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Short communication

Estimating the probability distribution of the incubation period for rabies using data from the 1948–1954 rabies epidemic in Tokyo

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ABSTRACT

Data of 98 rabies cases in dogs and cats from the 1948–1954 rabies epidemic in Tokyo were used to estimate the probability distribution of the incubation period. Lognormal, gamma and Weibull distributions were used to model the incubation period. The maximum likelihood estimates of the mean incubation period ranged from 27.30 to 28.56 days according to different distributions. The mean incubation period was shortest with the lognormal distribution (27.30 days), and longest with the Weibull distribution (28.56 days). The best distribution in terms of AIC value was the lognormal distribution with mean value of 27.30 (95% CI: 23.46–31.55) days and standard deviation of 20.20 (15.27–26.31) days. There were no significant differences between the incubation periods for dogs and cats, or between those for male and female dogs.

1. Introduction

Rabies is prevalent in many parts of the world, including in Asia, Africa, North and South America and some countries of Europe. Infection causes tens of thousands of human deaths annually, mostly in Asia and Africa. Dogs are the source of rabies in the vast majority of human rabies cases (WHO, 2015). In developed countries, rabies is found mainly in wild animals, from which infection can be transmitted to domestic animals and humans (WHO, 2005, 2008; Rupprecht and Gibbons, 2004).

The incubation period for rabies is very variable, depending on the virus strain, host species, and the site of exposure (proximity of the site of infection to the brain), number of virus particles in the infection and the immunological status of the exposed animal or person (Garg, 2014). The World Organization for Animal Health considers it to be up to 6 months (OIE, 2014). Data on the incubation period of rabies are available from a number of sources from both experimental studies in some species (Fekadu et al., 1982; Trimarchi et al., 1986; Soulebot et al., 1981) and natural infection studies (Advisory Group on Quarantine, 1998; Committee of Enquiry on Rabies, 1971). Some estimates of the incubation period from naturally acquired rabies cases are available (Advisory Group of Quarantine, 1998; Foggin, 1988; Hampson et al., 2009). However, it is difficult to estimate the precise incubation period as often the initial date of exposure is unknown. The incubation period distribution is one of the essential input variables to be used in assessing the risk of rabies introduction as well as in estimating the effect of rabies control measures.

Rabies was eradicated from Japan in 1956. However, the last major epidemic in Japan was observed in Tokyo and its neighboring prefectures from 1945 until 1954. We used data from dogs and cats with rabies (98 cases in total) in this epidemic in the period 1948–1954 to estimate the probability distribution of rabies incubation period in these species.

2. Materials and methods

We used diagnostic data from the Tokyo Metropolitan Research Laboratory of Public Health (TMRLPH) from 1948 to 1954 (Ueki, 2007). Based on the Domestic Animal Infectious Diseases Control Law (until July 1950) and Rabies Prevention Law (from August 1950), rabies in dogs and cats was a notifiable disease. A person who identifies biting dogs or other mammalian species with clinical signs compatible with rabies is obliged to report the event to the governor of the prefecture in which he lives. In Metropolitan Tokyo, these animals were first inspected by a Livestock Disease Con-

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Table 1
Age distributions of dogs and cats (by ownership and gender) used for estimation of incubation period.

Species	Gender/ownership		*n*	Age distribution (years)						
				0 < 1	1 < 2	2 < 3	3 < 4	4≤	Unknown	Mean[a]
Dog	Owned	Owned	86	52	17	9	6	1	1	1.2
	or stray	Stray	6	3	3	0	0	0	0	1.0
	Gender	Male	58	40	10	4	2	1	1	1.0
		Female	34	15	10	5	4	0	0	1. 4
	Subtotal		92	55	20	9	6	1	1	1.2
Cat	Gender	Male	2	1	0	0	0	0	1	6.0
		Female	4	0	1	1	1	1	0	3.0
	Subtotal		6	1	1	1	1	1	1	4.5
Total			98	56	21	10	7	2	2	1.3

Source: Ueki (2007).

[a] The mean age was calculated assuming that all animals within the bands 0 < 1, 1 < 2, 2 < 3 and 3 < 4 were aged 0.5, 1.5, 2.5 and 3.5 respectively. Animals of unknown age were ignored.

Table 2
Estimates of the parameters of incubation period for rabies of dogs and cats combined.

	Shape (95% CI)		Scale (95% CI)		Mean	Mode	Median	AIC[a]
Lognormal	3.09	(2.9–3.19)	0.66	(0.59–0.73)	27.30	14.18	21.94	806.4
Gamma	2.15	(1.6–2.87)	13.11	(9.41–17.08)	28.18	15.08	23.96	827.6
Weibull	1.34	(1.16–1.59)	31.09	(26.15–36.00)	28.56	11.09	23.64	839.9

[a] AIC = Akaike's Information Criterion.

trol Inspector or Rabies Control Inspector from Prefectural Public Health Centers. When rabies was suspected, inspectors instructed the owners to detain the suspected animals in their houses. The carcasses of animals that died or were euthanized during the detention were sent to the TMRLPH for confirmatory diagnosis. Confirmatory diagnosis was made by histological examination of the brain (detection of Negri bodies) and mouse inoculation test. In addition to these, the complement fixation test on brain tissue was used from 1953.

As a result of confirmatory diagnosis, a total of 884 rabies cases were detected in metropolitan Tokyo during the period from 1948 to 1954. Of those animals, 98 animals were accompanied by a document with some information on the initial date of exposure to rabies (date when the animal was first bitten by rabid or suspected animal). Other information available in the accompanying document included the species, breed, gender, age of the animal, and the date of onset of clinical signs. The incubation period for each animal was calculated by subtracting the initial date of exposure from the date of onset of clinical signs. The age distributions of these animals are shown in Table 1. We assumed that dogs and cats have the same incubation period distribution and included both species in this study. For 25 animals, the precise date of exposure was unknown but a rage of possible dates of exposure was available. For these animals, the initial date of exposure was assumed to be the median date of all these possible dates. We used three different two-parameter distributions to model the incubation period: lognormal, gamma and Weibull distributions, and compared the estimates. The parameters of distributions were estimated using maximum likelihood estimation (MLE) method. We created 10,000 Bootstrap samples of 98 animals to estimate the 95% confidence intervals of these parameters. In addition to the two parameters, we estimated the median, mode and mean of the incubation period. We calculated Akaike's Information Criterion (AIC) values to compare these MLE models. To examine whether the species and gender are a factor determining the duration of the incubation period, we also estimated the parameters of incubation period for dogs and cats, and male and female dogs separately and tested if there is a significant difference between them, using *t*-test with log-transformed data.

We used simulation software @Risk (Palisade Corporation) added into the Spreadsheet software microsoft excel 2013 to estimate the parameters and to create Bootstrap samples.

3. Results and discussion

The parameter estimates of the incubation period distribution for the three different assumptions are summarized in Table 2. Different distribution assumptions gave maximum likelihood estimates for the median incubation period that ranged from 21.94 to 23.96 days. The median incubation period was shortest with the lognormal distribution (21.94 days), and longest with the Gamma distribution (23.96 days). The mode incubation period was shortest with the Weibull distribution (11.09 days) and longest with the Gamma distribution (15.08 days). The best distribution in terms of AIC value was the lognormal distribution with mean value of 27.30 (95% CI: 23.46–31.55) days and standard deviation of 20.20 (15.27–26.31) days. The uncertainty associated with the parameters reflects the limited sample size in the data set.

Fig. 1 illustrates the density function of the incubation period together with the observed number of rabies cases with known incubation period. The lognormal distribution, which yielded best AIC value, visually best fits the observed data. The Weibull distribution is shifted leftward than lognormal and gamma distributions, because the Weibull distribution yielded a shorter mode incubation period than the lognormal and gamma distributions.

Using lognormal distributions, dogs and cats had mean incubation period values of 25.57 and 40.79 with standard deviation of 18.73 and 49.89 respectively, with no significant difference ($P = 0.35$). The incubation periods for male and female dogs had mean values of 24.16 and 30.96, and standard deviation of 15.34 and 24.82 respectively. The incubation period for male dogs appeared to be shorter than that for female dogs, but there was no significant difference between them ($P = 0.12$).

The incubation period estimated in our study appears to be longer than the incubation period observed in previous experimental studies but more or less comparable with the distributions previously estimated based on experimental and natural infection studies (Fekadu et al., 1982; Soulebot et al., 1981). An experimental study by Fekadu et al. (1982) using dogs inoculated with 1.7–4.7