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The final stages of dog rabies elimination from Japan

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Abstract

Rabies is a lethal zoonotic disease mainly transmitted to humans by dog bites. The purpose of this study was to assess the efficacy of rabies control policies in Japan, which resulted in the elimination of the disease from the country in 1957. Using historical records from the Kanto region (Chiba, Kanagawa, Saitama and Tokyo Prefectures) between 1947 and 1956 where the final canine cases were recorded, we undertook a descriptive epidemiological study, applying spatio-temporal scan statistics using SaTScan and estimating the effective reproduction number (R_t) for the clusters and each prefecture using the growth rates. There were 1,567 dog rabies and 161 human rabies cases recorded during this period. Vaccination coverage in registered dogs was over 70% after 1951, with much lower coverage in free-roaming and unregistered dogs. Eight clusters of dog rabies cases were identified: the first appeared in 1947 in Tokyo and was linked to three further clusters in peripheral prefectures between 1947 and 1951. Three more clusters occurred in Tokyo again between 1952 and 1954, and the last cluster was in Tokyo and Kanagawa between 1955 and 1956. R_t in the first cluster was 1.68, and R_t values in the others ranged between 1.18 and 1.86, with an exception of 4.05 in the smallest cluster in Tokyo in 1952 (10 cases). The moving average of R_t coincided with the clusters. As dog vaccination and dog management progressed, and the number of dog rabies cases declined, the moving average of R_t declined to below 1. Delays in the implementation of dog management policies in Kanagawa may have prolonged this last outbreak. These results demonstrate the effectiveness of coordinated control policy involving dog vaccination and management of free-roaming dog populations for rabies elimination.

KEYWORDS
basic reproduction number, effective reproduction number, rabies, spatio-temporal cluster

1 | INTRODUCTION

Rabies is an infectious disease caused by the rabies virus, which belongs to the genus *Lyssavirus* in the family *Rhabdoviridae*. It is a zoonosis that is infectious to all mammals and still causes an estimated 59,000 deaths globally each year (Hampson et al., 2015; Jackson, 2013). Over 99% of human infections are caused by dog bites, but the disease can be controlled by dog vaccination, and human deaths prevented by prompt provision of post-exposure prophylaxis (PEP) to bite victims (Wilde, 2007; World Health Organization, 2013).

Rabies has plagued humans since antiquity, with Aristotle describing the routes of transmission and symptoms of the disease in ancient Greece in the fourth century BC (Iwabuchi, 1970).

However, since Pasteur first developed a vaccine in 1885, efforts have been undertaken to eliminate rabies, primarily through vaccination (Rupprecht et al., 2002). In the Western Hemisphere and Western Europe, rabies in domestic dogs and humans is no longer considered a major public health threat (Velasco-Villa et al., 2017). In contrast, mass dog vaccination programmes have been limited in Asia and Africa, where 95% of human rabies cases occur (Hampson et al., 2009). In response to this situation, a global strategy 'Zero by 30' has been developed by WHO, OIE, FAO, and partners aiming to eliminate human deaths from dog-mediated rabies by 2030 (World Health Organization, Food and Agriculture Organization of the United Nations, & World Organisation for Animal Health, 2018). The strategy promotes access to effective vaccines and equitable health care systems, provision of education about rabies and dog management, development of policies and guidelines appropriate for each region and country, and consistent monitoring systems.

To eliminate dog-mediated rabies, historical knowledge from Japan and other countries that have successfully eliminated the disease should be useful. In Japan, following the end of World War II (WWII), only a few records of dog rabies outbreaks have been compiled, and the process that led to the elimination of rabies remains largely unknown.

The first recorded outbreak of rabies in Japan was in Nagasaki in 1732 (Figure 1a), the only place in the country with foreign trade at the time (Tojinbara, 2020b). During the Meiji era (1868–1912), with the establishment of the new modern government, outbreaks occurred in Oita and Nagasaki prefectures in 1892 and 1893, respectively (Veterinary Investigation Center, 1935). In the Nagasaki outbreak, post-exposure vaccination of 25 bite victims was applied for the first time in Japan in 1895 and was successful for all the individuals (Iwabuchi, 1970; Veterinary Investigation Center, 1935). The outbreak spread from Nagasaki towards the northeast, reaching the northernmost prefecture Hokkaido in 1906. Between 1915 and 1921, Japanese scientists developed a dog vaccine and began to implement dog vaccination (Umeno & Doi, 1921; Veterinary Investigation Center, 1936a). Coincidentally, dog rabies cases sharply increased nationwide in 1920 and caused an outbreak of 1,338 dog rabies cases in Osaka in 1923. The largest number of annual dog rabies cases in Japan, 3,240 cases, were recorded in 1924 (Iwabuchi, 1970; Kurosawa et al., 2017). As dog vaccination and dog management progressed, the incidence of dog rabies declined. Dog rabies remained only in Tokyo, the capital of Japan since 1936, and in 1943, only one case of rabies was recorded in Tokyo, and the disease was close to being eliminated from the country. However following WWII rabies resurged in 1944, and over 700 cases occurred in the Kanto region, where Tokyo is located. After the enactment of the Rabies Prevention Act in 1950, rabies was controlled, with no recorded outbreaks of rabies in dogs after 1956 and the last documented case in Japan occurring in a cat in 1957 in Hiroshima Prefecture, although the source of infection was never identified (Shimada, 1971; Tojinbara, 2011). Rabies did not spread to wildlife populations in Japan, and no positive case has been reported in the active surveillance started in 2014 (Ministry of Health, Labour and Welfare, 2014).

Impacts

- The detailed epidemiology of rabies in the process of elimination from Japan was described.
- The moving average of reproduction number became less than 1 as dog vaccination progressed.
- Unregistered and free-roaming dogs were the basis of the last epidemic wave in Tokyo.

The role played by the legal system in rabies elimination in Japan cannot be overlooked. In 1896, the Epizootic Disease Prevention Act was enacted and rabies was designated as a disease to be monitored by this law. Dogs that developed rabies were to be killed immediately. As a result of the development of the livestock industry and the need for increased control of livestock diseases, the Act on Domestic Animal Infectious Diseases Control was enacted in 1922, replacing the Epizootic Disease Prevention Act, and dog rabies was included in the new act. This act made it mandatory to quarantine all livestock and livestock products intended for import to or export from Japan. In 1929, rabies prevention services were transferred from the Ministry of Agriculture and Forestry to the Home Ministry and were recognized as a part of the public health service (Veterinary Investigation Center, 1936a, 1936b). After WWII, General Headquarters, the Supreme Commander for the Allied Powers ordered the development of legislation specifically for rabies prevention, and the Rabies Prevention Act was enacted in 1950. Under this law, dog registration, capture of free-roaming dogs, dog vaccination, and quarantine of animals brought into the country became mandatory, and a civil servant veterinarian was assigned to each prefectural health center as a rabies prevention specialist (Administrative Management Bureau, n.d.). In the Rabies Prevention Act, vaccination was obligatory for only owned dogs, and dog owners vaccinated their dogs by attending private veterinary clinics or vaccination campaigns held by prefectural governments (Takahashi-Omoe et al., 2008). Registered dog owners were notified about vaccination campaign by post, and dog vaccinations were performed twice per year until 1985 (once a year from 1986; Kadowaki et al., 2018). After vaccination, the owners of vaccinated dogs received certificate of vaccination from local authorities (Administrative Management Bureau, n.d.). In case a dog vaccinated had not been registered, the owner was recommended to get the dog registered by veterinarians (personal communication with a retired civil servant veterinarian). In the event of a rabies outbreak, the following measures were supposed to be undertaken by law (Act on Domestic Animal Infectious Diseases Control, and Rabies Prevention Act after 1950): (a) emergency vaccination of dogs, (b) tethering all owned dogs, (c) ban of the movement of dogs across prefectural borders, and (d) ban of dog exhibitions including other assembly events, following the orders of prefectural

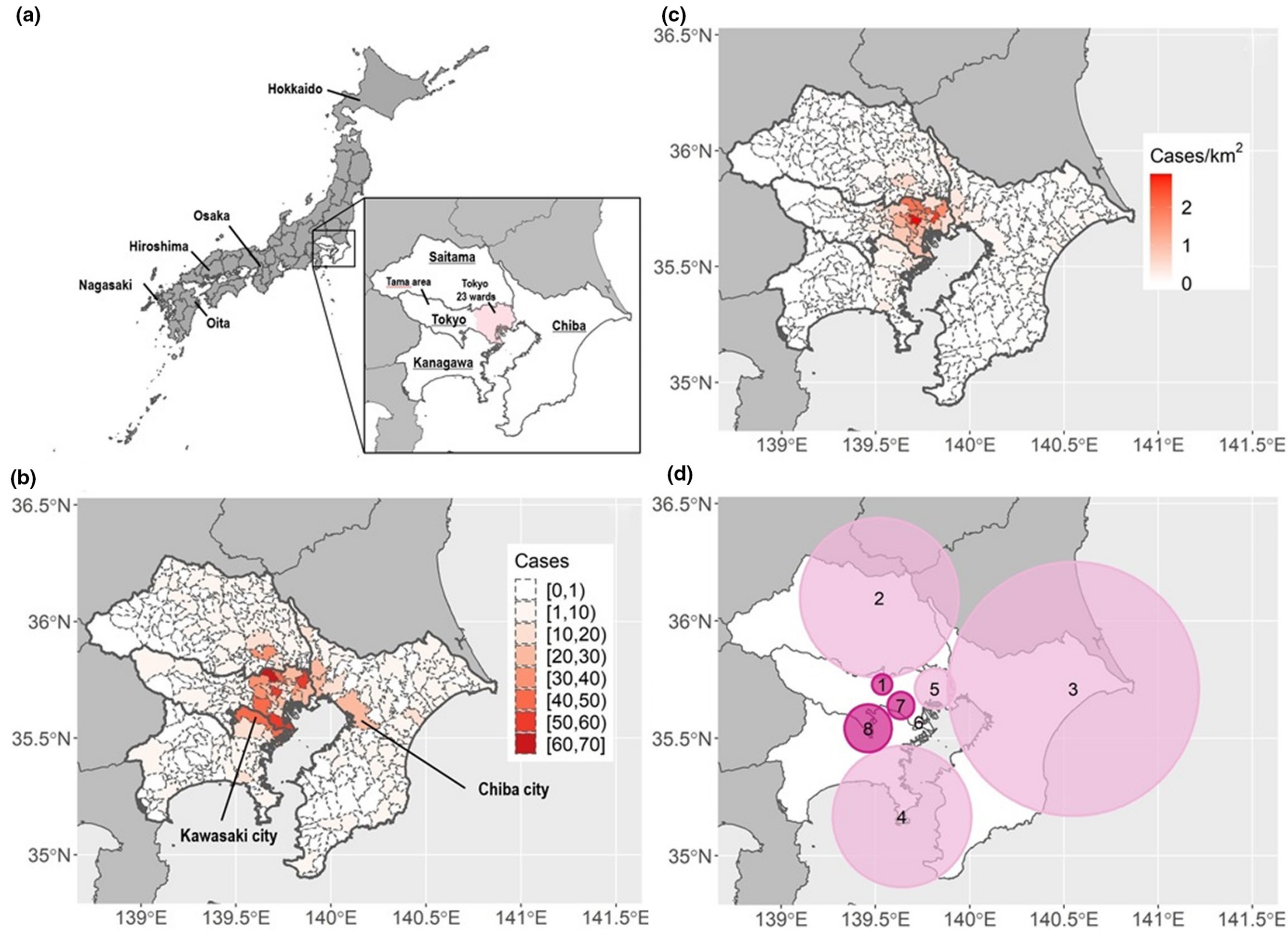

FIGURE 1 (a) Study area and the geographical distributions of (b) dog rabies cases in the Kanto region between 1947 and 1956, (c) dog rabies cases per square km between 1947 and 1956, and (d) spatio-temporal clusters detected by SaTScan, numbers in clusters indicate the order of occurrence.

governors (Administrative Management Bureau, n.d.; Veterinary Investigation Center, 1936b). The dog tethering order during rabies outbreaks was not included in the previous Act on Domestic Animal Infectious Diseases Control, but was first included in the Rabies Prevention Act of 1950 (Tojinbara, 2020a; Veterinary Investigation Center, 1936b). Therefore, owned dogs were commonly allowed free-roaming before the enactment of the act, and citizens gradually adapted the practice of tethering after that. The number of unowned stray dogs was high at the time of enactment of the Rabies Prevention Act, although correct number is not available. Under the Rabies Prevention Act, free-roaming dogs were captured by using dog catchers employed by prefectural and city health centers (Iwabuchi, 1970; Tojinbara, 2020a), and this motivated dog owners to leash their dogs. The officers in the centers notified the owners of captured dogs if they had registration tags, and otherwise notified to the chief officers of the city/township/village. The owners who noticed the disappearance of their dogs were allowed to find them in the centers. Unowned dogs were euthanized according to the act (Administrative Management Bureau, n.d.).

The purpose of this study is to describe the process of rabies elimination in the southern Kanto region, as well as in Japan, before and after the enactment of the Rabies Prevention Act following WWII. We evaluate the effectiveness of rabies control measures taken by each prefecture and share our findings to support the goal of Zero by 30.

2 | MATERIALS AND METHODS

2.1 | Study area

The study area covers four prefectures in the southern Kanto region (Tokyo, Kanagawa, Saitama, and Chiba) in the Tokyo metropolitan area (Figure 1a). The Tokyo metropolitan area is a megalopolis and had a population of 15,424,264 in 1955, which was 17.3% of Japan's population at the time (Statistics Bureau, 2020b). It is still the political and economic center of the country. Located in the middle of the Japanese archipelago, the majority of the metropolitan area is occupied by the Kanto Plain, the largest plain in Japan. The total area of the four prefectures is 13,211 km^2, which accounts for 3.6% of the total area of Japan. Tokyo and Kanagawa Prefecture, whose capital is Yokohama, were characterized by urbanization in 1955, and these prefectures had more than 85% of the population living in the city area (93.7% and 87.1%, respectively), as compared to Saitama and Chiba (50.1% and 49.7%, respectively; Statistics Bureau, 2020b).

2.2 | Data collection

The time series of the data presented in this study was from 1 March 1947, when official records of rabies started to be reported after WWII, to 4 June 1956, when the final canine case in Kanagawa Prefecture was reported.

The official prefectural notices of dog rabies including the dates of occurrence, diagnosis, outcome, and dog attributes [administrative unit, sex, and status of registration (registered, unregistered, free-roaming, or unknown; registered and unregistered are owned and free-roaming is not owned)] and newspaper articles related to rabies were collected from prefectural libraries of the four prefectures as well as peripheral prefectures outside the study area. Newspaper articles were used to complement missing data in the notices. In Kanagawa Prefecture, notices from 1947 to 1953 were untraceable. Therefore, data from the Kanagawa rabies registry between 1947 and 1951 were used to complement the prefectural notice (Kanagawa Prefecture, 1951). This registry is used by prefectural government officials to record information on dogs in the event of a rabies outbreak. Unfortunately, data from January 1952 to July 1953 were missing. For the other three prefectures, as the official prefectural notices were successfully accessed, and efforts to find rabies registry were not made. The prefectural notices should be the most accurate official records. The numbers of registered dogs, dogs receiving routine vaccinations, and free-roaming dogs captured by health centers in Tokyo from 1949 to 1956 were obtained from a published book (Ueki, 2007). Serial intervals were also collected from this book (from 1949 to 1956) and a report (from February to December 1944; Tojinbara, 2020b). The dates of reporting rabies used for calculating serial intervals were confirmed using prefectural notice and newspapers, which were collected from prefectural libraries.

Information on rabies control measures taken by the prefectures, such as the contents of the measure, implementation period, and target areas of the measures, was also collected from prefectural notices.

Shapefiles for administrative units were downloaded from the Ministry of Land, Infrastructure, and Transport's National Digital Information Service (Geospatial Information Authority, n.d.). The file contains 55 cities, 33 wards (23 wards in Tokyo, Figure 1a, and 10 wards in Yokohama City, Kanagawa), 156 towns, and 134 villages, comprising 378 administrative units.

For the incidence of rabies in humans from 1947 to 1956, the Ministry of Health and Welfare's Vital Statistics were used (Statistics Bureau, 2020a). Extracted data included the number of deaths by cause, age group, and sex by prefecture.

2.3 | Descriptive epidemiology

The spatial distribution of rabies incidence in dogs was mapped, with the number and density of dog rabies cases that occurred during the study period aggregated by administrative unit. The monthly dog rabies cases were examined for the entire study area and by prefecture. The proportions of administrative units where dog rabies occurred were compared between urban (cities and wards) and suburban/rural areas (towns and villages) using chi-square test.

The age structure and sex distribution of human rabies cases were compiled. The ratio between human and dog rabies cases each year was calculated to examine the impacts of prevention measures on human deaths due to rabies, in addition to the number of dog rabies cases. One-sample chi-square test was performed to examine the sex-bias in the proportion of male/female victims.

Kulldorff's space–time scan statistics using the Space–Time Permutation model were performed to detect spatio-temporal disease clusters (Kulldorff, 2020; Kulldorff et al., 2005). As inputs, the dates of the reports of dog rabies cases, the administrative unit name, and coordinates of the centroids of each administrative unit were entered into SaTScan version 9.6. We performed 999 simulations using a variable circular scan window of a size up to 50% of the population at risk.

For each of the clusters detected by the space–time scan statistics, we calculated the effective reproduction number (R_t), i.e. the number of secondary cases generated by a single infected individual in a population including vaccinated dogs, using Equation 1 (Wallinga & Lipsitch, 2007). Equation 1 is identical to that for basic reproduction number (R_0) (Wallinga & Lipsitch, 2007). R_0 is the number of secondary cases generated by a single infected individual in a totally susceptible population (Vynnycky & White, 2010). The study population included infected and vaccinated dogs, and R_t is used throughout this manuscript.

$$R_t = 1 / \sum_{w=0}^{\infty} T_{sw} \lambda^{-w} \tag{1}$$

where T_{sw} is the distribution of serial interval in a week unit time, i.e. the time between primary and secondary cases (Vynnycky & White, 2010), λ is the growth rate, and w is time in week. The growth rate was estimated from a generalized linear model with negative binomial errors. To calculate parameters of the serial interval distribution, a gamma distribution was fitted to time intervals derived from the onset of the nth and traced $n+1$th case documented in the published rabies histories in Tokyo (Tojinbara, 2020b; Ueki, 2007), using the fitdist function (Delignette-Muller et al., 2015).

2.4 | Epidemiological impacts of rabies control measures

The effectiveness of rabies control measures implemented in the four prefectures were compared by examining the case time series, the timing of interventions, and the R_t. During the study period, measures such as emergency vaccination, dog tethering orders, restrictions on dog movement, and prohibiting of exhibitions and other assembly events were implemented depending on the epidemiological situations (Administrative Management Bureau, n.d.). All prefectures also captured free-roaming dogs (Iwabuchi, 1970; Tojinbara, 2020a). The proportion of free-roaming dogs among dog rabies cases was calculated each year to determine their contribution to the rabies epidemics over time. Attributes of rabid dogs including their ownership and registration status were compared between prefectures. The number of vaccinated dogs was available only for Tokyo. As registration of owned dogs became more common, the temporal change in the proportion of vaccinated dogs was estimated and is presented together with the numbers of dogs administered rabies vaccines, of registered dogs, and of captured free-roaming dogs. At that time, dogs were vaccinated twice a year; thus, the vaccination coverage in the registered dog population was estimated using Equation 2. Although the correct number of free-roaming dogs was not known, vaccination coverage in the entire dog population in Tokyo was calculated using Equation 3, assuming that the total free-roaming dog population comprises captured dogs (that were not registered) plus up to 100,000 more unregistered free-roaming dogs based on an expert opinion (including unregistered owned dogs, theoretically).

$$\text{Vaccination coverage in the registered dog population} = \frac{\text{Number of vaccinations in the year}}{\text{Number of registered dogs in the year} \times 2} \times 100. \quad (2)$$

$$\text{Vaccination coverage in the entire dog population} = \frac{\text{Number of vaccinations in the year}}{(\text{Number of registered and free} - \text{roaming dogs in the year}) \times 2} \times 100. \quad (3)$$

The annual incidence of rabies per 1,000 dogs in each prefecture was calculated extrapolating from the dog population size as described above assuming that the human-to-dog ratio in each prefecture was equivalent to that in Tokyo, using Equation 4:

$$\text{Incidence per 1,000 dogs} = \frac{\text{Dog rabies cases in prefecture}}{\text{Estimated dogs in Tokyo} \times \frac{\text{Human population in prefecture}}{\text{Human population in Tokyo}}} \times 1{,}000 \quad (4)$$

R_t by prefecture was estimated for all dates when dog rabies cases were confirmed, using the estimation method developed by Wallinga and Teunis (2004). Briefly, we denote the serial interval of rabies using a gamma distribution, $w(\tau)$. The relative likelihood that case i was infected by case j (p_{ij}) is then the likelihood that case i was infected by j, normalized by the likelihood that case i was infected by any other case k (Equation 5).

$$p_{ij} = w\left(t_i - t_j\right) / \sum_{i \neq k} w\left(t_i - t_k\right). \quad (5)$$

The distribution of R_t for case j, R_j is

$$R_j \sim \sum_{i=1}^{i=n} \text{Bernoulli}\left(p_{ij}\right) \quad (6)$$

with an expected value

$$E\left(R_j\right) = \sum_{i=1}^{i=n} p_{ij} \quad (7)$$

where n is the total number of dog rabies cases in each prefecture. $Bernoulli\left(p_{ij}\right)$ in Equation 6 determines whether case i was actually infected by case j, which makes R_j the total number of secondary cases infected by case j. The average daily R_t was calculated as the arithmetic mean over R_j for all cases showing signs of rabies on day t. The calculation of the average daily R_t was iterated for 100 times to obtain median and 90% confidence interval, along the time series for all the dates where cases were recorded.

Analyses were performed using the statistical software R, version 4.0.0 (R Core Team, 2020).

This study investigated published prefectural notices and newspaper, and only accumulated data were presented. Therefore, ethical approval was not required.

3 | RESULTS

3.1 | Descriptive epidemiology

3.1.1 | Dog rabies

Between 1 March 1947 and 4 June 1956, there were 1,567 cases of rabies reported in dogs. Of the 378 municipalities that existed in 1955, 186 (49.2%) experienced cases of dog rabies. All outbreaks were observed in the Honshu Main Island, which contains Tokyo. Rabies occurred in more of the urban (80/88 cities and wards, 90.9%) than the suburban/rural areas (106/290 towns and villages, 36.6%, $x^2 = 77.7$, $df = 1$, $p < .001$). The outbreaks occurred mainly along the Tokyo Bay coast, including the 23 wards of Tokyo, Kawasaki city, and Chiba city (Figure 1b). The number of cases per unit area was highest in Shinjuku ward (2.87 cases/km^2 throughout study period), Tokyo, and the case density was also high in neighbouring areas (Figure 1c).

Epidemic peaks were observed, between 1949 and 1952 and between 1953 and 1954. The first outbreak spread across the entire study area of Tokyo, Kanagawa, Saitama, and Chiba, peaking in May 1950, with 76 cases detected that month (Figure 2a). The

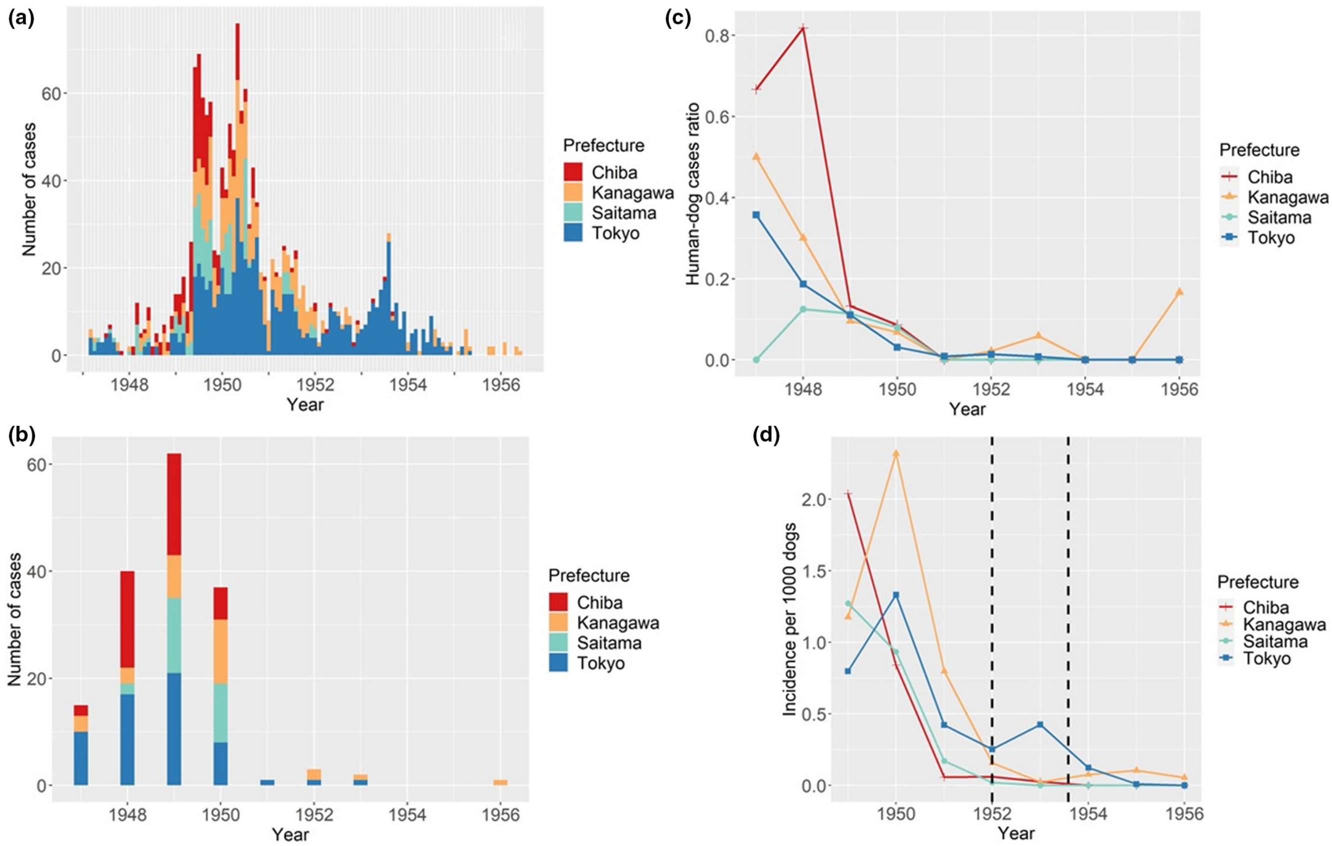

FIGURE 2 Epidemic curves for different measures of rabies across the Kanto region and by prefecture between 1947 and 1956. (a) Monthly dog rabies cases, (b) yearly human rabies cases (deaths), (c) the ratio of human rabies cases (deaths) per dog rabies case and (d) estimated annual rabies incidence per 1,000 dogs in each prefecture. No data was available for Kanagawa Prefecture in the period indicated with dashed lines.

TABLE 1 Radius, R_t, time frame, the numbers of cases, and prefectures in clusters detected by SaTScan

Cluster ID	Radius (km)	R_t(95% CI)	Time frame (epidemic growth in months)	No. of cases	Prefecture
1	4.8	1.68 (1.20–2.27)	June 1, 1947–September 1, 1947 (3)	7	Tokyo
2	37.8	1.21 (1.20–1.21)	August 29, 1947–March 30, 1950 (31)	150	Saitama
3	60.1	1.23 (1.22–1.24)	November 22, 1947–September 22, 1949 (22)	127	Chiba
4	33.4	1.86 (1.61–1.86)	September 26, 1950–November 13, 1951 (14)	55	Kanagawa
5	9.5	1.18 (1.17–1.19)	January 3, 1952–December 23, 1953 (23)	110	Tokyo
6	0	4.05 (2.34–6.41)	April 8, 1952–June 1, 1952 (2)	10	Tokyo
7	6.4	1.61 (1.39–1.85)	February 13, 1954–July 17, 1954 (5)	13	Tokyo
8	11.3	1.25 (1.20–1.30)	April 24, 1955–June 4, 1956 (14)	12	Tokyo

second outbreak occurred mainly in Tokyo, with 26 cases within a single month recorded in August 1953, while just one or two sporadic cases per month occurred intermittently in the other prefectures. After August 1953, the incidence of dog rabies began to decline, while sporadic cases continued in Kanagawa Prefecture until 1956, with the last dog rabies case in Japan occurring in this prefecture on 4 June 1956. Estimates of annual rabies incidence per 1,000 dogs correspondingly declined from a high of between one to two cases per 1,000 dogs in all prefectures after 1950, and from 1952 onwards remained low (<0.5 cases per 1,000 dogs) until elimination in 1956 (Figure 2d).

We identified eight clusters of dog rabies cases using Kulldorff's space–time scan statistics (Figure 1d). From 1947 to early 1950, four clusters were detected in Saitama, Chiba, the southern area of Kanagawa, and the Tama area of Tokyo. Additionally, from 1950 to 1956, four clusters were detected in the 23 wards of Tokyo that spanned into the northern area of Kanagawa. Among the clusters detected between 1947 and early 1950, those detected in Saitama, Chiba, and Kanagawa each had a radius of >30 km and covered a large area of the prefecture. In contrast, the clusters detected in Tokyo and Kanagawa between 1950 and 1956 had smaller radii of <10 km and were confined to a few localities within the prefectures (Table 1, Figure 1d). Cluster 6 did not have radius because the cluster was restricted to just one municipality. The foci of these outbreaks was also observed to shift from the periphery to the center of the Tokyo Bay area.

The serial interval for rabies was calculated from 174 pairs of intervals identified, with the mean estimated to be 5.9 weeks (95% CI: 1.5–12.6). R_t ranged between 1.18 and 1.86, with an exception of 4.05 in the small cluster from Tokyo in 1952 (Table 1, fitted lines to cumulative incidence were presented in Figures S1-S8).

3.1.2 | Human rabies

One hundred and sixty-one human deaths from rabies were identified between 1947 and 1956 (Figure 2c). Figure 3 shows the age distribution of cases by sex in relation to Japan's demography at that time. The male–female case ratio was 1.93, and significantly male-biased (106 males, 65.8% vs. 55 females, 34.2%, $x^2 = 15.5$, $df = 1$, $p < .001$). Around 50% of deaths (50.9%) were children in the age group 0–14 years (54 boys and 28 girls, respectively). There were more male deaths in the age group 45–49 years (9 people) than in the age group of 15–19 years (7 people), and a bimodal pyramid for children younger than 15 years and men in their late 40s was observed (Figure 3, background population pyramid of Japan was shown together with the case age-sex distributions).

The human-to-dog ratios of rabies cases by prefecture were generally high at the beginning of the observation period until 1950 and reduced to <0.1 human death per dog rabies case by 1950, with the exception of Kanagawa Prefecture, in 1956 when one human death occurred but 7 dog cases were identified. In the second dog rabies epidemic in 1953 and 1954, the ratio of human-to-dog cases remained low (Figure 2c).

3.2 | Epidemiological impacts of rabies control measures

Routine vaccination of registered dogs was in place before the Rabies Prevention Law was enacted (Administrative Management Bureau, n.d.; Ueki, 2007; Veterinary Investigation Center, 1936b). In Tokyo, all four measures (emergency vaccinations of owned dogs, dog tethering orders, restrictions on dog movement, and prohibiting of exhibitions and other assembly events) were carried out from March 1948 to July 1950, even before the enactment of the Rabies Prevention Act (Figure 4). After 1950, when the Rabies Prevention Act was enacted, the vaccination coverage of registered dogs in Tokyo remained above 80% (Figure 5). The emergency vaccinations were conducted to urge increasing vaccination coverage, as a part of routine vaccinations, targeted only owned dogs. Capture of free-roaming dogs was carried out mainly by dog catchers in each prefecture. In Tokyo, about 40,000–80,000 free-roaming dogs were captured each year after 1950. The vaccination coverage of the entire dog population (registered dogs plus free-roaming dogs estimated from the number of captured dogs plus 100,000) remained between 25% and 40% after 1950 (Figure 5).

In Saitama, the restrictions on dog movement and the ban on exhibitions and other assembly events and dog tethering orders were issued in August 1949. After the Rabies Prevention Act was promulgated and enforced in 1950, each prefecture became more active in implementing rabies prevention measures. These measures, which had been implemented for just a short period after each announcement (up to 2 months), were changed to a yearly basis in 1950. In Chiba, dog tethering orders and restrictions on dog movement were also introduced that year. By contrast, no prefectural records of these measures were available in Kanagawa until 1952 (efforts to raise awareness to prevent canine rabies entering from Tokyo around 1950 are qualitatively described in a book (Nakajima, 1978)). As a result, Saitama and Chiba eliminated rabies in 1952 and 1953, respectively. In 1953, the number of cases began to decline in Tokyo. In Kanagawa, the data in 1952 and first half (until July) of 1953 were not available and therefore rabies incidence was not known although human cases did occur in this period (Figure 2b). A limited number of monthly cases persisted in the prefecture until the final case was recorded in 1956 (cluster 8).

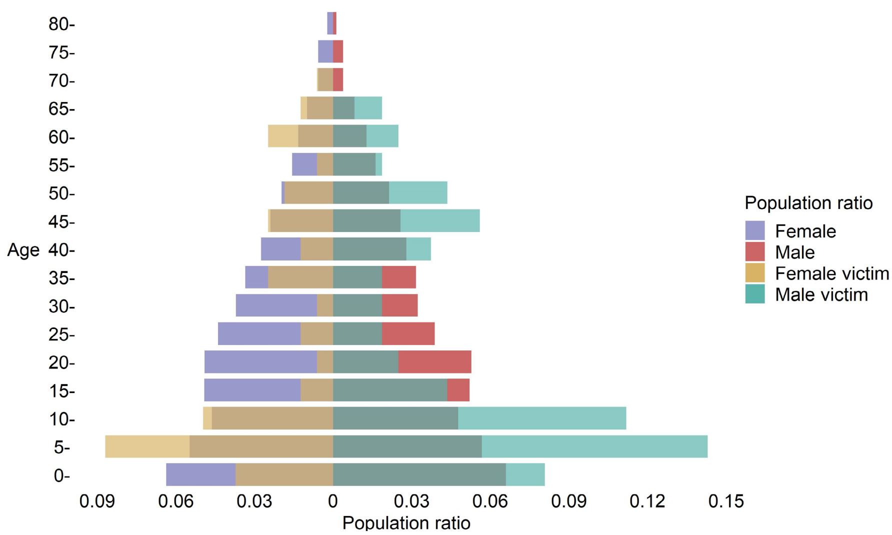

FIGURE 3 Age distributions of human rabies cases by sex, overlaid by population pyramid of Japan in 1950.

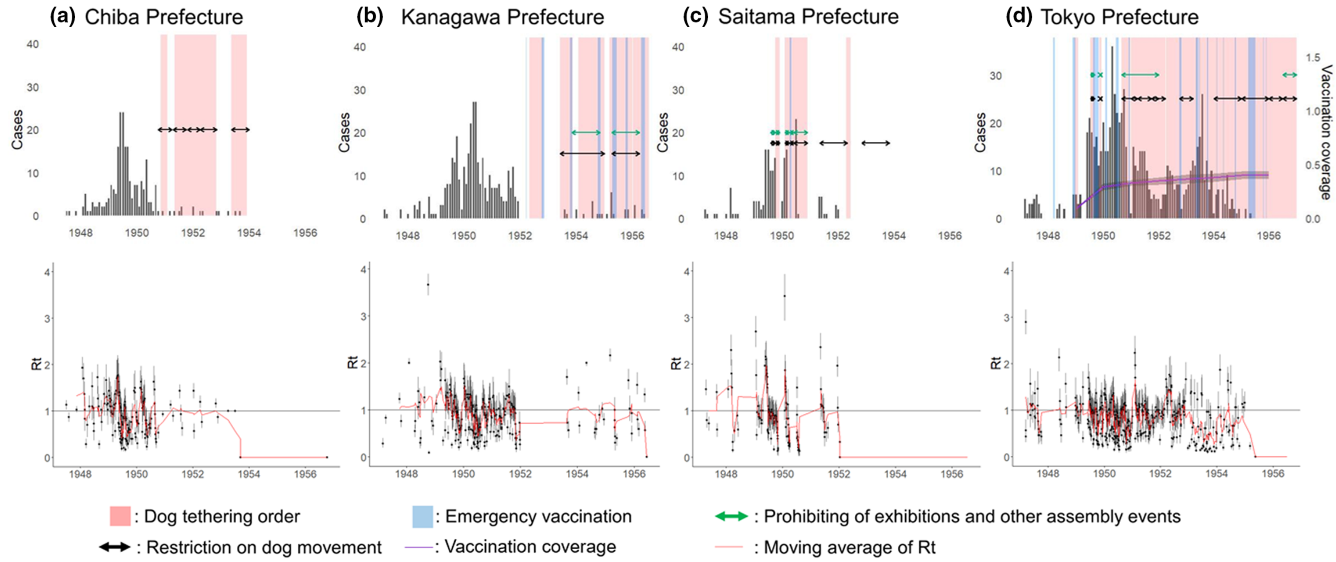

FIGURE 4 Temporal dynamics of dog rabies and countermeasures in each prefecture. Dog rabies case records between January 1952 and July 1953 were not available in Kanagawa Prefecture.

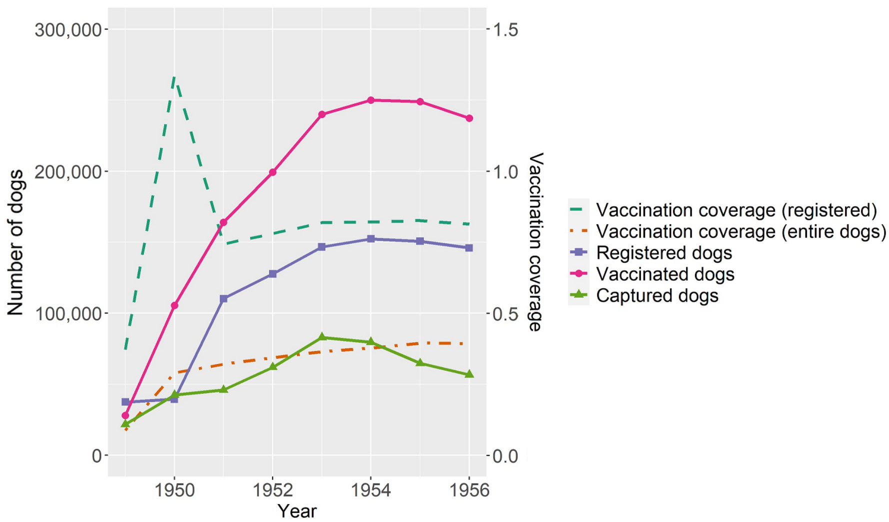

FIGURE 5 The changes of vaccination coverage and the numbers of registered, vaccinated and captured dogs. The vaccination coverage for registered dogs exceeded 100% in 1950 because dog registration had just begun. The vaccination coverage of entire dog population includes estimated unregistered and free-roaming dogs in background population.

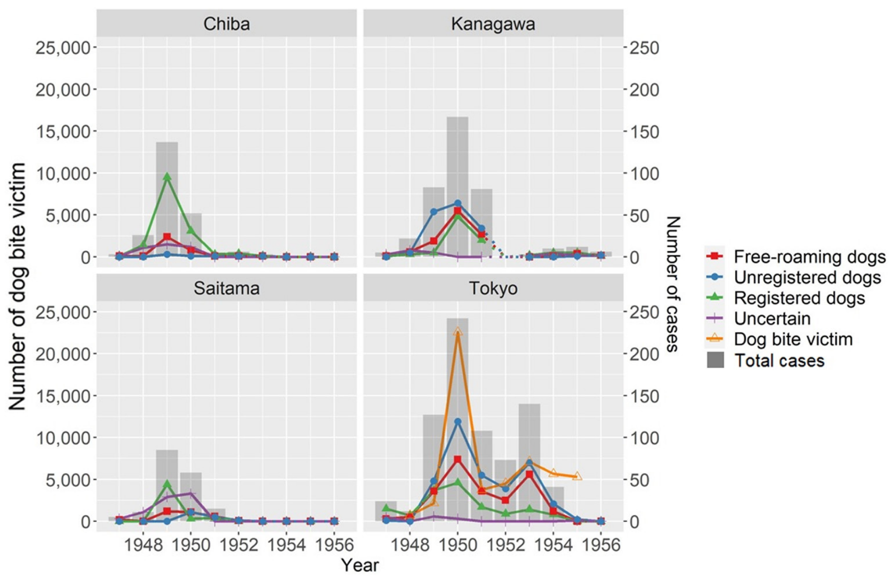

FIGURE 6 Numbers of rabid dogs recorded each year according to their attributes in each prefecture. The missing data in Kanagawa prefecture from 1952 to 1953 were drawn as dotted lines.

In all prefectures, daily R_t fluctuated around one for several years before declining to below 1 in all prefectures (Figure 4). Associations between the moving average of R_t and spatiotemporal clusters were observed in all the prefectures, and during these outbreaks R_t generally exceeded 1 (Table 1). Since 1950, the vaccination coverage of registered dogs remained high in Tokyo, with cases declining and R_t mostly below 1. However, following the cessation of dog movement restrictions in Tokyo Prefecture, R_t exceeded 1 briefly (in 1952, cluster 5), and subsequently declined when vaccination coverage in registered dogs exceeded 70%. In all the prefectures, the prohibition of assembly events and restrictions on dog movements generally coincided with a low R_t. No resurgence of cases were observed whilst dog movement restrictions were in place in Chiba and Saitama prefectures from 1952 onwards (Figures 4).

Attributes of rabid dogs varied widely among the prefectures. In Chiba, 64.2% (149/232) of all rabid dogs in the study period were registered dogs. By contrast, in Tokyo, rabid dogs were mostly free-roaming (32.1%, 247/770) and unregistered dogs (46.1%, 355/770). Similarly, in Kanagawa, rabid dogs were mostly free-roaming (29.6%, 115/389) and unregistered dogs (41.1%, 160/389; Figure 6). The proportion of rabid free-roaming dogs among dog rabies cases declined from 1953 in Tokyo (Figure 6). At a small scale (<5 cases), rabies cases in free-roaming and unregistered dogs persisted in Kanagawa prefecture, and newspaper articles reported a lack of dog catchers due to limited resource allocation and problems of free-roaming dogs in suburban areas of the prefecture (e.g., 'There is only one dog catcher in Kamakura, Zushi, and Hayama. We cannot even afford an assistant'. 12 March 1956, Asahi Shimbun Kanagawa edition).

4 | DISCUSSION

This study describes the epidemiology of rabies in the southern Kanto area, Japan, during the post-WWII period when rabies re-emerged and the Rabies Prevention Act was enacted. At the beginning of this period (from 1947 to 1949), human rabies cases increased in line with dog rabies cases. However, over time the incidence of human rabies deaths relative to dog cases declined, suggesting improved human rabies prevention (Figure 4b). There may be several reasons for this. The Rabies Prevention Act and other measures may have raised public awareness of the importance of rabies prevention and improved availability of PEP may have reduced mortality. The reduction of rabies cases among owned dogs may have also decreased the chance of rabies exposure. We could not test these hypotheses due to lack of data on persons who received PEP and the attributes of rabid dogs that bit rabies victims; dog bite injury data was only available in Tokyo. There are supporting reports that dog rabies vaccination resulted in dramatic decline in dog bite injuries (Lembo et al., 2010) and demand for costly human PEP (Cleaveland et al., 2003) in rural Tanzania.

Our estimates of R_t calculated from detected clusters of rabies cases were consistent with other studies, with R_0 in rabies outbreaks from around the world previously reported to range between 1.05 and 1.85 (Dürr & Ward, 2015; Hampson et al., 2009; Lu et al., 2021) (even higher R_0 such as 1.62–2.33 (Coleman & Dye, 1996) and 2.42 (Kurosawa et al., 2017) have been reported). R_0 can be calculated using R_t if the proportion of the dog population that was susceptible S_t is available; however, dog vaccination records were only reported in Tokyo, and numbers of unregistered and free-roaming dogs are not known. The highest R_t that we estimated (1.68 in Tokyo prefecture in 1948) suggested a further 40% of the unvaccinated population would have been needed to be vaccinated to reach herd immunity at this time ($Pcrit = 1–1/R_0$), if vaccination coverage was very low and R_t was considered to be close to R_0. Information on dog vaccination available from 1949 (Figure 4) suggests that this assumption is plausible. In Tokyo during this period, it was also documented that high birth rates led to many puppies being abandoned and becoming free roamings (Ueki, 2007).

Daily prefecture-specific R_t values fluctuated considerably, probably due to heterogeneity in vaccination coverage, variability in dog biting behaviour, and case detection. Nonetheless, the moving average of R_t corresponded to the identified spatio-temporal clusters. Increased R_t in clusters 5 and 6 in Tokyo in 1952, coincided with relaxation of between prefectures dog movement restrictions, possibly following spread from Kanagawa. In contrast, Chiba and Saitama Prefectures maintained dog movement restrictions in 1952 and did not experience resurgence, suggesting this control measure may have played a role. The restriction of dog movement between prefectures is a classic measure used in 1922 in the large-scale rabies epidemic in Osaka just before dog rabies vaccine became available (Kurosawa et al., 2017). It is noteworthy that relaxation of dog tethering order in Saitama Prefecture in 1951 and 1952 did not result in large scale or persistent rabies outbreaks, potentially due to restriction of between-prefectures dog movement and high vaccination coverage.

In Tokyo, vaccination coverage among registered dogs was on average maintained at >70% after 1950 and dog tethering orders were continuously in place since 1951. These measures, likely led to the sharp decline of R_t, and reduced second epidemic wave in 1953, which largely occurred in free-roaming and unregistered dogs that are unvaccinated. Although official records of vaccination for other prefectures are not available, given experience of nation-wide dog rabies vaccination since 1923 (Kurosawa et al., 2017), and the decline of dog rabies cases, vaccination coverage might have reached at high level by 1950 in Chiba, Kanagawa and Saitama Prefectures. Dogs were vaccinated twice a year (April–June and October–December) during the study period, but the level of efficacy from this vaccination protocol is not known. Even before the Rabies Prevention Law was enacted, when vaccination was required once a year, cases were declining until 1943 and other studies have reported that the vaccine was effective (Umeno & Doi, 1921). However, in the Rabies Prevention Law, dogs under 90 days of age are exempt from vaccination and it was reported that many of these became free-roaming before being vaccinated (Umeno & Doi, 1921). Finally, in 1956, dog rabies was eliminated from both Tokyo and Kanagawa Prefectures; however, even during these latter years of the dog rabies elimination effort, not all Tokyo residents complied with the tethering order (Ueki, 2007). In 1957, after rabies had been eliminated from Japan, the Tokyo Metropolitan Government's dog control ordinance made it mandatory for owners to keep their dogs confined outside, and other prefectures subsequently enacted similar ordinances (Ueki, 2007). In the ordinances, dogs must be tethered regardless of whether they are registered, and all free-roaming dogs can be captured as stray dogs while the tethering order is in effect, suggesting that public health authorities emphasized the importance of eliminating free-roaming dogs and the culture of not tethering in preventing rabies.

Kanagawa was the last prefecture where rabies occurred in Japan, possibly because of delays in the initial response to the outbreak and the shortage of dog catchers. According to a history book of rabies control in Kanagawa Prefecture, because of the establishment of ordinance designated cities: Kawasaki, Yokohama, and Yokosuka Cities, prefectural veterinary officers were dispatched to the new health offices, which caused a shortage of the officers in the prefecture (Nakajima, 1978). These factors may have contributed to increased numbers of free-roaming dogs and the persistence of this last focus of infection. In most rabies endemic countries, the majority of domestic dogs are not confined and are free-roaming (Sambo et al., 2014; Song et al., 2009; Townsend et al., 2013). Several studies were conducted to characterize home range size and contact networks of free-roaming domestic dogs for the planning of effective rabies control (Dürr et al., 2017; Warembourg et al., 2021). A simulation study of rabies incursions in Japan has shown that outbreak sizes would be larger if rabies spreads in free-roaming dog populations, suggesting that dog population management is important in rabies control and prevention (Kadowaki et al., 2018).

According to the above-mentioned history book in Kanagawa Prefecture, veterinary officers could not conduct rabies control until the Rabies Prevention Act was in place in 1950, because of the stoppage of the legal power due to the surrender in WWII (Nakajima, 1978). Once the rabies control activities started, wide spread dog rabies was eliminated in just 7 years. Rabies control responsibility came under public health sector in 1929 (Home Ministry, and Ministry of Health after 1938), and this clear responsibility, strengthened by the Rabies Prevention Act, played an important role in the success of rabies elimination. In the majority of Latin America and Caribbean countries, canine mass vaccination campaigns are coordinated by the health authorities, which dramatically reduced the dog-transmitted human rabies (Vigilato et al., 2013). In contrast, in many Asian and African countries, health authorities prevent human rabies deaths through PEP at a very high cost, while veterinary services suffer from limited budget, which is often further diverted for outbreaks of other diseases (Fitzpatrick et al., 2016; Lembo et al., 2010). A strategic framework to facilitate prioritization of rabies by national authorities and increasing capacity to control rabies through improving diagnostic capacity and canine rabies vaccination is bringing successes in the joint disease control between agriculture and health sectors in several countries such as Kenya and Haiti (Octaria et al., 2018). There were disputes and confusions in transferring responsibility of rabies control from Ministry of Agriculture and Forestry to the Home Ministry in Japan at the time (Veterinary Investigation Center, 1936a); however, the history tells us that it was a rational decision in concentrating the responsibility and limited resources into a single ministry.

Japan is currently free from rabies since 1957 (Shimada, 1971), but maintains mandatory annual dog vaccination. International organizations such as WHO, FAO, and OIE recommend that countries with rabies-free status should implement an embargo on certain animals, carnivores, and chiropterans, or import these animals under strict regulations (Wilde, 2007), continuously verify their free-status, ensure availability of laboratory diagnostic facilities, vaccines and serums for PEP, surveillance system, and develop and test a contingency plan for the possible introduction of canine rabies (World Health Organization Regional Office for South-East Asia, 2016). Hong Kong, a rabies-free region since 1988 maintains mandatory rabies vaccination policy to manage the risk of rabies introduction from China, but majority of rabies-free countries or region, such as the United Kingdom, Australia, Hawaii of the United States of America, and France do not rely on mandatory dog rabies vaccination (Yamada et al., 2019). With the strict quarantine policy, the risk of dog rabies introduction to Japan has been assessed to be very low (Kwan et al., 2017). The benefits for Japan to maintain mandatory dog rabies vaccination are high level of public and veterinary awareness of rabies prevention and a stable supply of animal rabies vaccines, but the cost is high (Kwan et al., 2018; Yamada et al., 2019). Scientific discussions on the maintenance of mandatory vaccination are on the way.

This study has three limitations. The dog rabies case data (dates and locations) were collected from notices issued by each prefecture and newspaper articles published at the time. Unfortunately, in Kanagawa, prefectural notices were unavailable from 1947 to 1953, and the Kanagawa rabies registry was used instead to compensate for this period. However, we were still unable to obtain data from January 1952 to July 1953 in the prefecture. According to the history of rabies in Kanagawa, 110 dog rabies cases occurred in this prefecture in 1952 and 1953 (Nakajima, 1978). The accuracy of our results would be improved if information on the dates and locations of these cases were available. Second, although there were rabies cases in unowned dogs recorded, the magnitude of underreporting in these free-roaming unowned dogs is not known. Third, we also estimated the average serial interval to be 5.9 weeks, which is longer than estimates from Tanzania (3.9 weeks (Hampson et al., 2009)), possibly because of undetected cases that lengthen intervals between linked cases. Another study on rabies outbreaks in Osaka, Japan between 1914 and 1933 reported the serial interval of 6.5 weeks (Kurosawa et al., 2017), suggesting investigation into historical data may result in longer serial interval than by real-time contact tracing. However, these quantitative differences have little effect on our overall conclusions.

In conclusion, this study provides useful insights into the elimination of rabies from Japan that has application to the current global strategy 'Zero by 30'. Over an 8-year period (1949–1956) in the aftermath of WWII mass dog vaccination was crucial to elimination, but vaccinations did not reach free-roaming and unregistered dogs, of which there were many in Japan at this time (Ueki, 2007). Rabies control was therefore enhanced in areas with large free-roaming and unregistered dog populations by dog registration, tethering owned free-roaming dogs, and restricting between-prefecture dog movements, suggesting that dog population management may also be useful in some rabies endemic countries today. Although currently endemic countries are not directly comparable with the situation in Japan 70 years ago, the findings of this study still provide valuable lessons about the feasibility of rabies elimination that are relevant today, particularly from densely populated urban areas. However, a caution is needed in using the findings from this study, because of the uncertainty of the estimated dog population. To eliminate rabies will require sustained dog vaccination effort and understanding of dog ownership practices for contextually appropriate measures.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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