Invited Review

A Comparative Review of Prevention of Rabies Incursion between Japan and Other Rabies-Free Countries or Regions

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SUMMARY: Although rabies still kills many people, the global eradication of human rabies is considered to be feasible. Progress towards eradication may differ among regions with differing socio-economic statuses; therefore, states that successfully eradicate this disease must be vigilant for rabies re-emergence. Here, we discuss challenges that remain concerning current rabies prevention measures and risk assessment results concerning possible rabies introduction and spread in rabies-free Japan. We summarize the preventative measures undertaken by representative rabies-free countries and regions. Our risk assessment results show that the risk of rabies reintroduction under current circumstances is very low, and that subsequent spread of the disease would be minimal because of quite low value of basic reproduction. The majority of rabies-free countries maintain their rabies-free status through strict import quarantine of carnivorous animals, efficient surveillance of animal rabies including wildlife, quick emergency responses, and raising public awareness of the disease. To maintain the current rabies-free status in Japan, we strongly recommend maintaining the current quarantine system and reinforcing stakeholder compliance for those involved in international movement of dogs. Moreover, sustainable surveillance systems targeting wildlife are indispensable.

1. Introduction

Rabies is a viral zoonotic disease caused by the rabies virus *Lyssavirus*, a member of the *Rhabdoviridae* family, and is one of the most feared viral infections in human history as patients with rabies syndrome invariably die from the disease. While there are no effective therapies, rabies is preventable due to safe and effective rabies vaccines. According to the most recent analysis (1), more than 59,000 people are estimated to succumb to rabies every year; most being children

<15 years of age living in rural areas in developing countries and regions, such as sub-Saharan Africa and southeast and south Asia. Rabies is transmitted through bites from rabid animals, and dogs are the major species involved not only in transmission of rabies to humans but also in the maintenance of the virus in nature (2). Elimination of canine rabies is the most important method of preventing human rabies, and this has been shown to be feasible through sustained vaccination campaigns (3-5). Most industrialized countries have succeeded in eliminating rabies from dog populations through intensive vaccination programs; however, in several developed countries, rabies has been shown to be established in wild carnivores, such as foxes, raccoon dogs, and raccoons, posing a considerable economic burden on these countries (6).

Once canine rabies has been eliminated from specific regions or countries, it is essential to maintain a rabiesfree status. Maintenance of a rabies-free status requires

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strict quarantine post-importation of animals as well as functional surveillance that can readily detect the introduction of rabid animals, including wildlife, as recommended by international organizations (7–9). However, some countries rely on the mandatory vaccination of domestic dogs to prevent the nationwide spread of rabies, in case a border control is breached. It is mandatory in Japan for owners to vaccinate their pet dogs; however, there have been discussions as to whether vaccination is actually necessary in a rabiesfree country.

We aimed to compare the currently adopted rabies prevention measures in Japan and in other rabies-free countries to determine whether compulsory vaccination of pet dogs is still required to maintain a rabies-free status.

2. Rabies in Japan

An ancient law enacted in 717 described a canine disease suggestive of rabies, indicating that rabies might have existed in Japan for more than a millennium. Since then, there have been numerous rabies outbreaks throughout Japan's history. A robust rabies prevention law was established in 1950 that helped to eradicate this serious zoonotic disease from the country. The last reported rabies case in Japan was identified in a cat in 1957. Since that time, rabies has not been reported in either terrestrial animals or flying animals such as bats, and only three cases of rabies involving people who had entered Japan have been reported.

3. Problem statement associated with current rabies preventive measures in Japan

The rabies control measures stipulated in Japan's current laws concerning the prevention of rabies have previously been described in detail elsewhere (10). In short, dog owners must register their pets and vaccinate them against rabies annually. Registered dogs must wear tags issued by local government authorities certifying registration and vaccination. In addition, dogs and other animals can be imported or exported only with following proper quarantine procedures. Details regarding quarantine procedures in Japan have been previously outlined by Takahashi-Omoe et al. (10). Dogs and cats from designated regions can be released from quarantine within 12 h if the animals have been microchipped, and if there is proven evidence that they have been continuously residing only in the designated regions since birth, or for at least 180 days, or since being directly imported from Japan. Dogs and cats from non-designated regions must be vaccinated against rabies, test positive for rabies neutralizing antibodies, and detained in the exporting country or region for >180 days.

If rabies were to be confirmed in Japan, then further measures, including restraint or isolation of rabid or suspected rabid dogs, declaration of infected areas, vaccination of dogs in the declared areas, capture and euthanization of stray dogs, and other associated measures would be implemented.

While rabies prevention laws currently remain effective, compliance with the law is declining. According to the Ministry of Health, Labour and Welfare (MHLW), there were 6,626,536 dogs registered to local governments in 2014; however, the Japan Pet Food Association estimated that the number of pet dogs owned by households in Japan was 10,346,000 in this same year. Because of this gap, the rabies vaccination rate is estimated to be approximately 45.8%, in contrast to 71.6% officially reported by the MHLW. Japanese institutions such as the Science Council of Japan and the Japan Veterinary Medical Association have expressed concerns regarding the risk of rabies introduction due to lower rabies awareness and reduced rates of rabies vaccination among pet dogs throughout Japan. However, the actual risk of rabies incursion and subsequent spread has remained unknown until recently, prior to the publication of studies that we introduce later in this report.

The mandatory vaccination of dogs remains a contentious issue among dog owners (11) and there is no established consensus regarding the relevance of mandatory canine rabies vaccinations in maintaining a rabies-free Japan. Despite differing opinions concerning the need for annual vaccination, there is agreement among parties that quarantine should be tightened because of the increasing threat of re-introduction of rabies and the risk of a rapid spread of the disease throughout the country, although the real threat of rabies in Japan remains unknown. Upon request of the MHLW, we conducted a quantitative risk assessment for rabies introduction into Japan. We also estimated the potential size of any outbreak of rabies among dogs, including owned dogs and strays, using two different prefectures as models in Japan. These results have been published elsewhere (12) and are summarized below.

4. Risk assessment for rabies in Japan

4–1. Risk of rabies introduction into Japan

Approximately 10 years ago, a risk assessment for the introduction of rabies in Japan was conducted, and the risk of rabies incursion was estimated to be once in approximately 1,000 years (unpublished). In that assessment, a mathematical model similar to that established by Jones et al. (13) was used. This model appears to overestimate the risk compared to the model currently used by the United Kingdom (UK) Animal Health and Veterinary Laboratory Agency (AHVLA), resulting in a >400-fold difference between the estimated risks according to these two models. We consider that the reason for this discrepancy is the difference in the parameters used in the two models, such as rabies incubation periods, vaccine efficacy, and canine rabies prevalence in exporting countries. Kamakawa et al. (14) also assessed the rabies outbreak risk and showed that the likelihood of a rabid dog being introduced into Japan from the United States was once in 4,932 years. The risk of rabies introduction associated with the importation of dogs generally, however, is not yet known. As such, we conducted an independent risk assessment employing the AHVLA model. The results showed that, under current regulations, the risk of the introduction of a rabid dog would be once in 49,444 years (15). If there was a 20% reduction in compliance, the risk would increase to once in 249 years, indicating the importance of policies that aim to ensure full compliance with laws and regulations in regard to the importation of dogs and other animals. Additionally, we conducted a further risk assessment to estimate the

risk of rabies introduction through the illegal landing of a dog carried, for example, by a Russian fishing boat. The results showed that rabies would enter Japan every 1,084,849 years, while the dog vaccination policy appeared to play no apparent role in reducing the risk of rabies introduction due to a low contact probability between an illegally landed Russian dog and a domestic companion dog (16).

4–2. Risk of rabies spread in Japan

As mentioned, the probability of rabies introduction into Japan under current regulations appears very low or negligible. However, the risk of introduction is not zero; therefore, it is prudent to evaluate the possible risk of rabies spread should rabies be introduced into Japan. We developed an individual-based spatial mathematical model modifying the previously published model (17). This model adjusted the basic reproduction number (\mathbf{R}_0) calculated using data collected from the literature describing past outbreaks in Japan, to reflect the prevailing manner of accommodating dogs in a modern society. R_0 was estimated to be 2.42 based on data derived from rabies outbreaks reported in Osaka Prefecture between 1914 and 1933 (18). We selected two prefectures, namely, Hokkaido and Ibaraki, as models with different demographics and environments. The mean outbreak size for Hokkaido was 22.8 dogs (95% CI: 1-142) in the absence of vaccination of pets, whereas that for Ibaraki was estimated to be 21.7 dogs (95% CI: 1–110) (12). With current vaccination coverage, the outbreak sizes were 3.1 dogs (95% CI: 1-14) and 4.7 dogs (95% CI: 1-37) for the respective prefectures. This model assumes that detection of rabid dogs fails for 30 days as a default, and that the rabies control program starts soon after. A further delay in an initial response of >60 days, in the absence of mandatory vaccination, slightly increases the outbreak size (mean, 22.9 dogs) in the Ibaraki Prefecture. The test results of the scenario analyses indicate that increasing capacities for capturing free-roaming dogs, emergency vaccination of animals, or detecting rabid and contacted dogs were less sensitive, while higher probabilities of an unintentional release of rabid dogs and that a rabid stray dog would select a stray dog to bite could cause a larger outbreak.

Collectively our analyses clearly showed that, in contrast to widely accepted assumptions, the risk of rabies introduction to Japan in addition to the subsequent spread of the disease within Japan is small, even in the absence of routine vaccination of domestic dogs.

4–3. Economic burden

The value of implementing a mandatory vaccination policy for domestic dogs in rabies-free Japan has been assessed through benefit-cost analysis using decision tree modelling (Kwan et al., submitted). The annual costs of implementing the current mandatory vaccination policy (Annual costs) have been estimated to be USD 160,472,075 (¥18,000,152,653, based on 1 USD = 112.17 Japanese yen). The economic burden of a dog rabies outbreak has been estimated to be USD 1,682,707 (¥188,749,244) under a mandatory vaccination policy, and estimated to be USD 5,019,093 (¥562,991,662) under the abolition of a vaccination policy. Using a damage-avoidance approach, the annual benefits of implementing the current vaccination policy (Annual

benefits) in expected value have been estimated to be USD 85.75 (\$9,619). The benefit-cost ratio (BCR = Annual benefits/Annual costs) has been estimated to be 5.35×10^{-7} . The estimated values of the BCR were very low (well below 1), strongly indicating that the implementation of the current mandatory vaccination policy in Japan is economically very inefficient. Scenario analyses further revealed that the maintenance of a preemptive dog vaccination policy in rabies-free Japan would not be economically efficient unless a number of conditions were satisfied, including amending the policy to one that requires less frequent re-vaccinations. It has been demonstrated that a vaccination schedule with a less frequent booster vaccine requirement is appropriate with the use of the domestic rabies RC-HL strain vaccine, i.e. a booster is required within one year after the primary vaccination and then every two to three years (19).

5. How to maintain a rabies-free status; recommendations by international organizations

Next, we aimed to determine whether recommendations or guidelines were available for rabies-free countries that could elaborate on the measures undertaken to maintain a rabies-free status.

The World Health Organization (WHO) is one of the leading international organizations that promotes the importance of rabies control at a global level. The WHO has also stated that rabies could be eradicated or eliminated through extensive vaccination of dogs. In 1984, the WHO Expert Committee on Rabies released its 7th report, and the Committee recommended that rabies-free countries should introduce a ban on the importation of animals at high-risk of carrying the rabies virus, or place a strict quarantine upon the importation of such animals (7). Subsequently, the Committee also recommended an alternative measure consisting of identification, vaccination, and serological testing, in addition to holding animals for at least four months in the exporting countries prior to embarkation if a strict quarantine could not be applied (8). The 2nd WHO Expert Consultation on Rabies report (9) recommended that rabies-free countries should implement an embargo on certain animals, carnivores, and chiropterans, in particular, or should import these animals under strict regulations stipulated by the veterinary authority of the importing country. The Consultation report also emphasized the importance of a functional rabies surveillance system that targeted not only domestic animals but also wildlife. Vaccination of dogs and cats in rabies-free countries is considered an additional measure that may be in place to maintain the rabies-free status in these countries. In 2012, the WHO Regional Office for South-East Asia published a report entitled "Strategic Framework for Elimination of Human Rabies Transmitted by Dogs in the South-East Asia Region" (20). In this document, it was recommended that rabies-free countries should continuously verify their rabies-free status in accordance with guidelines developed by international organizations, such as the World Organization for Animal Health (OIE) and the United Nations Food and Agriculture Organization (FAO), and that appropriate action at the point of entry should be taken. Stockpiling supplies for postexposure prophylaxis, with appropriate guidelines, as well as availability of diagnostic laboratories, was also recommended. The importance of developing and testing a contingency plan for the possible introduction of canine rabies together with that of installing a workable rabies surveillance system is also outlined in the strategic framework.

6. Measures taken in rabies-free countries or regions to maintain their rabies-free status

According to the Center for Disease Control and Prevention, USA, over 100 countries and political units did not report any indigenous rabies cases in 2015. From these, we selected several representative countries to scrutinize the measures they had adopted to maintain a rabies-free status, as follows.

6–1. United Kingdom (UK)

By 1902, the UK had succeeded in eliminating rabies due to the Metropolitan Streets Act, introduced in 1867, the General Rabies Order, and the Importation of Dogs Order, enacted in 1897 (21,22); however, rabies reemerged in 1918. Reinforcement of the legislation again led to rabies elimination in 1922 (22). Elimination was achieved through the reduction of rabies transmission using muzzles and leashes as well as prohibition of the movement of animals without relying on vaccination. Thereafter, a rabies-free status has been maintained in the UK. Until 2000, when a new policy, viz., the pet travel scheme (PETS) was introduced, the UK imposed a very strict 180-day quarantine policy to prevent the re-introduction of rabies through the movement of dogs and cats (23). In 2004, the European Union (EU) introduced a similar policy, the EU Pet Movement Policy (EUPMP) to protect member states against the introduction of rabies through the movement of pets. However, the restrictions enforced according to this EU policy, adopted by the UK in December 2011, were not as stringent as PETS. The AHVLA conducted a quantitative risk assessment to determine whether adopting the EUPMP would alter the risk of rabies introduction to the UK (24). The results of that study showed a 60-fold increase in the potential risk of rabies entry from once every 13,272 years to once every 211 years when the UK changed its pet movement policy from PETS to the EUPMP. This risk was further evaluated by the Det Norske Veritas, Ltd. in 2011 (25). According to their report submitted to the AHVLA, one rabies introduction in 211 years corresponded to one human fatality every 21,000 years. When comparing this risk with other health risks, they concluded that the individual risk of death from rabies was 100,000 times lower than the level of broadly acceptable risk (25).

In addition to strict importation restrictions, the UK does not take other measures to prevent rabies introduction and subsequent spread, such as mandatory vaccination of dogs and cats. From an animal welfare perspective, microchipping became compulsory in 2016. As the risk of introduction is not zero, the UK government prepared a contingency plan elaborating how to contain an outbreak should an incursion occur (26). This rabies disease control strategy may help to contain a possible outbreak due to the introduction of a rabid animal into the country.

6–2. Australia

Australia has been rabies-free for approximately 150 years. In 1867, a Tasmanian boy was bitten by a rabid dog and died (27,28). This is the only documented indigenous rabies case in this country. At that time, Australia had succeeded in eradicating canine rabies through culling stray dogs, as the rabies vaccine was not available until 20 years later. Since then, except for human cases due to the Australian bat lyssavirus, there have been no indigenous human rabies cases (29). Rabies cases involving other animal species have never been reported. Currently, dogs and cats can be imported from countries or regions approved by the Australian Department of Agriculture and Water Resources, as described in the "Final Policy Review" published by the Department (30). Approved countries are categorized into three groups, based on their rabies epidemiological status. Depending on the group, different requirements must be fulfilled to import dogs and cats into Australia. Any person wanting to export dogs or cats to Australia from unapproved countries or regions must move their animals to approved regions or countries prior to exportation to Australia. Animals originating from Group 3 regions or countries must be microchipped, vaccinated between 180 days and 24 months prior to shipping, and shown to have rabies-neutralizing antibodies with titers > 0.5 IU/ml.

To our knowledge, there are no published quantitative risk assessments addressing the probability of rabies introduction into Australia through the international importation of dogs and cats. However, the risk assessment conducted in the UK suggested that implementation of similar importation regulations was very effective; therefore, the risk of introducing rabies through the legal importation system is likely to be very small or negligible. Nonetheless, the recent spread of rabies in the Indonesian archipelago has raised concerns regarding the introduction of rabies into the northern regions of Australia due to the illegal importation of dogs on fishing or leisure boats originating from rabiesendemic islands in Indonesia (31,32). Based on a recent quantitative assessment, the risks of rabies entry into the Australian north-west Cape York peninsula, and rabies introduction to dogs residing in one of the communities via transport of rabies-infected dogs on illegal Indonesian fishing boats, have been estimated to be low (33). Moreover, several mathematical simulation models have predicted the extent of local rabies spread once the disease is introduced into the country, emphasizing the necessity of introducing effective prevention measures into the remote regions of northern Australia, as human populations in these regions are scarce, while the numbers of free-roaming canids, including dingoes, are substantial (34-36).

Animal rabies vaccinations are not mandatory in Australia; however, registration of dogs and microchipping for identification are compulsory. As a contingency plan, the Australian Veterinary Emergency Plan has been published by the Primary Industries Ministerial Council (37).

6-3. Hawaii

No indigenous rabies cases have been recorded or reported in Hawaii. In 1991, a bat was found in a shipping container arriving at the Honolulu harbor.

The container came from California, where rabies is endemic, so the bat was euthanized, and tested positive for the presence of the rabies virus (38). In 1967, Hawaii reported false-positive rabies cases in rats that led to a chaotic response. Hawaii then established a rabies surveillance system designed to detect rabies. Hawaii had initially established a 120-day quarantine policy in 1912 to protect the state from the entry of rabid animals. The current system allows the entry of dogs and cats after retention of the animals in a quarantine facility for five days or less if the animals are identifiable with microchips, have been vaccinated twice with effective rabies vaccines, are positive for rabies antibodies with titers >0.5 IU/ml, and are kept for at least 120 days in exporting countries (39). Animals that do not fulfill the above conditions must undergo the full 120-day detention in the facility. Hawaii conducted rabies importation risk assessments in 1996 and 2003 before making amendments to the importation requirements. According to the later assessment (40), rabies introduction into the state would occur once in approximately 150 years under the current regulations. In 2014, a white paper on risk analysis carried out by a private company was made available to the public via the Internet (41). In this document, the author concluded that the risk of rabies introduction would not increase substantially even if the quarantine periods currently applied were reduced to 60 days. Because of the historical absence of rabies in the state, no vaccination against rabies is required for dogs and cats if they are born in the state. However, according to federal rule, military dogs, as well as dogs in dog clubs, must be vaccinated. Owned but freely roaming cats must be injected with a microchip.

6–4. France

France declared a rabies-free status in terrestrial animals in 2000 after intensive efforts to eliminate rabies in red foxes through oral vaccination (42). However, since then, 14 cases of rabies in domestic animals have been reported (43). All involved illegally imported dogs and cats from rabies-endemic countries, particularly from north-African countries, and the rabies-free status of France did not change, except in one incidence because rabid animals were rapidly identified without involving a further spread of rabies. In 2008, tracking of a rabid dog found in a suburb of Paris identified a rabies transmission chain initiated by a dog illegally brought into France from Morocco (44). Because dogs residing in France had been involved in this outbreak, France lost its rabies-free status for two years. After two years of extensive and continuous surveillance, it was revealed that there were no more terrestrial animals suspected of being infected with the rabies virus in France, and France regained its rabiesfree status again in 2010. France appears vulnerable in terms of the introduction of rabies through the illegal import of carnivorous animals incubating the rabies virus. More than one million immigrants from rabiesendemic countries, mostly those from north Africa, now live in France, and many people visit their countries of origin during holidays, especially in the summer. Some of them acquire puppies to keep as pets on returning to France and bring these puppies without complying with the rules and regulations, allowing rabies introduction

to France. A quantitative assessment conducted by Napp et al. indicated that an introduction of rabies from Morocco into the EU would occur at a frequency of once every five years (45). This extremely high probability was considered to be due to the illegal importation of animals, and strict border control was expected to reduce the risk 270-fold. The actual numbers of rabid animals illegally imported from Morocco to Europe were much greater than the above estimates, but the difference was less than an order of magnitude between the estimate and the actual incidence, suggesting that the results obtained through mathematical modeling would be very important and useful to assess the risk of rabies introduction in rabies-free countries or regions. France adopted the EUPMP to prevent the introduction of rabies by carnivorous animals imported to France. However, the re-introduction risk appears high compared to other rabies-free countries because of the specific circumstances mentioned earlier. However, vaccination of domestic dogs and cats is not mandatory (46). It has been suggested that early detection of suspected rabid animals and subsequent prompt responses are the most important measures to contain the disease. To ensure the earliest rabies containment possible, sustained education of veterinarians, including small animal practitioners, is critical. Identification of individual animals is achieved through law-enforced implantation of microchips or tattooing for animal welfare reasons.

6-5. Hong Kong

Hong Kong has been a rabies-free region since 1988, and the last two outbreaks occurred in the 1950s and 1980s (47). The latter outbreak started in 1980 when a rabid dog was suspected to have been introduced from neighboring Guangdong, China, through fishing boat movements. Massive control efforts were undertaken including emergency vaccination, culling of stray dogs, and establishment of a restricted movement zone. This outbreak lasted until 1987 and, in total, 34 animal cases (32 dogs and two cats) and two indigenous human cases were recorded.

Hong Kong has rabies preventive legislation enforcing identification and vaccination of domestic dogs, stray dog management, control of illegal trading of dogs, control of dog fighting, control of known dangerous or large dogs in a public place, and a strict import regime for animal carcasses and animal products (47). In particular, dogs must be microchipped and vaccinated against rabies at the age of five months and then vaccinated once every three years. This mandatory vaccination policy is maintained to manage the substantial risks of rabies introduction from China where rabies is widespread, particularly in southern provinces such as Guangxi, Hunan, and Guangdong (48).

7. Conclusion

Rabies has been regarded as one of many neglected tropical diseases, but recently, it has received attention from the WHO, FAO, OIE, and other non-governmental organizations, such as the Global Alliance for Rabies Control and the Bill and Melinda Gates Foundation, among others, leading to sustained rabies control efforts to globally eliminate this notorious zoonotic disease (49,50). As noted in a statement in relation to sustainable development goal 3.3, global elimination of rabies has been set as a goal for 2030 by the United Nations, along with other neglected tropical diseases (51). However, as shown through the repeated re-emergence of rabies in countries that had previously eliminated the disease, maintaining a rabies-free status is very challenging. An examination of current control measures implemented in several rabies-free countries or regions clearly showed that countries or regions can prevent rabies introduction only through strict quarantine consisting of identification of animals, appropriate vaccination of animals prior to importation, and rabies antibody testing, assuring a titer of > 0.5 IU/ml.

Vaccination of pet dogs has been mandatory in Japan despite the absence of the disease for more than 60 years. Recommendations made by international organizations with regard to maintaining a rabiesfree status do not insist on compulsory vaccination. Some countries within the EU where the risk of rabies introduction is extremely high do not have legislation requiring their citizens to vaccinate their pet animals. Our risk assessment showed routine vaccination would shorten the duration of outbreaks as well as limit the extent of the outbreak; however, even in the absence of herd immunity to the rabies virus, any outbreak would be likely to cease spontaneously. Even when a rabid animal is illegally introduced to a rabies-free country, rabies outbreaks can be contained rapidly because the R₀ for rabies is low, as shown in previous studies (52-55) and supported in our study. However, the R₀ for rabies appears to differ depending on social structures, the attitudes of people, or their customs. To contain a rabies outbreak, a country or region must be well prepared for an such event and implement control measures, such as capturing free-roaming animals and undertaking emergency vaccination. To initiate effective rabies control responses, it is essential to have an effective surveillance system that can detect a rabid animal as soon as possible. This system must be supported by laboratories with the ability to adequately diagnose rabies cases in a variety of animal species.

Our results indicated compliance with the laws and regulations is most important in terms of reducing the risks of rabies introduction. Fraudulence or fabrication in preparing documents could lead to rabies introduction, as recently reported in France (56) and the United States (57). In these cases, veterinarians issued fabricated certificates necessary for the exportation of animals. Klevar et al. (58) reported that dogs imported from eastern European countries under current EUPMP regulations do not have sufficient antibody responses. There are growing concerns that some veterinary officers in eastern European countries are involved in exporting unvaccinated rescue dogs to other member states. Post-graduate education of veterinarians is of particular importance to ensure that quarantine systems are effective.

The findings of this paper, together with actual examples from certain rabies-free countries, strongly suggest that a rabies-free status in Japan can be maintained without conducting mandatory annual vaccination of domestic dogs, implying the need for a revision of the rabies prevention laws in the future. However, maintenance of an effective surveillance system that enables early detection of disease occurrence

supported through rapid and accurate diagnosis of the disease based on laboratory testing is a prerequisite for a rapid response to contain the disease. Although Japan and other rabies-free countries are currently equipped with a very effective surveillance system targeting terrestrial animals, it is important to maintain the system with appropriate budgets and sufficient staffing. At the same time, abolition of the mandatory vaccination program through a revision of the law would require a comprehensive review of the rabies prevention system in Japan, considering the benefits that are provided under the current system. Specifically, the mandatory vaccination program has contributed to a high level of public and veterinary awareness with regard to rabies prevention, along with a stable supply of animal rabies vaccines from the vaccine companies. Therefore, in the revised system, specific measures should be incorporated to maintain public and veterinary awareness and to secure animal vaccines for emergency use, in order to ensure the early detection of any rabies incursion into Japan and the control of rabies through vaccination for dogs after the incursion.

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REFERENCES

- 1. Hampson K, Coudeville L, Lembo T, et al. Estimating the Global Burden of Endemic Canine Rabies. PLoS Negl Trop Dis. 2015;9: e0003709.
- Hanlon C, Childs J. Epidemiology. In: Jackson AC, editor. Rabies: Scientific basis of the disease and its management. 3rd ed. Waltham, MA: Academic Press; 2013. p. 61-121.
- 3. Lembo T, Hampson K, Kaare MT, et al. E. The feasibility of canine rabies elimination in Africa: Dispelling doubts with data. PLoS Negl Trop Dis. 2010; 4:e626.
- 4. Lankester F, Hampson K, Lembo T, et al. Infectious disease. Implementing Pasteur's vision for rabies elimination. Science. 2014; 345:1562-4.
- Cleaveland S, Lankester F, Townsend S, et al. Rabies control and elimination: a test case for one health. Vet Rec. 2014;175:188-93.
- State D, Rupprecht CE, Roony JA, et al. Status of oral rabies vaccination in wild carnivores in the United States. Virus Res. 2005;111: 68-76.

- World Health Organization. WHO expert committee on rabies 7th report. Geneva.WHO TRS; 1984:709.
- World Health Organization. WHO expert committee on rabies 8th report. Geneva.WHO TRS; 1992:824.
- 9. World Health Organization. WHO expert consultation on rabies. Geneva.WHO TRS; 2013:982.
- Takahashi-Omoe H, Omoe K, Okabe N. Regulatory systems for prevention and control of rabies, Japan. Emerg Infect Dis. 2008;14:1368-74.
- JapanToday. Japan may be on brink of rabies epidemic. Available at http://www.japantoday.com/category/kuchikomi/view/japanmay-be-on-brink-of-rabies-epidemic> Accessed January 16, 2017.
- Kadowaki H, Hampson K, Tojinbara K, et al. The risk of rabies spread in Japan - a mathematical modelling assessment. Epidemiol Infect. 2018;146:1245-52.
- Jones RD, Kelly L, Fooks AR, et al. Quantitative risk assessment of rabies entering Great Britain from North America via cats and dogs. Risk Anal. 2005; 25:533-42.
- Kamakawa H, Koiwai M, Satomura S, et al. Quantitative assessment of the risk of rabies entering Japan through the importation of dogs and cats from the USA. Epidemiol Infect. 2009;137:1149-54.
- Kwan NCL, Sugiura K, Hosoi Y, et al. Quantitative risk assessment of the introduction of rabies into Japan through the importation of dogs and cats worldwide. Epidemiol Infect. 2017;145:1168-82.
- 16. Kwan NCL, Ogawa H, Yamada A, et al. Quantitative risk assessment of the introduction of rabies into Japan through the illegal landing of dogs from Russian fishing boats in the ports of Hokkaido, Japan. PrevVet Med. 2016;128: 112-23.
- Townsend SE, Sumantra IP, Pudjiatmoko, et al. Designing Programs for Eliminating Canine Rabies from Islands: Bali, Indonesia as a Case Study. PLoS Negl Trop Dis. 2013;7:e2372.
- Kurosawa A, Tojinbara K, Kadowaki H, et al. The rise and fall of rabies in Japan: A quantitative history of rabies epidemics in Osaka Prefecture, 1914–1933. PLoS Negl Trop Dis. 2017;11:e0005435.
- Kwan NCL, Yamada A, Sugiura K. Evaluation of the efficacy of the Japanese rabies RC-HL strain vaccine in domestic dogs using past and present data: Prediction based on logistic regression and metaanalysis. Prev Vet Med. 2017;147:172-7.
- World Health Organization Regional Office for South-East Asia. Strategic framework for elimination of human rabies transmitted by dogs in the South-East Asia region 2012. Available at: < http:// www.searo.who.int/entity/emerging_diseases/links/Zoonoses_ SFEHRTD-SEAR.pdf>. Accessed April 3,2019.
- Muir P, Roome A. Indigenous rabies in the UK. Lancet. 2005;365:2175.
- Steel JH, Fernandez PJ. History of rabies and global aspects. In: Baer GM,editor. The natural history of rabies.2nd ed. Boca Raton,FL: CRC Press; 1991.p.1-24.
- 23. Fooks AR, Roberts DH, Lynch M, et al. Rabies in the United Kingdom, Ireland and Iceland. In:King AA, Fooks AR, Aubert M, et al. editors. Historical perspective of rabies in Europe and the Mediterranean basin: a testament to rabies by Dr. Arthur A. King. Paris:OIE: 2004.p.25-32.
- Goddard AD, Donaldson NM, Horton DL, et al. A quantitative release assessment for the noncommercial movement of companion animals: Risk of rabies reintroduction to the United Kingdom. Risk Anal. 2012;32:1769-83.
- Spouge J, Comer P, editors. Interpretation of Rabies Risk Assessment: Final Report.London:Det Norske Veritas; 2011. Available at http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.394.8967%rep=rep1&type=pdf> Accessed April 7, 2016.
- Rabies Disease Control Strategy,2011. London:DEFRA. Available at <https://www.gov.uk/government/uploads/system/ uploads/attachment_data/file/69523/pb13585-rabies-controlstrategy-110630.pdf> Accessed January 27, 2016.
- 27. Kippen R. Rabies in Tasmania. Chainletter, Newsletter of the Founders and Survivors Project. 2010;6:4-5.
- Sparkes J, Fleming PJ, Ballard G, et al. Canine rabies in Australia: A review of preparedness and research need. Zoonoses Public Health. 2015; 62:237-53.
- 29. Garg SR. Rabies in man and animals. New Delhi: Springer India; 2014.
- 30. Department of Agriculture, Australian Gov. Biosecurity Advice 2013-22. Release of the final policy for the importation of dogs and cats and their semen from approved countries. Available at <http:// www.agriculture.gov.au/biosecurity/risk-analysis/reviews/finalanimal/dogs_and_cats/ba2013-22-final-policy-importation-dogscats-semen-approved-countries> Accessed April 7, 2016.

- Forman AJ. The threat of rabies introduction and establishment in Australia. Aus Vet J. 1993;70:81-3.
- Brookes VJ, Ward MP. Expert Opinion to Identify High Risk Entry Routes of Canine Rabies into Papua New Guinea. Zoonoses Public Health. 2017; 64:156-60.
- Hudson EG, Brookes VJ, Ward MP. Assessing the risk of a canine rabies incursion in Northern Australia. Front Vet Sci. 2017;4:141.
- Dürr S, Ward MP. Development of a novel rabies simulation model for application in a non-endemic environment. PLoS Negl Trop Dis. 2015;9: e0003876.
- Sparkes J, McLeod S, Ballard G, et al. Rabies disease dynamics in naive dog populations in Australia. Prev Vet Med. 2016; 131:127-36.
- Johnstone-Robertson SP, Fleming PJS, Ward MP,et al. Predicted spatial spread of canine rabies in Australia. PLoS Negl Trop Dis. 2017;11:e0005312.
- 37. Animal Health Australia. Disease strategy: Rabies (Ver.3.0). Australian Veterinary Emergency Plan (AUSVETPLAN),3rd ed. Primary Industries Ministerial Council, Canberra, ACT. Available at <https://www.animalhealthaustralia.com.au/our-publications/ ausvetplan-manuals-and-documents/> Accessed April 7, 2016.
- Sasaki D, Middleton CR, Sawa TR, et al. Rabid bat diagnosed in Hawaii. Hawaii Med J. 1992; 51:181-5.
- Animal Quarantine Station. Hawaii rabies quarantine: Information Brochure. Available at <http://hdoa.hawaii.gov/ai/files/2013/01/aqsbrochure.pdf> Accessed January 29, 2016
- 40. Foppoli JM. Hawaii rabies import analysis-2002; Movement of dogs and cats from rabies endemic areas to Hawaii, Office of the State Veterinarian, Hawaii Department of Agriculture. Personal communication.
- 41. Fitzpatrick BG. Conducting quantitative pathogen risk analyses via Monte Carlo simulation. White Paper April 2014, Tempest Tech. Available at <http://tempest-tech.com/wordpress/wp-content/ uploads/2014/03/White-Paper_Hawaii_Final.pdf> Accessed April 7, 2016
- 42. Toma B. Fox rabies in France. Euro Surveill. 2005;10:220-2.
- Rabies surveillance. France, Rabies-Bulletin-Europe, Available at http://www.who-rabies-bulletin.org/default.aspx Accessed April 7, 2016.
- French multidisciplinary investigation team. Identification of a rabid dog in France illegally introduced from Morocco. Euro Surveill. 2008;13:1-2.
- Napp S, Casas M, Moset S, et al. Quantitative risk assessment model of canine rabies introduction: application to the risk to the European Union from Morocco. Epidemiol Infect. 2010;138:1569-80.
- 46. EFSA Panel on Animal Health and Welfare. Opinion of the Scientific Panel on Animal Health and Welfare (AHAW) on a request from the Commission regarding an assessment of the risk of rabies introduction into the UK, Ireland, Sweden, Malta, as a consequence of abandoning the serological test measuring protective antibodies to rabies. EFSA Journal 2006;436:1-54.
- Center for Health Protection. Scientific Committee on Emerging and Zoonotic Diseases Prevention and Control of Rabies. Available at http://www.chp.gov.hk/files/pdf/prevention_and_control_of_ rabies_r.pdf> Accessed November 29, 2016.
- Hou Q, Jin Z, Ruan S. Dynamics of rabies epidemics and the impact of control efforts in Guangdong Province, China. J Theor Biol. 2012;300:39-47.
- 49. Briggs DJ. An effective communication campaign: Nine years of world rabies day & end rabies now campaign. Global elimination of dog-mediated human rabies; the time is now. Global conference book of abstracts, Available at http://www.who.int/rabies/Book_of_abstracts.pdf?ua=1 Accessed April 7, 2016.
- 50. WHO and Bill & Melinda Gates Foundation. Report of the sixth meeting of the International Coordinating Group of the World Health Organization and the Bill & Melinda Gates Foundation project on eliminating human and dog rabies. Available at http://www.who.int/rabies/WHO_HTM_NTD_NZD_2015.1.pdf> Accessed April 7, 2016.
- United Nations. Sustainable Development Goal 3. Available at https://sustainabledevelopment.un.org/sdg3 Accessed April 7, 2016.
- 52. Coleman PG, Dye C. Immunization coverage required to prevent outbreaks of dog rabies. Vaccine. 1996;14:185-6.
- 53. Zhang J, Jin Z, Sun GQ, et al. Analysis of Rabies in China: Transmission Dynamics and Control. PLoS One. 2011;6:e20891.
- Zhang J, Jin Z, Sun GQ, et al. Modeling seasonal rabies epidemics in China. Bull Math Biol. 2012; 74:1226-51.

- 55. Hou Q, Jin Z, Ruan S. Dynamics of rabies epidemics and the impact of control efforts in Guangdong Province, China. J Theor Biol. 2012;300:39-47.
- 56. OIE Rabies, France. Available at <http://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?reportid=17787> Accessed April 7, 2016.
- Sinclair JR, Wallace RM, Gruszynski K,et al ; The Centers for Disease Control and Prevention. Rabies in a dog imported from Egypt with a falsified rabies vaccination certificate — Virginia, 2015. MMWR Morb Mortal Wkly Rep. 2015;64:1359-62.
 Klevar S. Høgasen HR, Davidson RK, et al. Cross-border transport
- Klevar S. Høgasen HR, Davidson RK, et al. Cross-border transport of rescue dogs may spread rabies in Europe. Vet Rec. 2015;176:672-4.