International Journal of Infectious Diseases 38 (2015) 77–82

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Human rabies in Zhejiang Province, China☆

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ARTICLE INFO

Article history:
Received 9 April 2015
Received in revised form 15 July 2015
Accepted 16 July 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Human rabies
Epidemiology
Immunization

SUMMARY

Objectives: To explore the epidemiological characteristics of human rabies in Zhejiang Province, China.
Methods: Descriptive and statistical analyses were performed using data collected through interview with human rabies cases or their relatives during 2007 to 2014. A standardized questionnaire was used to collect the data.
Results: Two hundred and one cases of human rabies were diagnosed in Zhejiang Province between 2007 and 2014, with a gradually declining annual incidence. Of the rabies cases identified, 61.2% were aged 40–65 years, and the male to female ratio was 2.30:1; 63.7% of cases occurred in the summer and autumn. The two most reported occupations were farmer (69.2%) and rural laborer (15.4%). Wenzhou, Jinhua, and Huzhou were the three cities with the most reported cases. The majority of cases (92.8%) were attributed to canines, and 71.0% of animal vectors were household animals. Less than half of the cases (41.4%) sought wound treatment after exposure. Post-exposure passive immunization was given to 9.7% and active immunization to 2.3%. Cases with a wound on the head/face only had a significantly shorter incubation than those with wounds at other sites ($p < 0.05$); cases with a wound on the hand only had a significantly shorter incubation than those with a wound on the lower limb below the knee only ($p < 0.001$). Non-resident cases were significantly younger ($p < 0.001$) and had a shorter disease duration ($p = 0.015$) than locally resident cases.
Conclusions: The majority of rabies cases occurred among 40–65-year-old male residents of northern, mid-west, and southeast Zhejiang Province. Further health education is needed to increase the coverage of post-exposure prophylaxis (PEP) in people exposed to possible rabid animals and rabies vaccine use in household animals.

1. Introduction

Rabies is a preventable viral zoonosis with almost 100% mortality in the human. It is normally transmitted from an infected animal through a bite or scratching. People can also become infected when infectious material (usually saliva) comes into direct contact with the mucosa or fresh skin wounds. Dogs are the infection source of the vast majority of human rabies cases worldwide.[1] Bats are an important source of human rabies in the Americas, and it is becoming an emerging public health threat in Australia and Western Europe. The highest incidence of human rabies occurs in Asia and Africa, where rabies potentially threatens over three billion people.[1] It is estimated that there are 20 565 human rabies cases annually in India.[2]

The incidence of human rabies in China has declined since 2007.[3] However China is still a high rabies burden country, with 1172 human rabies cases (0.0866 per million) reported in China in 2013.[4] The 2013 Chinese yearbook of health statistics indicated that rabies was the third most common cause of human death among category A and B notifiable infectious diseases in 2012, following AIDS and tuberculosis.[5] (The notifiable infectious diseases in China are classified as category A, B, or C on the basis of the incidence, spread, mortality, and severity of the disease. The requirements for the reporting of these three categories of disease are different.) There are some published studies that have attempted to characterize and explore the current rabies epidemic in China at the national level, while studies on human rabies at the provincial level are limited. As is well known, China is the country with the largest population and is the third vastest territory in the world. A study at the provincial level could be of value, as this would provide more specific and deeper explorations and analyses of the local impact of the epidemic. To this end, a retrospective epidemiological analysis of the human rabies surveillance data

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http://dx.doi.org/10.1016/j.ijid.2015.07.013

from Zhejiang Province for the period 2007–2014 was performed and is reported below.

2. Methods

All human rabies cases that are diagnosed in hospital must be recorded in the National Notifiable Disease Surveillance System (NNDSS) within 24 h after diagnosis, as required by the Law of the People's Republic of China on Prevention and Treatment of Infectious Diseases. Human rabies was defined according to the National Monitoring Project of Human Rabies (Trial) and Diagnostic Criteria for Rabies (WS 281-2008). A standard questionnaire was used to interview rabies cases or their relatives by staff from the Center for Disease Control and Prevention after acquiring the basic information through NNDSS. The questionnaire collected the following data: demographic profile (name, age, gender, occupation, and address), exposure history and wound treatment, information on post-exposure prophylaxis (PEP), clinical presentation, and information on the animal vector. The categories of exposure were classified as per the World Health Organization (WHO) recommendations. Definitions of some of the epidemiological and clinical characteristics are given in Table 1.

EpiData software version 3.1 (EpiData Association, Odense, Denmark) was used to establish a database and enter data. The epidemiological and clinical characteristics of human rabies cases were described using frequencies for categorical variables and the median (with quartiles in brackets) for quantitative variables. The Chi-square test and Wilcoxon rank test were used to compare the differences between frequencies and medians, respectively. A significant difference was noted if $p < 0.05$. SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) was used to perform all the statistical analyses.

3. Results

3.1. General overview

There were 201 human rabies cases reported in Zhejiang Province during the period 2007–2014. The number of cases and rabies-epidemic counties declined gradually from year to year (Table 2). The summer and autumn represented high-incidence seasons for human rabies in Zhejiang, with 25.4% and 38.3% of cases occurring in these two seasons, respectively; 19.4% and 16.9% of cases occurred in spring and winter. The age distribution of cases ranged from 4 years to 84 years, with a median age of 50.00 (38.50–60.00) years (Figure 1); 61.2% of cases were aged 40–65 years. One hundred and forty cases were male, and the male to female ratio was 2.30:1. Among the 162 cases who reported their registered household address, 45 were non-residents from other provinces. (Non-resident cases were those whose registered household address was not in Zhejiang Province, regardless of where they acquired the infection.) Guizhou Province was the most frequently reported province of residence for cases from outside Zhejiang; this is also the province with the second highest incidence of human rabies in China.

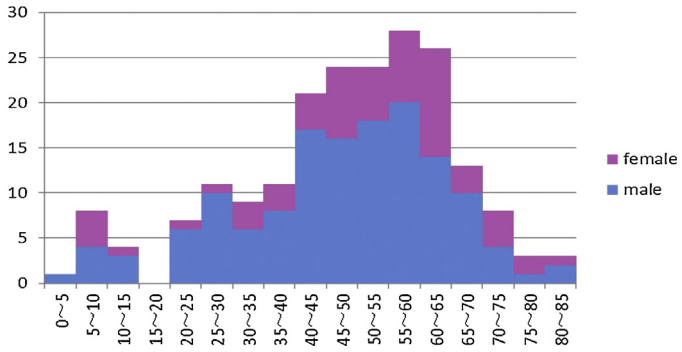

Figure 1. Age distribution of human rabies cases in Zhejiang Province, 2007–2014.

The non-resident cases were significantly younger than the locally resident cases (median age 34.00 vs. 56.00; $p < 0.001$). The male to female ratio was similar between these two types of cases (2.46 vs. 2.34; $p = 0.898$). The most commonly reported occupation among the 201 cases was farmer (69.2%), followed by rural laborer (15.4%); 5.0% of cases were students. The three cities with the highest numbers of cases were Wenzhou (36 cases), Jinhua (34 cases), and Huzhou (23 cases); 46.27% of total cases were reported in these three cities. Changxing (13 cases) in Huzhou and Yueqing (nine cases) in Wenzhou were the two counties with the highest cumulative numbers of rabies cases between 2007 and 2014 (Figure 2).

3.2. Exposure and incubation

Of the 181 cases with a known history of animal exposure, 92.8% were attributed to dogs and 2.8% to cats (Table 3). Of the animal vectors, 71.0% had a recognized owner (54.6% belonged to the case and 16.5% to a neighbor) and 23.9% were stray animals. Some history of rabies vaccination was reported for 3.8% (3/78) of the owned animals. A bite (89.9%) was the most common exposure type. According to the WHO categories of exposure, 84.0% of cases were classified as category III exposure and 16.0% as category II

Table 1
Definitions of the epidemiological and clinical characteristics

Characteristic	Definition
Animal vector	The indicated animal that transmitted the rabies virus to the human case according to the interview.
Animal source	The source of the animal involved, whether domestic, stray, wildlife, or other, and whether it was hosted by the case him/herself or a neighbor if the animal was domestic.
Exposure type	The route of exposure, including a bite or scratching by a potentially rabid animal, or contamination of open wounds or mucous membranes with saliva or other potentially infectious material.
Exposure category	Category I: Touching or feeding animals, licks on intact skin, contact of the intact skin with secretions or excretions of a rabid animal or human; Category II: Nibbling of uncovered skin, minor scratches or abrasions without bleeding; Category III: Single or multiple transdermal bites or scratches, licks on broken skin, contamination of the mucous membrane with saliva from licks, and exposure to bats.
Post-exposure prophylaxis	The recommended prophylaxis for the prevention of rabies in humans exposed to the rabies viruses, consisting of local treatment of the wound as soon as possible, a course of potent, effective rabies vaccine, and the administration of rabies immunoglobulin when indicated.
Incubation	The time interval between exposure and the onset of clinical signs.
Duration of disease	The time interval between the onset of clinical signs and death.

Table 2
Annual distribution of human rabies cases in Zhejiang Province, 2007–2014

Year	No. of cases	No. of cities reporting cases	No. of counties reporting cases
2007	57	10	39
2008	38	9	24
2009	31	10	23
2010	25	9	20
2011	18	6	14
2012	14	10	13
2013	9	6	7
2014	9	6	9
Total	201	10	63

Table 3
Exposure characteristics of human rabies cases in Zhejiang Province, 2007–2014

Exposure characteristic		*n* (%)
Animal vector	Canine	168 (92.8)
	Cat	5 (2.8)
	Ferret badger	3 (1.7)
	Mouse	2 (1.1)
	Pig	1 (0.6)
	Other	2 (1.1)
Animal source	Self-owned	96 (54.5)
	Neighbor-owned	29 (16.5)
	Stray	42 (23.9)
	Wild	6 (3.4)
	Other	3 (1.7)
Exposure type	Bite	160 (89.9)
	Scratch	14 (7.9)
	Other	4 (2.2)
Exposure category	III	142 (84.0)
	II	27 (16.0)
Wound position	Head/face	15 (8.7)
	Trunk	1 (0.6)
	Arm	19 (11.0)
	Hand	85 (49.1)
	Lower limb above knee	8 (4.6)
	Lower limb below knee	45 (26.0)
Incubation	≤30 days	20 (11.6)
	31–60 days	44 (25.4)
	61–90 days	32 (18.5)
	91–180 days	33 (19.1)
	181–365 days	20 (11.6)
	366–730 days	6 (3.5)
	>730 days	18 (10.4)

exposure. Wounds were most commonly on the hand (49.1%), followed by the lower limb below the knee (26.0%). Compared to locally resident cases, more non-resident cases had a wound on the head/face (7/39 vs. 4/107; Chi-square = 6.37, $p = 0.012$), and fewer non-resident cases were classified as category III exposure (2/39 vs. 21/105; Chi-square = 6.37, $p = 0.030$).

The median incubation for the 173 cases with reported exposure dates was 75 days (46–189 days). Cases with a wound on the head/face only (median 29.00 (12.75–69.25) days) had a significantly shorter incubation than those with a wound on the hand only (median 63.50 (37.00–122.00) days; $p = 0.011$), arm only (median 66.00 (57.75–263.25) days; $p = 0.015$), and lower limber below the knee only (median 109.00 (72.00–290.00) days; $p < 0.001$). The incubation for cases with a wound on the hand only was significantly shorter than for those with a wound on the lower limb below the knee only ($p < 0.001$). The incubation for non-resident cases was non-significantly longer than for locally resident cases (median 104.00 (46.00–194.00) days vs. median 70.00 (45.50–172.25) days; $p = 0.512$).

3.3. Treatment and symptoms

After exposure, 72 (41.4%) cases sought wound treatment; 65.3% of these cases treated the wound themselves at home, while 36.1% received treatment in a medical institution (Table 4). The wound treatment rate and the distribution of treatment sites were not significantly different between non-resident and locally resident rabies cases ($p > 0.05$). The frequency of vaccination for cases who reported their immunization history was 9.7% (17/176), but only 1.1% (2/176) had finished the full regimen. All 17 cases who received active immunization after exposure were classified as category III exposure, and most of them were exposed in the hand and head/face (Table 5). Four of these 17 cases were immunized more than 24 h after exposure and 16 cases only received one dose of rabies vaccine at their first visit. Among the vaccinated cases, six were non-resident. Four of 142 category III exposure cases received passive immunization. Two cases were injected with equine rabies immune globulin

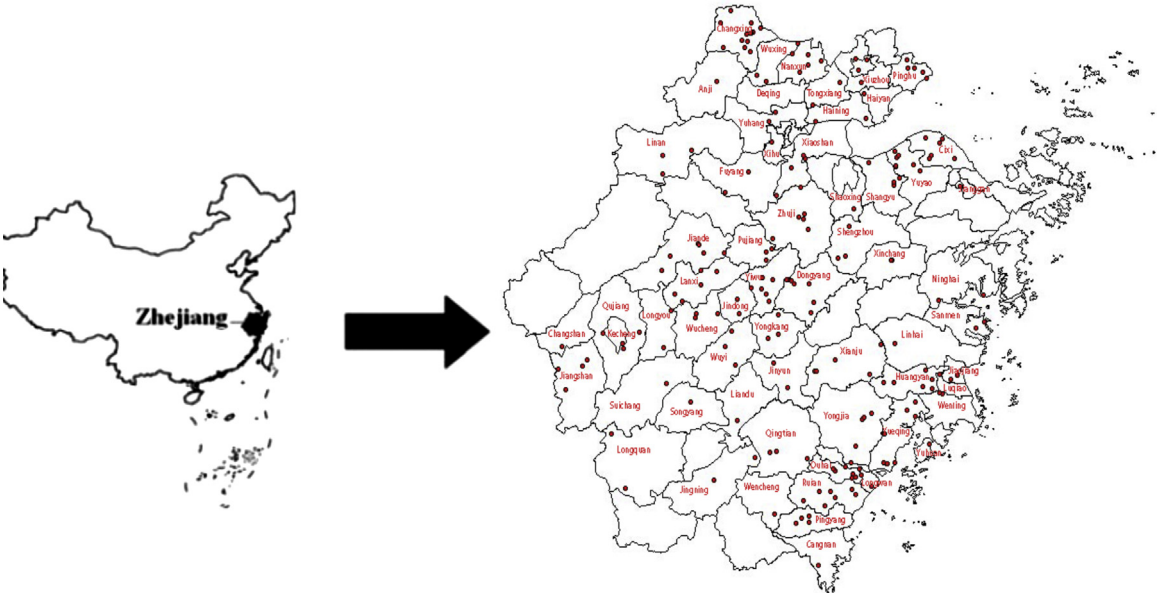

Figure 2. Geographical distribution of human rabies in Zhejiang Province, 2007–2014; each dot represents a reported rabies case.

Table 4
Post-exposure prophylaxis and clinical characteristics of human rabies cases in Zhejiang Province, 2007–2014

Characteristic			*n* (%)
Wound treatment	Wound treatment	Yes	72 (41.4)
		No	102 (58.6)
	Site of treatment	Home	47 (65.3)
		Medical institution	26 (36.1)
Post-exposure prophylaxis	Active immunization	Yes	17 (9.7)
		No	159 (90.3)
	Finished the full regimen of active immunization	Yes	2 (11.1)
		No	15 (83.3)
		Unknown	1 (5.6)
	Passive immunization	Yes	4 (2.3)
		No	172 (97.7)
Clinical manifestation	Fidgeting	Yes	137 (74.9)
		No	46 (25.1)
	Hydrophobia	Yes	147 (80.3)
		No	36 (19.7)
	Aerophobia	Yes	113 (71.5)
		No	45 (28.5)
	Photophobia	Yes	62 (39.5)
		No	95 (60.5)
	Tics	Yes	70 (44.6)
		No	87 (55.4)
	Lunacy	Yes	35 (22.3)
		No	122 (77.7)
Duration of disease	≤2 days		49 (24.4)
	3–5 days		93 (46.3)
	6–8 days		37 (18.4)
	≥9 days		22 (11.0)

(ERIG) and two others were administered human rabies immune globulin (HRIG). Only one case completed PEP (passive plus active immunization) in accordance with the WHO guidelines. This was a 5-year-old locally resident boy who was seriously bitten by a stray dog. He underwent debridement and suturing under general anesthesia and was then immunized with HRIG and human rabies vaccine using the Zagreb regimen at 8 h after exposure. Unfortunately the boy developed the symptoms of rabies 61 days later.

The median duration of disease for the 201 cases was 4 (3–6) days. All of the cases died from rabies. There was no significant difference in disease duration for cases with wounds at different positions ($p > 0.05$). However, non-resident cases had a significantly shorter disease duration than locally resident cases (median 3 (2–4.5) days vs. median 4 (3–6) days; $p = 0.015$). The most commonly reported clinical manifestations were hydrophobia (80.3%), fidgeting (74.9%), and aerophobia (71.5%). Tics (44.6%), photophobia (39.5%), and altered mental status (22.3%) occurred in some cases.

4. Discussion

Zhejiang Province is located in the southeast of China and is one of the most developed provinces. It has 11 cities and 90 counties, with Hangzhou as its provincial capital. From 2007 to 2014, the number of human rabies cases in Zhejiang Province decreased steadily (especially in 2008), which reflects the epidemic trend of human rabies in China.[6,7] The number of counties that reported rabies cases each year also declined. This demonstrates that the geographical distribution of human rabies has continued to narrow and the epidemic has eased in Zhejiang Province.

In contrast to the age distribution across the whole of China[6,8] and in other countries, human rabies was most commonly reported in individuals between the ages of 40 and 65 years in Zhejiang Province; the percentage of cases under 15 years of age was less than 7%. This may be the consequence of enhanced attention from parents, a greater willingness to pay for the treatment of their children after exposure, and better availability and accessibility of education resources for students. Non-resident human cases were significantly younger than locally resident ones, which might be the result of differences in age structure between these two populations in Zhejiang Province. There are many laborers from less developed provinces seeking jobs in the more developed provinces (such as Zhejiang) in China, and they are always young and strong.

Table 5
Exposure and treatment of human rabies cases administered human rabies vaccine after exposure in Zhejiang Province, 2007–2014

Case number	Exposure category	Wound position	Wound treatment	Immunization		
				Time between exposure and immunization	Active	Passive
1	III	Head/face	Suturing	<24 h	One dosage at first visit; incomplete full regimen	HRIG
2	III	Hand	Washing with water only	49 days	One dosage at first visit; incomplete full regimen	Not used
3	III	Lower limb below knee	Washing with water only	<24 h	One dosage at first visit and the full regimen finished	Not used
4	III	Hand and arm	Washing, debridement, and suturing	<24 h	One dosage at first visit; incomplete full regimen	Not used
5	III	Hand	Washing with water only	3 days	One dosage at first visit; incomplete full regimen	Not used
6	III	Hand	Washing	<24 h	Only one dosage at first visit	Not used
7	III	Head/face	Unknown	<24 h	One dosage at first visit; incomplete full regimen	Not used
8	III	Head/face	Unknown	<24 h	One dosage at first visit; incomplete full regimen	Not used
9	III	Head/face	Washing and suturing	<24 h	One dosage at first visit; incomplete full regimen	Not used
10	III	Hand	Washing	<24 h	One dosage at first visit; incomplete full regimen	Not used
11	III	Head/face	Washing	1 day	One dosage at first visit; incomplete full regimen	Not used
12	III	Head/face	Washing	<24 h	One dosage at first visit; incomplete full regimen	Not used
13	III	Head/face	Washing	<24 h	Only one dosage at first visit	ERIG
14	III	Hand	Washing	<24 h	One dosage at first visit; incomplete full regimen	ERIG
15	III	Hand	Washing	<24 h	Only one dosage at first visit	Not used
16	III	Hand	Sterilizing with alcohol	<24 h	Only one dosage at first visit	Not used
17	III	Head/face	Washing, debridement, and suturing under general anesthesia	8 h	Two dosages at first visit; complete full regimen	HRIG

HRIG, human rabies immune globulin; ERIG, equine rabies immune globulin.

Similar to the gender distribution of human rabies in other provinces of China, more cases were male than female. This may be associated with the fact that males perform more outdoor activities and subsequently have more exposure opportunities, especially in rural areas, than females.[6,7,9] For the same reason, the occupation of farmer was high-risk for human rabies, as was rural laborer. Student (5.0%) was a less frequently reported occupation in Zhejiang Province compared to the whole nation. Song et al.[8] reported that 13.3% of cases in China during 2005–2012 were students. Human rabies cases were mainly clustered in three parts of Zhejiang Province: the north, mid-west, and southeast. The economic situation, mobility of the population, and circulation of rabies virus between animals may have played a part in the geographical distribution of human rabies in Zhejiang.[6] Further investigations are needed to explore the reason.

The exposure investigation revealed that dogs were the main transmitter of human rabies in Zhejiang Province, followed by cats. Furthermore, greater than 70% of animal vectors were owned household animals. A study conducted by Hu et al.[10] indicated that the estimated immunization coverage of dogs in rural areas of China ranged from 1.2% to 2.8%. This is far lower than the 70% coverage that is regarded as necessary to maintain an inter-canine immune barrier, according to the WHO.[11,12]

The median incubation period was 75 (46–189) days for human rabies cases in Zhejiang Province. This is slightly longer than the incubation period stated by the WHO (1–3 months). The incubation period was different for cases with different exposure sites. Cases with a wound on the head/face only had the shortest incubation compared to those with wounds at other sites, followed by those with wounds on the hand only. This difference is related to the degree of innervation at the site of viral entry and the proximity of the bite to the central nervous system.[13] Studies conducted in Henan and Guangxi provinces of China found that the exposure site, age, vaccine inoculation, and wound depth all have an influence on the incubation period.[14,15]

Although most of the human rabies cases had a category III exposure, there were still some human rabies cases with a category II exposure, which demonstrates the importance of timely and appropriate PEP for exposure without bleeding. Only 41.4% of cases had their wound treated, and 36.1% of these cases were treated in a medical institution after exposure. Timely and thorough local wound treatment is of paramount importance. It has been shown in animal studies that thorough wound cleansing alone, without other PEP, can reduce the likelihood of rabies.[16,17] However, people often fail to recognize the importance and necessity of local wound treatment.[18–20] In the few cases in which some PEP was applied, untimely and unstandardized PEP and suturing of the wound may have been the reasons for failure of the PEP.

Passive immunization can provide immediate passive rabies virus neutralizing antibody to exposed people before the body has time to respond to active rabies immunization. Due to the costliness and short supply of rabies immunoglobulin in developing countries, many people will not receive passive immunization after exposure.[21] In previous investigations it was found that only 8–33.33% of the category III exposure population received passive immunization in China,[22–24] and less than 7% of human rabies exposure clinic attendants were administered HRIG in Zhejiang Province (unpublished data). A total 609 325 exposed persons visited human rabies exposure clinics in Zhejiang Province in 2014, with 93.01% of visitors accepting active immunization (unpublished data). The surveys conducted by Lin et al.[24] in Zhejiang Province indicated that about 87.7% of people would seek health care after a possible rabies exposure, which means about 128 049 (18.4%) persons do not receive vaccination after exposure each year. The case–control studies conducted by Zhang et al.[25] and Gong et al.[26] concluded that leaving the wound without treatment, no timely inoculation of vaccine and no injection of HRIG/ERIG, and using only one dosage for the first injection are all risk factors for failure to prevent clinical rabies following exposure to the infection. Furthermore, Fescharek et al.[27] have reported that anesthetics and surgical stress may increase the risk of post-exposure rabies treatment failure, as the immune response will be depressed after the application of anesthetic drugs.

The duration of disease was short, only around 4 days, and it was slightly but significantly shorter for non-resident cases than for locally resident cases. This may be related to the difference in demographic characteristics and accessibility to better treatment between these two types of resident. Non-residents are generally younger and in poorer economic and social conditions than local residents. The lack of family support for these cases may also lead them to succumb to the disease slightly quicker.

In summary, the incidence of human rabies in Zhejiang Province decreased gradually from 2007 to 2014. Male farmers or rural laborers aged 40–65 years, living in the northern, mid-west, and southeast regions of Zhejiang Province, represent the highest risk population for human rabies in Zhejiang. A failure to receive timely and standard prophylaxis after exposure is one of the primary reasons for the occurrence of human rabies. Regarding the fact that more than 90% of human rabies cases were transmitted by dogs in Zhejiang Province and that the coverage with animal rabies vaccine in household canines is extremely low in China, the control and eventual elimination of rabies in dogs will benefit human health, as has been demonstrated in Western Europe and North America. However, no effective control measures for dog rabies, such as mass dog vaccination, have been applied effectively to date in China. The large number of dogs, lack of a strict dog registration system, and lack of manpower and resources are all obstructions to mass dog vaccination in China. Pre-exposure prophylaxis and PEP have become especially important for the control and prevention of rabies in humans. The cost of PEP can be covered in part by medical insurance schemes for urban workers in Zhejiang Province. However, famers and most laborers are not included in this scheme. The cost of PEP (especially passive immunization) is always too high to be affordable for most famers and laborers. About 18.4% of persons will not receive vaccination after exposure and the immunization rate with rabies immunoglobulin is extremely low in Zhejiang Province. Further health education and other effective actions are necessary to increase the coverage with PEP in the exposed population and to increase rabies vaccine use in homebred animals.

Acknowledgements

This study was supported by the National Basic Research Program of China (973 Program; Grant No. 2012CB955504), the National Natural Science Foundation of China (NSFC; Grant No. 81273139), and the Science Technology Research and Development Program of Shandong (Grant No. 2014GGH218019).

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

Conflict of interest: There are no conflicts of interest regarding this study.

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