

FIGURE 1 | Distribution of reported human rabies cases and cases of one dog biting multiple people in Shanghai.

during the same period was collected from the district center for disease control and prevention in Shanghai.

Definition of cases

According to the national guidelines [17], human rabies cases were classified into clinically diagnosed cases and confirmed cases, on the basis of epidemiological history, clinical symptoms and laboratory test findings. Clinically diagnosed cases were defined as cases meeting at least one of the following criteria: (i) symptoms of severe rabies and (ii) history of dog bite and paralytic rabies. Confirmed cases were defined as clinical diagnosed cases with laboratory evidence of rabies virus (RABV) infection, detected with direct fluorescent antibody testing, reverse-transcriptase polymerase chain reaction or viral isolation testing of clinical specimens. Local cases and imported cases were defined as those involving injury or bites by dogs inside and outside of Shanghai, respectively. Cases of one dog biting multiple people (dog bites/attacks) were defined as those in which a dog injured two or more people within 2 days.

Data analysis

The epidemiological characteristics of human rabies were analyzed. Temporal distributions were analyzed by year and month in WPS office (version 2019). Statistical analysis was performed in SPSS software (version 20.0). Frequency, median, rate and composition ratio were used for quantitative analysis. The chi-squared test was used to evaluate differences among sub-groups; Fisher's exact test was used if 25% of the cells had expected counts less than five. The correlation between the number of cases and dog bite/attack events was determined with Pearson correlation analysis. Maps were created in ArcGIS 10.1 (Environmental Systems Research Institute, Inc., Redlands, CA, USA). A P value < 0.05 was considered to indicate a statistically significant difference.

Spatial modelling

The predicted risk of humans contracting dog-mediated rabies was quantified with a Bayesian spatial regression model [18,19]. We assumed that the studied area was divided into N contiguous districts denoted $i=1,2,\ldots, N$, and used Y_i to represent the number of cases in each district I. We assumed that Y_i ($i = 1,2,\ldots,N$) comprised an independent identical distribution of random variables following a Poisson distribution. The Poisson distribution function was

$$Y_i \sim Poisson(e_i r_i),$$

where e_i is the expected number of cases, and r_i is the relative risk. The number of cases and the population were known quantities. The relative risk was modeled as

$$\log(r_i) = \alpha + \beta_1 X_i + \beta_2 b_i + \mu_i,$$

where α is a common intercept for the entire area, X_i is the number of dog bites/attacks,

$$b_i = \begin{cases} 0, & urban \\ 1, & suburban \end{cases}$$

μ_i is a random effect term, μ_i is unstructured noise following a normal distribution, and $\mu_i \sim N(0,\sigma_u^2)$.

The estimates of the posterior and predictive quantities of interest were obtained in R software.

Ethical statement

This study was approved by the Institutional Review Board of the Shanghai Municipal Center for Disease Control and Prevention under approval number (2023-54).

RESULTS

Epidemic trends

A total of 43 human rabies cases were reported in Shanghai during 2006–2021, consisting of 33 local cases and 10 imported cases. The imported cases were distributed across six provinces: four cases from Anhui Province; two cases from Sichuan Province; and one case each from Guizhou, Shanxi, Shannxi and Henan provinces. All cases were clinically diagnosed cases. The average annual incidence rate was 0.01/100,000, and the highest reported incidence rate, 0.04/100,000 occurred in 2006, with a total of seven cases (Fig 2). No cases were reported in 2015, 2019, 2020 and 2021.

Demographic characteristics

Of the 43 human rabies cases, 35 were in males, and 8 were in females, with a sex ratio of 4.38:1. Cases occurred in people 3 to 87 years old; the median age was 52 years. The local human rabies cases were distributed across all age groups, and the estimated annual incidence were high in the age groups of 50–59, 10–19, and ≥60 years, whereas the imported cases occurred mainly in children and young adults, and no cases reported in ages of 10–19 and ≥50 years (Table 1).

Spatio-temporal patterns and disease course

A total of 33 local human rabies cases were distributed across seven suburban districts: 11 cases in Pudong new district, 7 cases each in Jinshan and Fengxian, 4 cases in Chongming, 2 cases in Jiading, and 1 case each in Minhang and Qingpu districts (Fig 1). No cases were reported in urban districts. Cases occurred throughout the year; 57.89% (22/43) of cases were associated with injury during May through August, and the peak occurred in July (Fig 3).

The most frequently injured body parts were the hands (48.84%, 21/43), then the face (13.95%, 6/43). The median incubation period from dog bite to the onset of illness was 64 days. People bitten on the face had shorter incubation periods than those bitten on other body parts (Fig 4). Most (75.61%, 31/41) cases developed symptoms within 3 months after dog bites/attacks, and 90.24% (37/41) had a symptom onset within 1 year after injury. The history of

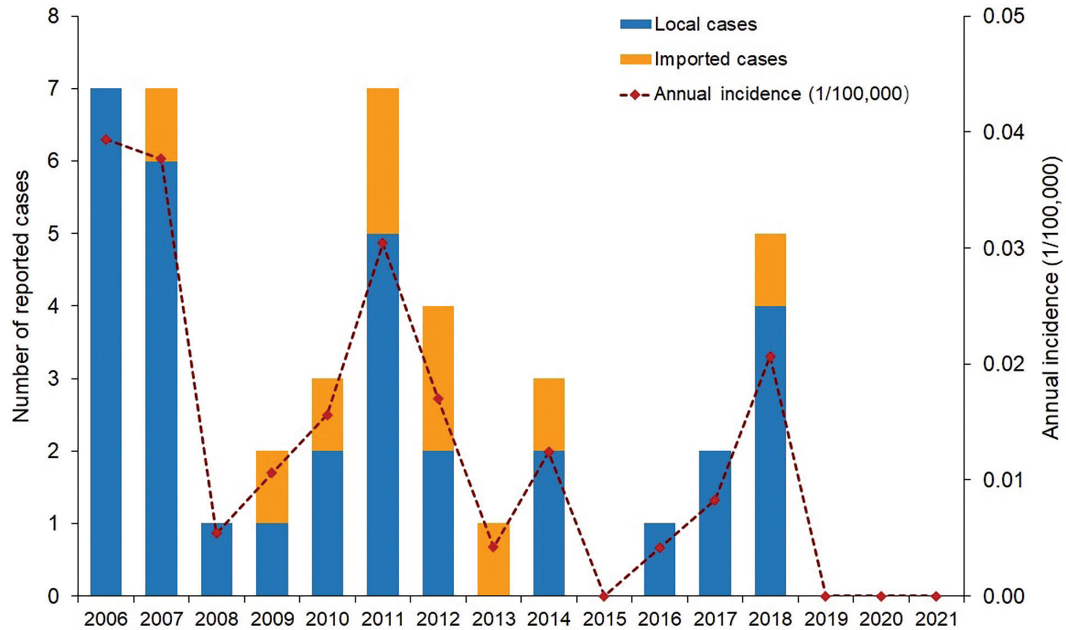

FIGURE 2 | Number of reported human rabies cases and annual incidence in Shanghai, 2006–2021.

TABLE 1 | Demographics of human rabies cases in Shanghai, 2006–2021.

Characteristics	Cases by type		Total cases	P value*
	Local cases	Imported cases		
	N	N		
Sex				0.096
Male	25	10	35	
Female	8	0	8	
Age				0.004
0–9	2	2	4	
10–19	2	0	2	
20–29	1	4	5	
30–39	5	2	7	
40–49	5	2	7	
50–59	9	0	9	
≥60	9	0	9	
Duration of hospitalization				0.835
0–5	25	7	32	
6–9	4	2	6	
≥10	4	1	5	

*Fisher's exact test was used to evaluate differences among groups.

dog attack or contact history were unavailable in two cases. All 43 cases were in patients who were hospitalized and died after the onset of illness. The median time between onset of illness and death was 3 days, and the range was 1 to 16 days. In 95.35% (41/43) of cases, the individuals died within 2 weeks after the onset of illness.

The outcome of all 43 cases was death. Among these cases, 37 individuals did not seek PEP after exposure; five had visited private clinics or township health centers for treatment but did not receive standardized treatment; and one individual, who was one of several victims of a single dog, was injured on the face and lip, and received

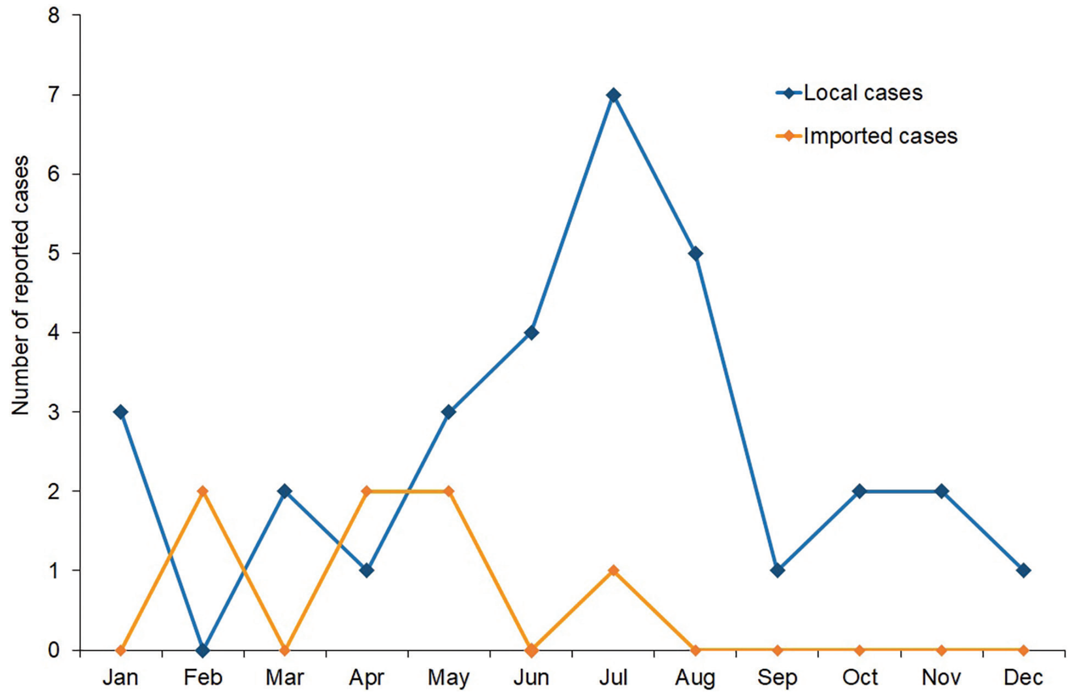

FIGURE 3 | Seasonal pattern of human rabies cases in Shanghai, 2006–2021.

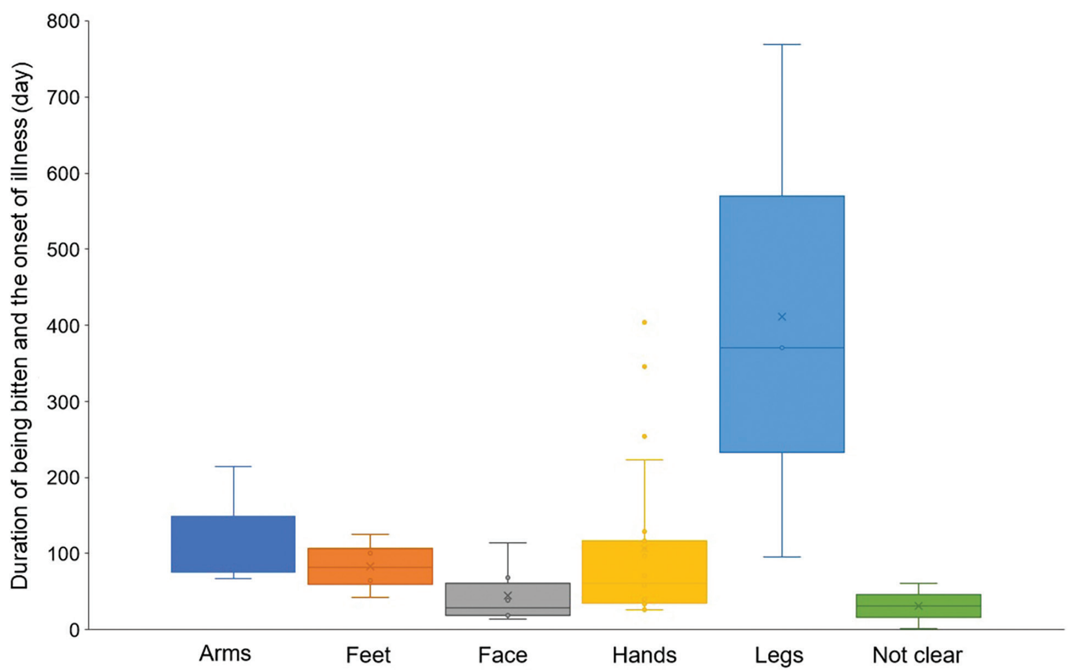

FIGURE 4 | Durations of the onset of illness after being bitten, by bitten body part, 2006–2021. The median, range and upper and lower quartiles, and discrete values of the data are divided into discrete duration ranges.

immediate treatment, but died after the third dose of immunization.

Correlation between reported cases and dog bites/attacks

A total of 310 events of one dog biting multiple people (dog bites/attacks) occurred, and 1,431 people were injured during 2006–2021. All 15 districts except Huangpu District reported events of one dog biting multiple people. All injured people received PEP as required and healed, except for one death in a person who had been bitten on the face and lips 13 days prior, who had received rabies immunoglobulin and three doses of vaccine. The number of human rabies cases and events of dog bites/attacks were significantly correlated (P=0.010), with a correlation coefficient of 0.624 (Fig 5).

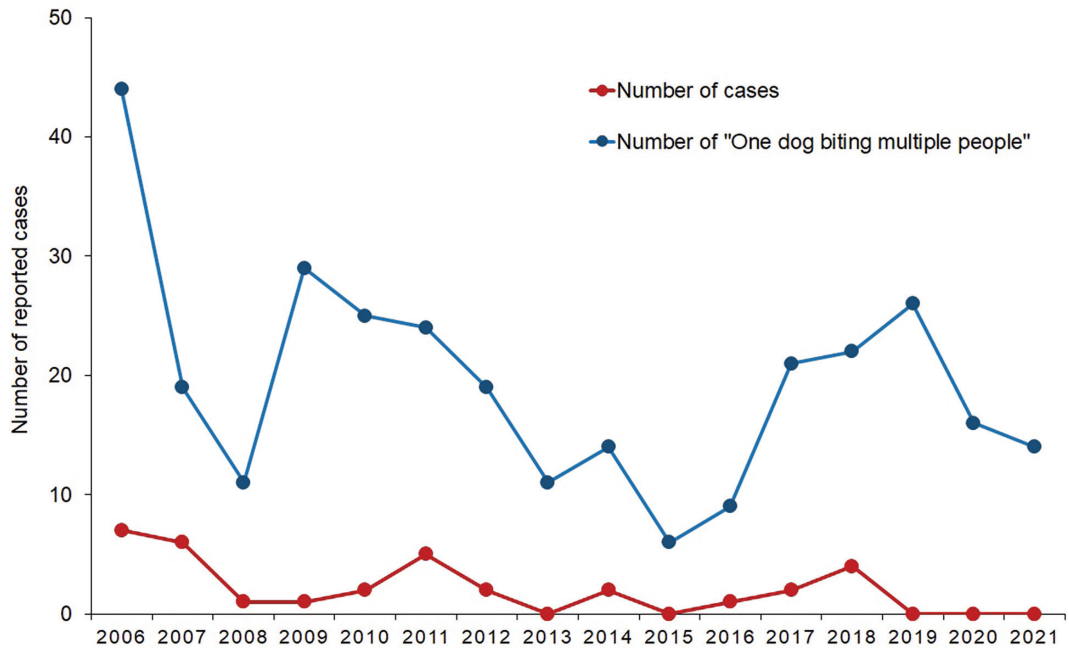

FIGURE 5 | Correlation between the number of human rabies cases and cases of one dog biting multiple people.

TABLE 2 | Fitting parameters of the predictive Bayesian spatial regression model.

Parameter	Value	Std	P
$\alpha + \mu$	−18.35992731	0.083543329	0.858542125
β_1	−0.015188359	3.448694014	0.004486309
β_2	11.82519641	1.966883422	3.98E-07

Prediction of risk of human rabies transmission

The predictive risk of each district was assessed according to the number of cases, dog bites/attacks and the local population. According to the prediction outcome based on a Bayesian spatial regression model, the fitted parameters of β_1 and β_2 were −0.015188359 and 11.82519641, respectively (Table 2). The predict risk of human rabies transmission in suburban districts of Jinshan, Fengxian and Chongming were relatively high, whereas all urban districts and Baoshan and Songjiang suburban districts were low (Fig 6).

DISCUSSION

Rabies control is a model for "One Health" implementation, as its proven methodologies demonstrate the effectiveness of collaboration at the human-animal interface, including at community and municipal level [20,21]. The WHO has called for elimination of dog-mediated human rabies deaths worldwide by 2030; central to this strategy is a "One Health" approach, which recognizes the close links among human, animal and environmental health, and promotes intersectoral collaboration to overcome public health challenges [3,22,23]. China has achieved remarkable progress in the control and prevention of human rabies through concerted stakeholder efforts [24,25]. The number of human rabies cases decreased 94%, from 3,300 cases in 984 counties in 2007 to 202 cases in 143 counties in 2020 [5,26]. The incidence of human rabies in Shanghai was found to plateau, and the cases were scattered and occurred primarily in suburban districts. Historically, the highest incidence of human rabies in Shanghai occurred in 1950, reaching 1.98/100,000; subsequently, during 1958–1988, only two imported cases and no local human rabies cases were documented [27,28]. After that, the number of reported cases has remained at four or fewer per year until 2006.

Our results indicated that most human rabies cases in Shanghai were in males (81.40%) and people ≥50 years (41.86%), followed by children; these findings were similar to those in other areas of China [5,29]. Another WHO report has indicated that children under 15 years of age are the highest risk population, accounting for 40% of total cases globally [16]. The reasons for these findings might be that most cases in the WHO report were from rural areas in Africa and Asia, where the rates of dog immunization are low, and that young children have high chances of contact with dogs. This study found that 75% of the onset of illness occurred within 3 months after dog attack, and the median period was 64 days, in agreement with the duration of 1–3 months described in a WHO position paper in 2018 [30].

Standardized PEP is a crucial step in preventing rabies, consisting of immediate, thorough wound treatment, a series of rabies vaccinations and, if indicated, administration of rabies immunoglobulin or monoclonal antibodies [16,29]. The fatality rate was 100% in this study, and no

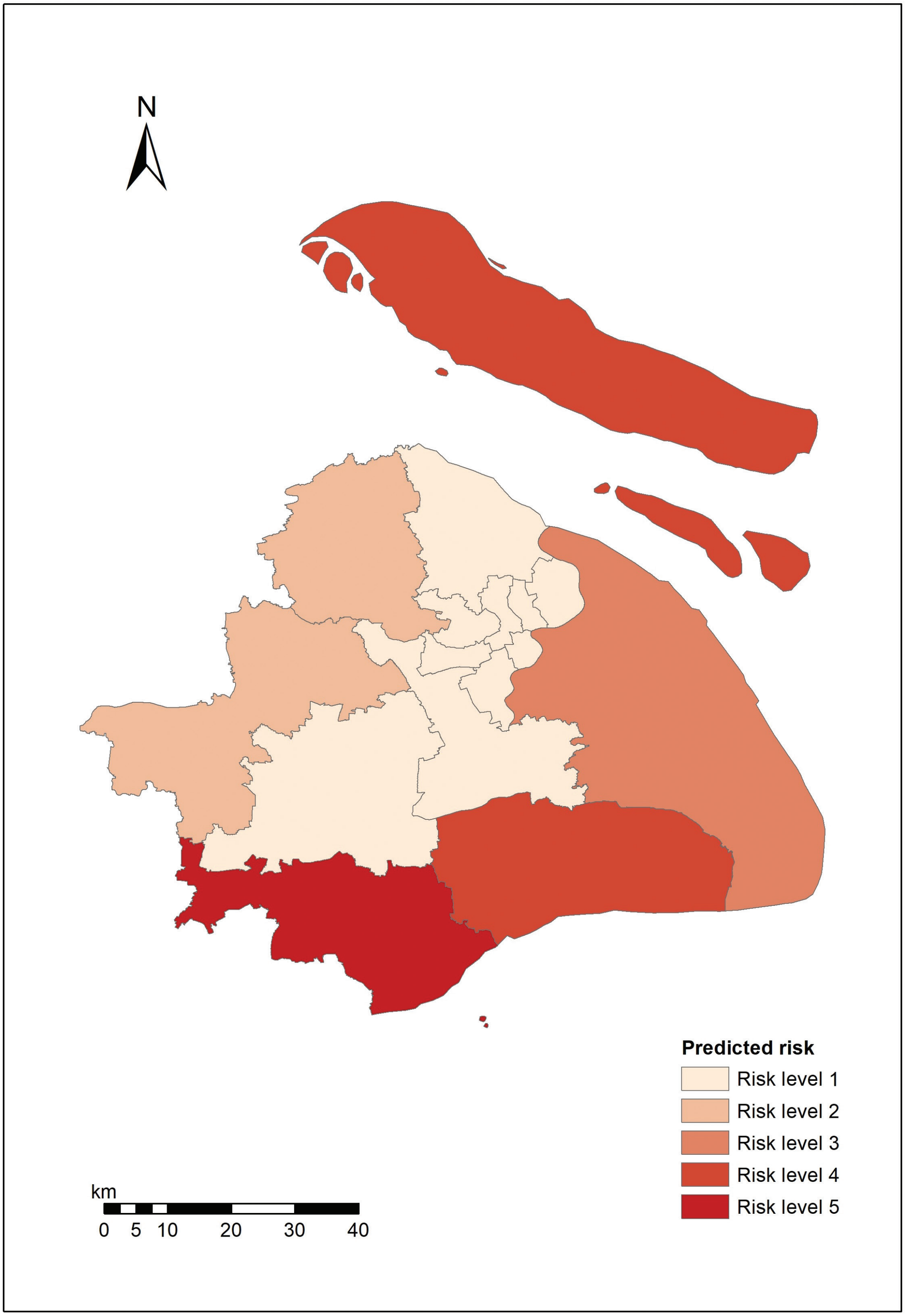

FIGURE 6 | Predicted risk of human rabies transmission among districts in Shanghai.

cases were treated with the entire standardized PEP process. The main reason for the lack of standardized treatment was variability in healthcare seeking behavior and a lack of adherence to recommended treatment guidelines, although PEP is available; these factors have been demonstrated to be associated with rabies deaths [31].

In recent years, the RABV positive rate in cases of one dog biting multiple people has been found to exceed 80%, according to laboratory testing [25]. Similarly, one study has reported that three of four dogs involved in cases of one dog biting multiple people in Shanghai from May to June of 2019 were RABV positive, including one pet dog and two stray dogs [32]. According to the technical guidelines [17], surveillance systems for human rabies in China have been strengthened, particularly for cases of one dog biting multiple people. After a human or animal epidemic, or the occurrence of one dog biting multiple people, an emergency response must be rapidly initiated, and reporting must be submitted promptly. In the past 5 years, no districts except Huangpu and Jing'an in the central urban area of the city have reported cases of one dog biting multiple people, thus suggesting that animal rabies among dogs in the city and the risk of human rabies have persisted. According to the National Animal Rabies Prevention and Control Plan, a 90% immunization rate among registered dogs was achieved in all counties by 2020 [8]. Therefore, continued routine dog management and immunization should be included in the surveillance system.

Our model indicated that the predicted risk of human rabies transmission in suburban districts was higher than that in urban districts in Shanghai. Because the number of predictors weas limited, consisting of only the number of cases and dog bites/attacks, bias might have been introduced in this study. Previous studies have used other predictors, such as the number of dogs, dog immunization coverage, and social or economic factors, which might have increased the predictive accuracy [18,33].

Several limitations should be considered in interpreting the results from this study. First, the sample size was relatively small. Although dog bites/attacks occurred in almost all districts, the number of human rabies cases was low, primarily because of high awareness of health care and seeking of medical treatment among residents in urban areas. Second, the data were from only one city and might differ from those in other cities. Third, all cases were clinically diagnosed without laboratory testing, and could not be determined to be confirmed cases.

CONCLUSION

This study indicated that the incidence of human rabies cases in urban and suburban areas in Shanghai was relatively low, particularly in urban areas. Nevertheless, dog bites/attacks still occurred, and a risk of transmission persists. Continued strengthening of surveillance, multisectoral collaboration and whole-society participation should be a high priority to end human deaths from dog transmitted rabies.

ACKNOWLEDGEMENTS

This study was supported by the Shanghai Science and Technology Agriculture Project (2020–02–08–00–03–F01460), Key Young Talents Training Program for Shanghai Disease Control and Prevention (21QNGG06) and Talent Training Project for Public Health.

CONFLICTS OF INTEREST

The authors declare no competing interests.

REFERENCES

1. Fooks AR, Jackson AC (Eds). Rabies: Scientific Basis of the Disease and its Management. San Diego, CA: Academic Press Inc.; 2020.
2. WHO. Guide to introducing human rabies vaccine into national immunization programmes. Geneva: World Health Organization; 2022.
3. WHO. Zero by 30: the global strategic plan to end human deaths from dog-mediated rabies by 2030. Geneva: World Health Organization; 2018.
4. Zhou H, Vong S, Liu K, Li Y, Mu D, Wang L, et al. Human rabies in China, 1960-2014: a descriptive epidemiological study. PLoS Negl Trop Dis. 2016;10(8):e0004874.
5. Liu Z, Liu M, Tao X, Zhu W. Epidemic characteristics of human rabies - China, 2016-2020. China CDC Wkly. 2021;3(39):819-821.
6. Yin W, Dong J, Tu C, Edwards J, Guo F, Zhou H, et al. Challenges and needs for China to eliminate rabies. Infect Dis Poverty. 2013;2(1):23.
7. The Central People's Government of the People's Republic of China. Medium and long-term control plan on epidemic diseases in animals (2012–2020). Beijing; 2012.
8. Ministry of Agriculture of the People's Republic of China. National control plan on animal rabies in China (2017–2020). Beijing; 2017.
9. Tan J, Wang R, Ji S; Nanjing Agricultural University research group of The Challenge Cup Rabies Research Group; Su S, Zhou J. One Health strategies for rabies control in rural areas of China. Lancet Infect Dis. 2017;17(4):365-367.
10. Wang X, Rainey JJ, Goryoka GW, Liang Z, Wu S, Wen L, et al. Using a One Health approach to prioritize zoonotic diseases in China, 2019. PLoS One. 2021;16(11):e0259706.
11. Bai BK, Xu Z, Shen HH. Infectious disease surveillance in China. J Infect. 2015;71(6):698-700.
12. Zhang H, Wang L, Lai S, Li Z, Sun Q, Zhang P. Surveillance and early warning systems of infectious disease in China: from 2012 to 2014. Int J Health Plann Manage. 2017;32(3):329-338.
13. Wang L, Wang Y, Jin S, Wu Z, Chin DP, Koplan JP, et al. Emergence and control of infectious diseases in China. Lancet. 2008;372(9649):1598-1605.
14. The National Bureau of Disease Control and Prevention. General Situation of National Legal Infectious Diseases, 2020. Beijing; 2021.
15. Gao L, Lin XB, Zhang Q, Jiang LM, Wang P. Epidemiological features of human rabies in China from 2004 to 2012. Internat J Epidemiol Infect Dis. 2014;41(3):176-178.
16. WHO. Rabies. Available from: https://www.who.int/news-room/fact-sheets/detail/rabies.
17. WHO. Rabies. Geneva: World Health Organization; 2018.
18. China CDC. Technical guidelines for human rabies prevention and control (2016). Beijing: Chinese center for disease control and prevention; 2016.
19. Huang F, Zhou S, Zhang S, Zhang H, Li W. Meteorological factors-based spatio-temporal mapping and predicting malaria in central China. Am J Trop Med Hyg. 2011;85(3):560-567.
20. Degeling C, Brookes V, Lea T, Ward M. Rabies response, One Health and more-than-human considerations in Indigenous communities in northern Australia. Soc Sci Med. 2018;212:60-67.
21. Nadal D, Beeching S, Cleaveland S, Cronin K, Hampson K, Steenson R, et al. Rabies and the pandemic: lessons for One Health. Trans R Soc Trop Med Hyg. 2022;116(3):197-200.
22. Minghui R, Stone M, Semedo MH, Nel L. New global strategic plan to eliminate dog-mediated rabies by 2030. Lancet Glob Health. 2018;6(8):e828-e829.

23. Tidman R, Thumbi SM, Wallace R, de Balogh K, Iwar V, Dieuzy-Labaye I, et al. United against rabies forum: the One Health concept at work. Front Public Health. 2022;10:854419.
24. Chen Q, Ma X, Rainey JJ, Li Y, Mu D, Tao X, et al. Findings from the initial Stepwise Approach to Rabies Elimination (SARE) Assessment in China, 2019. PLoS Negl Trop Dis. 2021;15(3):e0009274.
25. Yin W, Fu ZF, Gao GF. Progress and prospects of dog-mediated rabies elimination in China. China CDC Wkly. 2021;3(39):831-834.
26. Song M, Tang Q, Rayner S, Tao XY, Li H, Guo ZY, et al. Human rabies surveillance and control in China, 2005-2012. BMC Infect Dis. 2014;14:212.
27. Hu J, Xu T, Wu Z, Shi Y, Zhao L, Shen X, et al. [A study on the epidemiological characteristics and the preventive measures of rabies in Shanghai]. Zhonghua Liu Xing Bing Xue Za Zhi. 2001;22(1):11-13.
28. Shi Y, Hu JY, Shen RH, Zhao LL, Yang JP, Tao LN. [Study on the epidemiological characteristics and preventive measures of rabies in Shanghai from 2001-2005]. Zhonghua Liu Xing Bing Xue Za Zhi. 2006;27(12):1098-1099.
29. Yin WW, Wang CL, Chen QL, Dong GM, Li YH, Zhu WY, et al. [Expert consensus on rabies exposure prophylaxis]. Zhonghua Yu Fang Yi Xue Za Zhi. 2019;53(7):668-679.
30. WHO. Rabies vaccines: WHO position paper – April 2018. World Health Orgnization; 2018.
31. WHO. Rabies vaccines: WHO position paper. Geneva: World Health Organization; 2018.
32. WHO: WHO Expert Consultation on Rabies. Third Report. Geneva: World Health Organization; 2018.
33. Pepin KM, Davis AJ, Streicker DG, Fischer JW, VerCauteren KC, Gilbert AT. Predicting spatial spread of rabies in skunk populations using surveillance data reported by the public. PLoS Negl Trop Dis. 2017;11(7):e0005822.