Doctoral Thesis

Epidemiological studies of the effectiveness and appropriateness of today's Japanese rabies prevention system

（日本における狂犬病予防対策の有効性および妥当性に関する疫学研究）

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論文の内容の要旨

論文題目　**Epidemiological studies of the effectiveness and appropriateness of today's Japanese rabies prevention system**
（日本における狂犬病予防対策の有効性および妥当性に関する疫学研究）

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日本では、1950 年に制定された狂犬病予防法により狂犬病対策が強力に推進された結果、当時年間 1000 例ほど報告されていた犬の狂犬病は清浄化が進み、1956 年の 6 頭の発生を最後に現在まで報告されていない。一方、世界的には、狂犬病がない国・地域は極めて少なく、狂犬病予防法に基づき清浄国・地域として認めてられているのは、豪州、ニュージーランド、ハワイ、フィジー、グアム、アイスランドの 6 カ国・地域である。

国際獣疫事務局（OIE）は、清浄国は狂犬病の侵入を防ぐため、特定の哺乳類、特に食肉目と翼手目の輸入を禁じたり、その国の獣医部局が許可した方法によってのみ輸入を認めたりする措置を講じることができるとしている。また、清浄国はサーベイランスを徹底し、狂犬病の侵入をいち早く検出できる体制を整備すべきとしている。そのほかにワクチン接種などを実施することもできるとしている。日本では、狂犬病予防法に基づき犬の所有者は年 1 回のワクチン接種が義務付けられるとともに、犬および猫を輸入する際には輸出国での 2 回ワクチン接種、抗体検査、180 日間の待機からなる厳しい輸入検疫規則が適用されている。

清浄国におけるワクチン接種の必要性については、狂犬病の侵入リスク、仮に侵入した場合のまん延リスクなどを考慮して判断する必要がある。日本への狂犬病の侵入経路にはさまざまな経路がある。動物検疫所を通じて毎年約 1 万頭の犬・猫が輸入されているほか、在日米軍により毎年 1000～2000 頭の犬・猫が輸入されている。また、北海道に寄港するロシア船からの不法上陸犬についても侵入源としての危険性が指摘されている。本研究は、これらの侵入経路を通じた日本への狂犬病の侵入リスクを定量的に評価するとともに、仮に侵入した場合の狂犬病がまん延予測に有用なデータの収集、現在日本で使用されている狂犬病ワクチンの有効免疫付与期間の推定、狂犬病ワクチン接種策の経済的な効率性を明らかにすることを試みたものであり、以下の 5 章からなる。

第1章　<u>日本への犬および猫の輸入に伴う狂犬病侵入リスクの定量的評価</u>

動物検疫所および米軍を通じた犬・猫の輸入に伴う侵入経路として計 14 の経路からなるシナリオツリーを作成し、各シナリオに関係する事象に文献調査などにより推定した確率分布を当てはめることにより、侵入リスクを推定した。その結果、現行の輸入規則が守られる限り侵入リスクは 49,444 年（90%予測区間（PI）: 19,170～94,641 年）に 1 回であるが、遵守しない者が 20%いると 249 年に 1 回であること

が判明した。また、シナリオア分析の結果、輸出国でのワクチン接種回数を 1 回に減らしても、また、輸出国での待期期間を 90 日に短縮しても侵入リスクは大幅に増大しないことが確認された。

第2章　北海道に寄港するロシア船からの不法上陸犬を通じた狂犬病侵入リスクの定量的評価

ロシア船は犬が海難事故防止に役立つとの迷信の下、犬を乗船させる習慣がある。狂犬病に感染した犬が乗船し、北海道の港で不法上陸し、日本の動物と接触し侵入の原因となる可能性があるとの前提の下、不法上陸犬による狂犬病侵入リスクの評価を行った。その結果、ロシア船からの不法上陸犬による侵入リスクは多数のロシア漁船が寄港していた 2000 年前後に比べ大幅に低下し、現状（2006～2015 年のデータ）では 108 万年に 1 回程度であることが判明した）。

第3章　日本の飼育犬間の接触頻度および狂犬病を想定した飼育者の行動の評価

仮に狂犬病に感染した動物が日本に侵入した場合、飼育犬間での接触が感染拡大の原因となることが予想される。そこで、飼育犬間の接触率や飼育者の行動様式に関する情報は日本での狂犬病のまん延予測に有用であるとの考えの下、これらの情報の入手するためペット保険会社を通じて被保険犬の所有者に質問票を配布したところ、全国 46 都道府県の犬の所有者 1151 人から回答を得た。その結果、散歩中に飼育犬が他の飼育犬と接触する確率は 0.83 (95%信頼区間（CI）: 0.81～0.85)であり、一日平均接触回数は 2.73 (95%CI: 2.42～3.11) 回であった。この結果を基にした多重線形回帰分析を行ったところ、犬の散歩中の接触率は飼育者の社会学的行動、犬の飼育されている地域における犬の飼育密度、犬の体型に影響を受けることが示唆された。また、散歩中に犬による咬傷事故等が発生した場合の飼育者の行動については比較的高い評価結果が得られ、狂犬病のまん延防止の観点から適切な行動をとることが予測された。

第4章　日本製の狂犬病ウイルス RC-HL 株犬用ワクチンの有効性評価

日本で使用されている動物用狂犬病ワクチンは、狂犬病ウイルス RC-HL 株より精製された不活化ワクチンであり、1 回接種による免疫付与期間は 1 年間として承認されている。2012～2015 年に狂犬病ワクチン接種を受けた飼育犬 144 頭が保有する抗体価のデータを用いてロジスティック回帰分析を行った。その結果、1 回のワクチン接種で 12 カ月間十分な抗体価を維持した犬の割合は 74.7% (95%PI: 51.4～90.5%)と推定された。2～4 回および 5 回以上接種した犬が十分な抗体価を維持する確率は、それぞれ 96.6%（95%PI：83.1～99.3%）および 98.7%（95%PI：96.9～99.6%）であった。さらに、36 カ月間十分な抗体価を維持できる確率は、1 回接種の犬では 33.4%（95%PI：11.4～71.6%）であるが、2～4 回および 5 回以上ワクチン接種された犬では、それぞれ 83.0%（95%PI：39.4～97.1%）および 93.0%（95%

PI：59.7～99.2%）と推定された。先行研究の結果を基にしたメタ解析の結果では、1回接種の犬では少なくとも12カ月間十分な抗体価を維持した犬の割合は83.8%（95%CI：66.1～97.5%）と推定され、少なくとも2回以上接種した犬では94.7%（95%CI：87.7～99.1%）と推定された。

第5章　<u>日本における狂犬病ワクチン接種義務付け政策の便益費用分析</u>

狂犬病ワクチン接種を実施することにより侵入時のまん延を防止することができるが、毎年ワクチン接種の費用が必要となる。第1章および第2章の侵入リスク評価の結果並びに自治体関係者とのインタビュー調査結果などを基に推定した狂犬病ワクチン接種にかかる年間費用、狂犬病発生時の防疫にかかる費用をもとに便益費用分析を行った。その結果、狂犬病ワクチン接種の実施にかかる年間費用は180億円（90%PI：167～222億円）と推定された。狂犬病ワクチン接種策を継続した場合、狂犬病が発生した時の経済損失は1.9億円（90%PI：1.3～2.5億円）となり、一方で、仮にワクチン接種策を廃止した場合の経済損失は約3倍の5.6億円（90%PI：4.5～6.9億円）と推定された。狂犬病の侵入リスクを考慮すると、ワクチン接種策による年間利益の期待値は9619円（90%PI：6251～13,112円）となり、費用便益比は5.35×10^{-7}（90%PI：3.46×10^{-7}～7.37×10^{-7}）と1を大幅に下回り、経済的には日本の狂犬病ワクチン接種策は非常に非効率的であることが示唆された。

以上の結果から、日本への狂犬病の侵入リスクは現行制度の下では極めて小さく、そのような中でとられている狂犬病ワクチン接種策は、侵入時の経済損失を抑える効果はあるが、経済的には非常に非効率な政策であることが判明した。このような状況の中、将来ワクチン接種回数を減らす場合には現行の毎年1回から2、3年に1回に減らしても有効な免疫を有する犬の割合はほとんど変化しないことも判明した。これらの結果は、日本における狂犬病対策の見直しの検討にあたり有用な情報を提供すると期待する。

General introduction

1. What is rabies

Rabies is a deadly zoonotic disease caused by viruses in the *Lyssavirus* genus of the *Rhabdoviridae* family that affects the central nervous system of all mammals (class *Mammalia*), including humans (OIE 2018b). While rabies in humans can be caused by several species of *Lyssavirus* such as European bat lyssavirus (EBLV) and Australian bat lyssavirus (ABLV) (Hicks et al. 2012), this doctoral thesis focuses on the species *Rabies lyssavirus*, which is formerly referred to as classical rabies virus (RABV), genotype 1 of *Lyssavirus*.

2. Rabies situation in the world

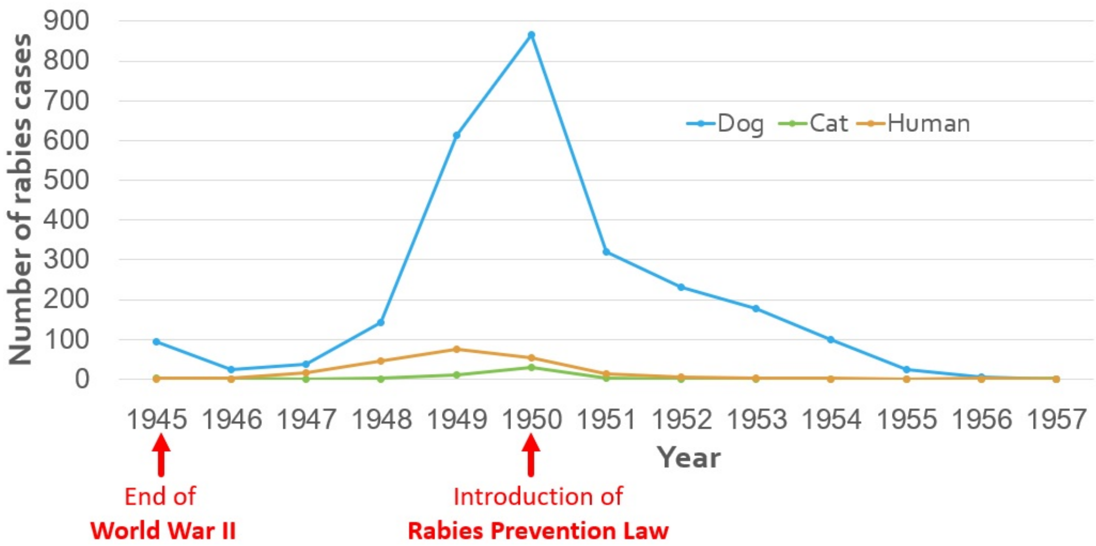
It is estimated that rabies still inflicts more than 59,000 human death, over 3.7 million disability-adjusted life years (DALYs) and US$8.6 billion economic losses worldwide each year (Hampson et al. 2015). The virus is particularly present in the saliva and brain of infected animals and therefore is most commonly transmitted via the saliva of an infected animal, where more than 95% of human rabies cases are due to bites from infected dogs – commonly known as dog-mediated rabies (WHO 2018b). The incubation period of rabies is highly variable from several days to several months and years depending on a number of factors such as site of exposure (exposures closer to the head generally have a shorter incubation period) and the concentration of the virus inoculated; importantly, the mortality rate of this disease is almost 100% for both animals and humans once clinical signs develop (Singh et al. 2017).

While dog-mediated rabies has been eliminated in North America, western Europe and parts of Asia and South America, it is still endemic in over 100 countries and regions, predominantly in developing countries in Africa and Asia. Despite rabies is a 100% vaccine-preventable disease, about 80% of human cases occur in poor, rural communities of the developing world where over 40% of deaths occur in children aged under 15 years, which is a direct result of low public awareness and limited access to timely, appropriate, affordable post-exposure prophylaxis (PEP) (WHO 2018b). Therefore, rabies is considered a major neglected tropical disease and there are numerous international efforts to reduce the disease burden, e.g. Zero by 30 is the latest global strategic plan where the World Health Organizaton (WHO), the World Organisation for Animal Health (OIE), the Food and Agriculture Organization of the United Nations (FAO) and the Global Alliance for Rabies Control (GARC) have joined forces, as the “United Against Rabies collaboration”, to reach the goal of ending human deaths from dog-mediated rabies by 2030 (WHO 2018c).

3. Rabies situation in Japan

Japan has been free from rabies since 1958 under the OIE standards (in Terrestrial Animal Health Code Article 8.14.3.) (OIE 2018b). The history of rabies in Japan was reviewed in Kurosawa et al. (2017) with a focus on quantitatively analysing the rabies epidemic in Osaka Prefecture during 1914–1933. The Rabies Prevention Law was enacted in 1950 and it eventually guided the elimination of rabies in Japan, where the final cases occurred in six dogs in 1956 and a cat in 1957 (Fig. 1). Together with the Domestic Animal Infectious Diseases Control Law and the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases, the Rabies Prevention Law forms the legal framework of the current rabies prevention system in Japan, which is described in detail by Takahashi-Omoe et al. (2008).

Fig. 1 Number of rabies cases in Japan during 1945–1957 before eradication of the disease



4. Rabies prevention system in Japan

There are essentially two arms of the rabies prevention system in Japan, i.e. an internal arm managed by Ministry of Health, Labour and Welfare of Japan (MHLW) and an external arm managed by Ministry of Agriculture, Forestry and Fisheries (MAFF). The internal arm consists of daily domestic preventive measures including the registration and rabies vaccination of domestic dogs and population management of stray dogs. Dog owners are obliged to register their dogs and vaccinate them against rabies annually (starting from 91-day old). Registered dogs must wear two collar tags issued by local governments certifying registration and vaccination.

The external arm of the prevention system consists of an import regime for dogs, cats and other designated animals (i.e. raccoons, foxes and skunks) entering Japan managed by Animal Quarantine Service (AQS) under MAFF. Such import regime involves identification of the animal with microchip, two-time rabies vaccination, neutralizing antibody titration test and a waiting period of 180 days (Fig. 2). For dogs and cats from designated regions including Iceland, Australia, New Zealand, Fiji, Hawaii and Guam (Fig. 3), they can be released within 12 hours upon arrival at the quarantine station after the animal undergoes import inspection and meet the requirements of being microchipped and having been continuously resident in the designated region since birth, for at least 180 days immediately before export to Japan or since being directly imported from Japan.

Fig. 2 Import regime for dogs and cats into Japan from non-designated countries or regions

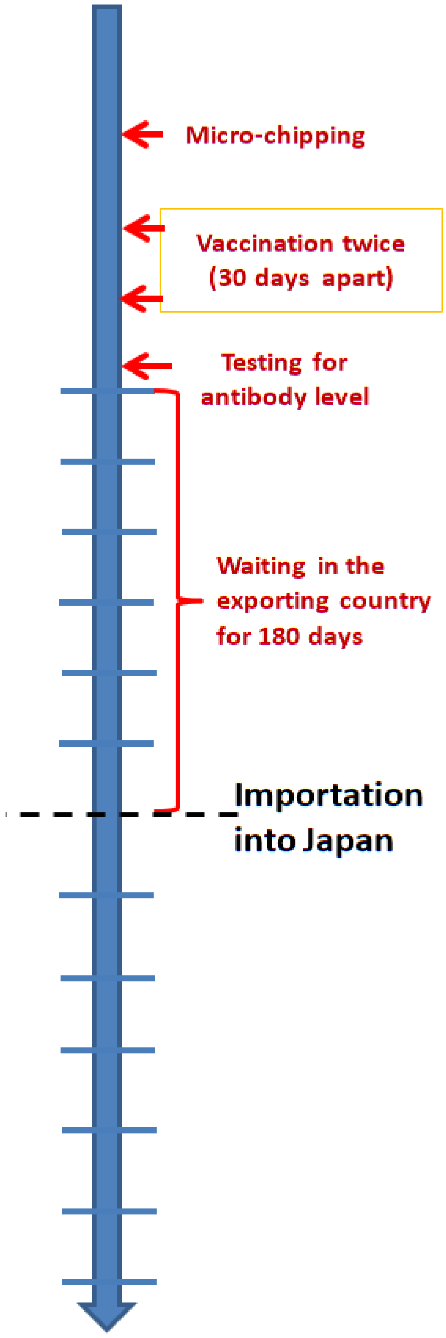


Fig. 3 Six countries and regions designated as rabies-free by MAFF

While this rabies prevention system has now been successful in maintaining Japan's rabies-free status for over 60 years, there has been no amendment to the system over recent years and its appropriateness to today's society has prompted massive debate. Firstly, the current import regime is considered very strong and strict, particularly when compared to the one adopted in European Union (EU) where the waiting period is much shorter (i.e. 21 days for movements within EU and from non-EU listed countries, 3 months for movements from non-EU unlisted countries) and the requirement of serological testing is restricted only to unlisted countries (Goddard et al. 2012). Secondly, Japan is one of the few rabies-free countries/regions which still implement mandatory vaccination of domestic dogs (Yamada et al. 2018). Importantly, there is no international standard on the prevailing conditions that should prompt a rabies-free country/region to implement a pre-emptive vaccination policy (WHO 2018b). The implementation of mandatory annual rabies vaccination of domestic dogs has been very controversial in today's Japan, particularly given the low compliance from dog owners (i.e. estimated vaccination rate is 43%) and the huge efforts and resources in maintaining such policy.

At an international level, the arguments raised in this thesis are already acknowledged by World Organisation for Animal Health in its Performance of Veterinary Services (PVS) Evaluation Report of the Veterinary Services of Japan (OIE 2016) which highlights that "… the low rate of annual vaccination of dogs against rabies; this requirement should, in any case, be reviewed given the length of time since rabies occurred in Japan and the strong border control measures in place" and also "Animal and veterinary public health programmes could be made more sustainable by undertaking regular formal reviews considering the long term strategic plans for the livestock industry and including the use of economic assessments such as cost-benefit and cost effectiveness analyses. In particular long standing programmes such as the requirement to vaccinate dogs annually against rabies … should be reviewed".

5. Structure of this doctoral thesis

From the perspective of veterinary public health, this doctoral thesis comprises a series of five epidemiological studies which aimed to assess from different angles the effectiveness and appropriateness of the rabies prevention system in today's Japan. The effectiveness of the import regime managed by AQS as mentioned above will be quantitatively assessed in Study 1 and the potential in relaxing the regime to promote compliance (from travellers and commercial importers) will also be discussed. Study 2 will assess the risk of introduction of rabies into Japan through the illegal landing of dogs from Russian fishing boats at the ports of Hokkaido, which is a historically famous entry pathway considered by many as a high-risk pathway. Study 3 will evaluate the contact rate among companion dogs during dog-walking and also the behaviour/practice of dog owners towards potential cases of rabies, with an aim to provide scientific data for future studies as it is considered that rabies, once it is introduced into Japan, would initially spread among the domestic pet dog population. Study 4 will evaluate the efficacy of the Japanese dog rabies vaccine using past and present data, thereby examining whether the current annual booster requirement (i.e. dogs have to be re-vaccinate every year) is scientifically justified or not. Finally, Study 5 will utilise the findings from Studies 1 to 4 to conduct a benefit-cost analysis to quantitatively assess whether the current policy of annual rabies vaccination of domestic dogs is economically efficient in the long term or not.

Since the epidemiology of rabies has already been extensively reviewed in various scientific publications (Singh et al. 2017; OIE 2018b, 2018c; WHO 2018b), such information would not be described again in this general introduction. Instead, epidemiological information on this disease would be specifically discussed in the following five epidemiological studies when necessary. The evidence-based recommendations provided by this doctoral thesis will be valuable in strengthening and amending the current Japanese rabies prevention system to face the challenges in modern society.

Study 1

Quantitative risk assessment of the introduction of rabies into Japan through the importation of dogs and cats worldwide

This study has been published in Epidemiology & Infection, vol. 145, no. 6, pp. 1168–1182, http://doi.org/10.1017/S0950268816002995

Summary

A strict import regime for dogs and cats has been adopted in Japan since 2004 consisting of identification of the animal with microchip, two-time rabies vaccination, neutralizing antibody titration test and a waiting period of 180 days. The present study aims to quantitatively assess the risk of rabies introduction into Japan through the international importation of dogs and cats and hence provide evidence-based recommendations to strengthen the current rabies prevention system. A stochastic scenario tree model was developed consisting of 14 entry pathways where rabies be introduced into Japan. The probability of infection in a single dog or cat imported into Japan is estimated to be 2.16 X 10^{-9} (90% PI: 6.65 X 10^{-11} – 6.48 X 10^{-9}). The number of years until the introduction of a rabies case is estimated to be 49,444 (90% PI: 19,170 – 94,641) years. The current import regime is effective in maintaining the very low risk of rabies introduction into Japan and responding to future changes including increases in import level and rabies prevalence in the world. However, non-compliance or smuggling activities could substantially increase the risk of rabies introduction. Therefore, policy amendment which could promote compliance is highly recommended. Scenario analysis demonstrated that the waiting period could be reduced to 90 days and the requirement for vaccination could be reduced to 1-time vaccination, but the serological testing should not be ceased.

1. Introduction

Under the Rabies Prevention Law enforced since 1950, Japan has a strict regime for the importation of dogs and cats from countries and territories in the world. An old regime consisting of rabies vaccination, a waiting period of 30 to 180 or 30 to 365 days (depending on the type of vaccine used in the country of origin) and a 14-day quarantine upon arrival in Japan was in place until October 2004. In response to a sharp increase in puppies being imported from Southeast Asia since the early 2000s, the government of Japan adopted a new import regime in November 2004 for dogs and cats and other designated animals at risk of rabies infection including raccoons, foxes and skunks. The new regime consists of identification of the animal with microchip, a two-time rabies vaccination (not necessary for dogs and cats from designated rabies-free regions including Australia, New Zealand, Fiji, Guam, Hawaii and Iceland), neutralizing antibody titration test and a waiting period of 180 days (Takahashi-Omoe et al. 2008; Kamakawa et al. 2009). In addition, this new regime allows those animals that do not meet the aforementioned requirements to be imported into Japan if they are quarantined for 180 days at the airport or port upon arrival. According to the quantitative risk assessment by Kamakawa et al. (2009), this regime reduced the risk of rabies introduction into Japan by 25 to 70-fold when compared with the previous regime.

Importation of pets into Japan is mainly managed by the Ministry of Agriculture, Forestry and Fisheries of Japan (MAFF) through the Animal Quarantine Service (AQS) and there are over 8,000 dogs and cats imported each year. Apart from this, there is also a considerable number of dogs and cats (over 1,100) imported into Japan each year through the United States Force Japan (USFJ). The introduction of rabies into Japan through the international importation of dogs and cats (majority through airplane and a few through ship) is considered a major risk pathway given the country is geographically isolated by the sea and based on the field experiences in Western Europe and the United States (Ribadeau-Dumas et al. 2016; Hercules et al. 2018)

Quantitative risk assessment (QRA) has been widely used to provide scientific evidence for policy decisions relating to rabies at both a national and international level (Jones et al. 2005; EFSA 2006; Goddard et al. 2012). This study aims to quantitatively assess the risk of rabies introduction into Japan through the international importation of dogs and cats, with particular emphasis on evaluating the effectiveness of the current import regime. The risk is quantified as: 1) the probability of infection in a single dog or cat imported into Japan; 2) the annual probability of importing at least one infected dog or cat into Japan and 3) the number of years until the introduction of a rabies case into Japan. The results of this study will be useful in informing science-based decisions should the current import regime in Japan be amended in the future.

2. Material and methods

2.1 Risk pathways

A stochastic scenario tree model was developed based on Goddard et al. (2012) with specific re-parameterization to accommodate the situation in Japan. In this model, a total of 14 entry pathways through which rabies may be introduced Japan were identified (Fig. 1.1). Pathway 1 to 12 represent the risk of rabies introduction associated with the international importation of dogs and cats into Japan through AQS, while Pathways 13 and 14 represent a simplified entry pathway associated with the importation of dogs and cats through USFJ based on the assumption that all animals would undergo a quarantine of 180 days.

<u>Pathway 1</u>: A rabies-infected animal is selected; it is vaccinated but not protected, i.e. antibody level does not rise to a satisfactory level; neutralizing antibody titration test reveals a false-positive result; the animal does not show clinical signs after the 180-day waiting period and upon arrival in Japan; it passes the inspection by an animal

health official of AQS and is released into Japan, resulting in entry of one rabies case.

Pathway 2: same as Pathway 1 except that the animal is not inspected by an AQS official upon arrival in Japan. This scenario is used to test the effect of smuggling. It is assumed that custom inspection will be avoided in situations where the animal deliberately or inadvertently becomes stowaway in the traveller's luggage.

Pathway 3: this is used in scenario analysis to test the effect of non-compliance of the owner or smuggling. In this scenario, the animal is vaccinated but not protected, and the owner provides forgery documents in an attempt to avoid the antibody testing and the 180-day waiting period; as a result, the waiting period is assumed to be 1 day as a worst case scenario; the animal then passes the inspection and is released into Japan.

Pathway 4: same as Pathway 3 except that the animal is not inspected; this pathway is also used in scenario analysis to test the effect of smuggling.

Pathway 5: same as Pathway 3 except that the owner/breeder also forges the documentation for vaccination, i.e. the imported animal is not vaccinated against rabies.

Pathway 6: same as Pathway 5 except that the animal is not inspected.

Pathway 7 to 12: serves as the counterpart of Pathway 1 to 6 respectively; these pathways assume that a healthy animal is being selected from the start, but is infected with rabies during the waiting period and does not show clinical signs upon arrival.

Pathway 13: Since the compliance level in USFJ is uncertain due to limited data, the following risk pathway is assumed: a rabies-infected animal, without vaccination and testing of antibody level, arrives in Japan and undergoes a quarantine period of 180 days at the USFJ facility; it does not show clinical signs during the quarantine and is released afterwards, resulting in entry of one rabies case. This is considered the most likely pathway due to the unanticipated nature of military service and so it is assumed that the service member would have very limited time to prepare for the necessary import procedures.

Pathway 14: this is used to test the effect of non-compliance of the personnel of USFJ by modelling the scenario where an animal without complete documentation is not subject to the mandatory 180-day quarantine.

2.2 Country Groupings

A total of 147 countries/territories with exportation of dogs and/or cats into Japan during 2010–2013 were included in the model, which are grouped into 6 regions with 22 sub-regions (Table 1.1).

2.3 Parameter estimation

An alphabetical list of parameters and quantities used in the current model is shown in Table 1.2.

2.3.1 Incubation period of rabies in dogs and cats (*IP*)

This was modelled using a lognormal distribution with a mean of 35 days and a standard deviation of 36.8 days based on estimates described in Goddard et al. (2012).

2.3.2 Probability that an animal from a sub-region (*s*) is incubating rabies ($P_{I,s}$) (Fig. 1.2)

This probability was estimated based on the maximum annual incidence ($I^{(max)}$) of dog and cat rabies in each exporting country (*j*) during 2010 to 2013 (Rabies - Bulletin - Europe; OIE WAHIS Interface):

$$I_j^{(max)} = \max\left(I_j^{(2010)}, I_j^{(2011)}, I_j^{(2012)}, I_j^{(2013)}\right)$$

$$I_s = \sum_j I_j^{(\max)}$$

The maximum annual incidence was considered for two reasons: (i) incidence provides a direct estimate of the probability or risk of a disease (Thrusfield 2008) and (ii) the effect of under-reporting would be taken into account by considering the maximum number of cases. The maximum number of unobserved rabies cases at a particular instance of time was calculated by multiplying I_s with the mean of the incubation period ($\overline{IP}$) and dividing the product by 365. Assuming new rabies cases follow a Poisson process, a gamma distribution was used to describe the uncertainty of the Poisson mean (Vose 2008):

$$\lambda_s = Gamma\left(\left(I_s \times \frac{\overline{IP}}{365}\right) + 1{,}1\right)$$

Finally, $P_{I,s}$ is given by dividing λ_s with the companion dog and cat population in the corresponding sub-region ($N_{companion,s}$) based on international databases (FEDIAF 2012; OIE WAHIS Interface). The $P_{I,s}$ estimated for each sub-region is assumed to be representative of all the countries within the sub-region taking into account the effect of incomplete or unavailable data on rabies cases and/or companion animal population for individual country.

2.3.3 Probability that an animal becomes infected during the waiting period (P_{I*})

For each sub-region, this probability was given by:

$$P_{I*,S} = 1 - \left(1 - P_{I',S}\right)^{T}$$

where *T* is the exposure time of 210 days (30-day interval between vaccinations + 180-day waiting period) and $P_{I',S}$ is the daily probability of an animal becoming infected with rabies given by:

$$\frac{Gamma(I_s + 1,1)}{365 \times Ncompanion, s}$$

The number of rabies cases was assumed to be zero for the following rabies-free countries/regions recognized by AQS: Australia, New Zealand, Fiji, Guam, Hawaii and Iceland; hence the P_I for the regions Australia/New Zealand, Melanesia, Micronesia and Polynesia was assumed to be zero.

2.3.4 Probability that an unprotected animal passes the neutralizing antibody titration test (P_{ST+})

This was calculated using data in Cliquet et al. (1998) and the methodology in Goddard et al. (2012). Two serological tests, Fluorescent Antibody Virus Neutralization (FAVN) and the Rapid Fluorescent Focus Inhibition Test (RFFIT) were included and their specificities (Sp_{FAVN} and Sp_{RFFIT}) were estimated to be Beta (124.8, 1.1248), having mean value of 0.99 and 90% prediction interval (PI) of 0.973 – 0.999, and Beta (92.97, 5.132), having mean value of 0.948 and 90% PI: 0.906 – 0.979, respectively. P_{ST+} was given by:

$$1 - \frac{Sp_{FAVN} + Sp_{RFFIT}}{2}$$

The mean value of P_{ST+} was estimated to be 0.031 (90% PI: 0.014 – 0.053).

2.3.5 Probability that the animal is not protected against rabies after two-time vaccination (P_{NP})

The AQS follows the international standard of World Organisation for Animal Health (OIE) and test results of antibody level must be greater than or equal to 0.5 IU/mL to be regarded satisfactory (Takahashi-Omoe et al. 2008). Therefore, P_{NP} was calculated based on this cut-off using the method described in Goddard et al. (2012) which combines the data of four vaccination studies (Sihvonen et al. 1995; Bahloul et al. 2006; Kallel et al. 2006; Minke et al. 2009). Three rabies vaccines, Rabisin (Rb), Madivak (Md) and Nobivak (Nb), were considered and P_{NP} was given by:

$$\frac{(1 - P_{Rb+})^2 + (1 - P_{Md+})^2 + (1 - P_{Nb+})^2}{3}$$

The mean P_{NP} was estimated to be 0.056 (90% PI: 0.017 – 0.11). For animals that are infected with rabies before vaccination (Pathway 1 to 4), the P_{NP} was assumed to be 1.

2.3.6 Probability that an infected animal does not show clinical signs upon arrival

in Japan (P_{NCS})

For Pathway 1 and 2, the animal was assumed to be infected immediately before vaccination and this probability was estimated to be 0.0061 by calculating the probability that the incubation period is longer than the exposure time:

$$P_{NCS} = P(IP > T)$$

where *T* is the exposure time of 210 days.

For Pathway 7 and 8, infection was assumed to occur any time during the waiting period and this probability was estimated to be 0.16 given by:

$$P_{NCS} = \frac{\sum_{t=1}^{T} P(IP > t)}{T}$$

where *T* is 210 days.

For Pathway 13, the P_{NCS} is estimated to be 0.0098 based on a *T* of 181 days (one day for arrival and a 180-day quarantine). For other pathways used in scenario analysis where the waiting period is assumed to be 1 day, P_{NCS} was estimated to be 0.9999.

2.3.7 Compliance parameters

These included three probabilities: probability that an animal is vaccinated (P_V), probability that an animal is serologically tested (P_{ST}) and probability that an animal is inspected by AQS officer (P_C); they were set as 1 in the baseline model and were decreased to 0.9 (90% compliance) and 0.8 (80% compliance) in the scenario analysis.

It was assumed that owners who do not vaccinate their animal would also not take the animal for serological testing and so parameter P_{ST} was always set as 0 for Pathway 5, 6, 11 and 12.

2.3.8 Probability that an animal passes the inspection by AQS officer (P_{C+})

This probability was set as 1 in both the baseline model and scenario analysis assuming that all animals not showing clinical signs of rabies or accompanied with forgery documentation would be able to pass the inspection.

2.3.9 Annual number of dogs and cats imported from each sub-region through AQS and USFJ ($N_{aqs,s}$ and $N_{usfj,s}$)

The maximum annual number of importation during 2010–2013 was chosen in order to calculate the risk for the worst case scenario (Fig. 1.3).

2.4 Risk estimation and model outputs

The formulas for the probability of rabies introduction through each risk pathway (for each sub-region (s)) are:

Pathway 1: $R_{s,1} = P_{I,S} \times P_V \times P_{NP} \times P_{ST} \times P_{ST+} \times P_{NCS} \times P_C \times P_{C+}$

Pathway 2: $R_{s,2}$=$P_{I,S} \times P_V \times P_{NP} \times P_{ST} \times P_{ST+} \times P_{NCS} \times (1 - P_C)$

Pathway 3: $R_{s,3}$=$P_{I,S} \times P_V \times P_{NP} \times (1 - P_{ST}) \times P_{NCS} \times P_C \times P_{C+}$

Pathway 4: $R_{s,4}$=$P_{I,S} \times P_V \times P_{NP} \times (1 - P_{ST}) \times P_{NCS} \times (1 - P_C)$

Pathway 5: $R_{s,5}$=$P_{I,S} \times (1 - P_V) \times (1 - P_{ST}) \times P_{\mathrm{NCS}} \times P_C \times P_{C+}$

Pathway 6: $R_{s,6}$=$P_{I,S} \times (1 - P_V) \times (1 - P_{ST}) \times P_{NCS} \times (1 - P_C) P_{C+}$

Pathway 7: $R_{\mathrm{s},7}$=$(1 - P_{I,S}) \times P_V \times P_{NP} \times P_{ST} \times P_{ST+} \times P_{I^*,S} \times P_{NCS} \times P_C \times P_{C+}$

Pathway 8: $R_{s,8}$=$(1 - P_{I,S}) \times P_V \times P_{NP} \times P_{ST} \times P_{ST+} \times P_{I^*,S} \times P_{NCS} \times (1 - P_C)$

Pathway 9: $R_{s,9}$=$(1 - P_{I,S}) \times P_V \times P_{NP} \times (1 - P_{ST}) \times P_{I^*,S} \times P_{NCS} \times P_C \times P_{C+}$

Pathway 10: $R_{s,10}$=$(1 - P_{I,S}) \times P_V \times P_{NP} \times (1 - P_{ST}) \times P_{I^*,S} \times P_{NCS} \times (1 - P_C)$

Pathway 11: $R_{s,11}$=$(1 - P_{I,S}) \times (1 - P_V) \times (1 - P_{ST}) \times P_{I^*,S} \times P_{NCS} \times P_C \times P_{C+}$

Pathway 12: $R_{s,12}$=$(1 - P_{I,S}) \times (1 - P_V) \times (1 - P_{ST}) \times P_{I^*,S} \times P_{NCS} \times (1 - P_C)$

Pathway 13: $R_{s,13}$=$P_{I,S} \times P_{NCS} \times P_C \times P_{C+}$

Pathway 14: $R_{s,14}$=$P_{I,S} \times (1 - P_C)$

The probability of infection in a single dog or cat imported from each sub-region was calculated by summing up the $R_{s,i}$ of Pathways from 1 to 12 (for AQS) and of Pathways 13 and 14 (for USFJ):

$$R_{aqs,s} = \sum_{i=1}^{12} R_{s,i}$$

$$R_{usfj,s} = \sum_{i=13}^{14} R_{s,i}$$

The annual risk was calculated as the annual probability of importing at least one infected dog or cat into Japan. First, the annual probability of rabies introduction from sub-region *s* was calculated by taking into account the $N_{aqs,s}$ and $N_{usfj,s}$ respectively:

$$P_{aqs,s} = 1 - (1 - R_{aqs,s})^{N_{aqs,s}}$$

$$P_{usfj,s} = 1 - (1 - R_{usfj,s})^{N_{usfj,s}}$$

The annual probability of rabies introduction for each region was then given as:

$$P_{aqs,r} = 1 - \prod_{s} (1 - P_{aqs,s})$$

$$P_{usfj,r} = 1 - \prod_{s} (1 - P_{usfj,s})$$

Finally, the annual probability of rabies introduction through the importation of dogs and cats worldwide via AQS and USFJ, respectively, was calculated:

$$P_{aqs,worldwide} = 1 - \prod_{r} (1 - P_{aqs,r})$$

$$P_{usfj,worldwide} = 1 - \prod_{r}(1 - P_{usfj,r})$$

These two probabilities were combined to give a final probability representing the risk of rabies introduction into Japan through the importation of dogs and cats worldwide via both AQS and USFJ:

$$P_{worldwide} = 1 - (1 - P_{aqs,worldwide})(1 - P_{usfj,worldwide})$$

The number of years until the introduction of a rabies case into Japan was then estimated: $Y_{worldwide} = 1/P_{worldwide}$.

2.5 Model implementation

The model was developed in @Risk Version 6.3 (Palisade, Ithaca, New York) within Microsoft® Excel 2013, and was run with 50,000 iterations using Latin Hybercube sampling for each simulation. Results of model outputs are presented as: Mean (5th percentile – 95th percentile).

2.6 Sensitivity and scenario analyses

To assess the effect of uncertainty in the current model, sensitivity analysis was performed using Spearman's correlation coefficient to rank all model input parameters according to their contributions to the variance of model output $Y_{worldwide}$. Scenario analysis was performed to assess the effect of changes in selected input parameters summarized in Table 1.3.

3. Results

3.1 Risk quantification

The lists of model outputs for each sub-region and region are shown in Table 1.4, 1.5 and 1.6. For the probability of infection in a single dog or cat imported into Japan, the $R_{aqs,worldwide}$ is estimated to be 1.62 X 10^{-9} (90% PI: 5.76 X 10^{-12} – 7.14 X 10^{-9}), while the $R_{usfj,worldwide}$ is estimated to be 4.04 X 10^{-9} (90% PI: 1.74 X 10^{-9} – 3.39 X 10^{-9}), giving a $R_{worldwide}$ of 2.16 X 10^{-9} (90% PI: 6.65 X 10^{-11} – 6.48 X 10^{-9}). For the annual probability that at least one infected dog or cat is imported into Japan, the $P_{aqs,worldwide}$ is 2.02 X 10^{-5} (90% PI: 5.15 X 10^{-6} – 4.65 X 10^{-5}), while the $P_{usfj,worldwide}$ is 5.45 X 10^{-6} (90% PI: 4.51 X 10^{-6} – 6.51 X 10^{-6}), giving a $P_{worldwide}$ of 2.57 ; X 10^{-5} (90% PI: 1.06 X 10^{-5} – 5.22 X 10^{-5}). In terms of the number of years for the introduction of one rabies case, $Y_{aqs,worldwide}$ is 78034 (90% PI: 21,479 – 194,204), while $Y_{usfj,worldwide}$ is 185,762 (90% PI: 153,500 – 221,892), giving an overall $Y_{worldwide}$ of 49,444 (90% PI: 19,170 – 94,641).

3.2 Sensitivity analysis

The results of the sensitivity analysis are shown in Fig. 1.4. The top five most correlated parameters include $P_{V+,Nb}$, Sp_{RFFIT} $P_{V+,Rb}$, $P_{V+,Md}$ and Sp_{FAVN}..

3.3 Scenario analysis

The effect of different scenarios on the number of years until the introduction of a rabies case ($Y_{worldwide}$) was investigated and results are shown in Fig. 1.5. From this analysis, it was concluded that non-compliance would significantly increase the risk of rabies introduction, with $Y_{worldwide}$ decreasing to 249 (90% PI: 231 – 268) years with an 80% compliance level (Fig. 1.5a). Increases in the number of imports and rabies cases would also increase the risk of rabies introduction respectively as $Y_{worldwide}$ is reduced to 9,878 (90% PI: 3,771 – 18,723) years with a 5-fold increase in the import level (Fig. 1.5b) and to 5,030 (90% PI: 1,845 – 10,051) years with a 10-fold increase in the number of cases (Fig. 1.5c). The scenario where rabies vaccines with poor efficacy are used in the exporting country (which may represent less-developed countries) was tested and $Y_{worldwide}$ was predicted to decrease to 7,015 (90% PI: 3,590 – 12,457) years if the efficacy falls to 50% (Fig. 1.5d). In addition, if the required number of rabies vaccination is changed from two times to one time due to policy amendment, $Y_{worldwide}$ would decrease to 18,453 (90% PI: 7,608 – 37,553) years (Fig. 1.5e). If the compulsory serological testing were to be ceased, there would be a large increase in risk of rabies introduction as $Y_{worldwide}$ was estimated to be 1,971 (90% PI: 811 – 4,004) years (Fig. 1.5f). The risk of rabies introduction would also increase as the waiting period is shortened as, with a 1-day waiting period, $Y_{worldwide}$ was estimated to be 7,996 (90% PI: 3,963 – 14,566) years (Fig. 1.5g). The impact of using different probability distributions for the incubation period was also assessed (Fig. 1.5h); the risk of rabies introduction would decrease with the use of a shorter incubation period, e.g. $Y_{worldwide}$ would increase to 68,224 (90% PI: 24,492 – 131,171) years with an incubation period of lognormal (27.3, 20.2) estimated from the 1947–1954 Tokyo epidemic (Tojinbara et al. 2016). This is because the probability that the infected animal does not show clinical signs upon arrival in Japan (P_{NCS}) would decrease as the incubation period is shortened. For the final scenario analysis (5i), under the policy amendment recommended by the author, i.e. a 90-day waiting period and one-time vaccination, the risk of rabies introduction would only increase 4-fold with $Y_{worldwide}$ decreasing to 12,314 (90% PI: 4,971 – 24,350) years.

4. Discussion

The risk of rabies introduction into Japan through the importation of dogs and cats worldwide identified in this study is very low. The number of years until the introduction of a rabies case ($Y_{worldwide}$) is especially large when compared to the results of similar QRA performed by others such as the United Kingdom (UK) which estimated 211 (90% PI: 177 – 247) years (Goddard et al. 2012) and Taiwan which estimated 1822 years (median; 5th percentile is 473 years) (Weng et al. 2010). This difference is considered to be due to Japan's stricter policy requiring two-time vaccination (hence a smaller P_{NP}) and a lower importation level (four times lower when compared with the value included in the UK model). Both UK and Taiwan have a strict import regime resembling that of Japan. Taiwan's regime additionally requires a 21-day quarantine upon arrival and a second serological testing. The results from Goddard et al. (2012) were estimated according to the European Union Pet Movement Policy (EUPMP), which was implemented in 2012. Compared to the previous UK Pet Travel Scheme (PETS), the EUPMP has a shorter waiting period (i.e. it was shortened from 180 days to 21 days for EU and listed countries or 3 months for unlisted countries) and the requirement of serological testing restricted only to unlisted countries.

In terms of the number of dogs and cats imported via AQS and USFJ (Fig. 1.3), the total $N_{aqs,s}$ is 11,445, while the total $N_{usfj,s}$ is 1690 which is 6.8-fold lower. The United States of America (mainland) (USA) from the sub-region North America is the highest exporter contributing to 41% of the total $N_{aqs,s}$ and 86% of the total $N_{usfj,s}$ (the N_{aqs} and N_{usfj} from USA is 4362 and 1458, respectively). Eastern Asia (mostly from China, Republic of Korea and Taiwan) is the second highest exporter (N_{aqs} is 2,979) contributing to 26% of the total $N_{aqs,s}$. In terms of the probability that an imported animal is incubating rabies (Fig. 1.2), the $P_{I,S}$ is highest for Middle Africa with a mean of 3.44 X 10^{-4} (90% PI: 2.68 X 10^{-4} – 4.88 X 10^{-4}). Nonetheless, there was no importation of dogs and cats from this sub-region during 2010–2013. The $P_{I,S}$ is lowest for Western Europe with a mean of 3.51 X 10^{-8} (90% PI: 4.44 X 10^{-9} – 9.00 X 10^{-8}). In terms of the overall annual probability of rabies introduction, the $P_{aqs,worldwide}$ is highest for South-Eastern Asia with a mean of 5.95 X 10^{-6} (1.47 X 10^{-6} – 1.4 X 10^{-5}), while the $P_{aqs,usfj}$ is highest for North America with a mean 3.56 X 10^{-6} (90% PI: 2.68 X10^{-6} – 4.55 X 10^{-6}).

Illegal importation or smuggling of animals is a serious issue which could greatly compromise a country's import regime in preventing the introduction of diseases and its effect on the risk of rabies entry has been evaluated in various QRA (Jones et al. 2005; Ramnial et al. 2010; Weng et al. 2010 Goddard et al. 2012). The impact of smuggling or non-compliance was assessed in the current model by considering the probability of vaccination (P_V), serological testing (P_{ST}) and border control (P_C), and the result indicates that the risk of rabies introduction into Japan would increase 12-fold with even a rate of 1% non-compliance (Fig. 1.5a). Because there are numerous routes by which an animal could be smuggled into Japan, it is difficult to estimate the exact degree of smuggling activity; by assuming non-compliance levels of 1% to 20%, the result of our scenario analysis could be over-estimating the actual risk of smuggling. Nonetheless, this analysis is essential in highlighting the importance of continuing professional training of personnel in border control.

Moreover, scenario analysis demonstrated that the introduction of serological testing into the import regime since 2004 is effective in reducing the risk of rabies introduction into Japan by 22-fold (Fig. 1.5f), agreeing with the results in Kamakawa et al. (2009). The waiting period, on the other hand, could be reduced to between 90 and 150 days without considerably increasing the risk of rabies introduction (Fig. 1.5g). Indeed, when the waiting period was reduced to 90 days, the risk of rabies introduction only increased 1.3-fold. The reduction in waiting period has been a topic in import policy because this could promote better animal welfare and also potentially discourage smuggling activities (Jones et al. 2005; Weng et al. 2010; Goddard et al. 2012). Although it is difficult to measure the relationship between the strictness of the import regime and the level of smuggling activities, there is potential for policy amendment to promote compliance. Indeed, under the recommended policy amendment with a 90-day waiting period and a single vaccination (Fig. 1.5i), the risk of rabies introduction is still very low and would only increase 4-fold with $Y_{worldwide}$ decreasing to 12,314 (90%

PI: 4,971 – 24,350) years. Since even an 1% non-compliance could greatly increase the risk under the current rabies prevention system in Japan, any change in policy that might promote compliance would be advantageous. The recommended policy amendment, which describes a relaxation of the current system, does not markedly increase the risk of rabies introduction into Japan and would most probably lead to increased compliance, thereby greatly reducing the overall risk of rabies introduction.

The incubation period (*IP*) distribution of rabies is a fundamental input variable commonly used in QRA. Tojinbara et al. (2015) have recently estimated an *IP* of lognormal (27.3, 20.2) based on the 1947–1954 Tokyo epidemic. In the current model, the *IP* distribution of lognormal (35, 36.8) combines the results of experimentally infected animals (Soulebot et al. 1981; Fekadu et al. 1982; Trimarchi et al. 1986; Bingham 1999) and naturally infected animals or naturally acquired cases (Committee of Enquiry on Rabies 1971; Foggin 1988; Advisory Group on Quarantine 1998; Fooks et al. 2008). Data from experimentally infected animals would yield a shorter *IP* of lognormal (23.7, 15); it is expected that these animals were challenged with a high viral dose and so they manifested clinical signs much quicker than infected animals in real life, in which case the *IP* estimated using these data is an underestimation of the true *IP*. On the other hand, data from naturally infected animals or naturally acquired cases would yield a longer *IP* of lognormal (39.7, 41.9) but there is uncertainty relating to these data as it is not known when the animals were infected. Therefore, a scenario analysis using these different *IP* distributions was performed and it indicates that the risk of rabies introduction would decrease with a shorter incubation period (Fig. 1.5h).

In terms of the risk associated with importation of rabies from the United States of America (mainland), our study estimated a Y_{aqs} of 542,167 years (median) which is 110 times longer than the result in Kamakawa *et al.* [2] which is 4932 years (median). This big difference is mainly due to the effect of re-parameterization for example the probability that the animal is infected during waiting period ($P_{I^*,S}$) and the specificities of FAVN and RFFIT (Sp_{FAVN} and Sp_{RFFIT}), thereby highlighting the importance of continued scientific research for improved parameter estimation.

In QRA it is good practice to perform sensitivity analysis to assess the uncertainty in the model because uncertainty reflects lack of precise knowledge of the input variables and could be reduced in future risk assessment with further research (Thrusfield 2008; OIE 2018a). In the current model, sensitivity analysis was performed using Spearman's rank correlation and it indicates that uncertainty is largely attributed to input variables related to vaccine efficacy and the specificity of the serological test, i.e. $P_{V+,Nb}$, Sp_{RFFIT} $P_{V+,Rb}$, $P_{V+,Md}$ and Sp_{FAVN} (Fig. 1.4). This result suggests that further studies on the efficacies of rabies vaccine and serological test used in exporting countries could benefit the parameterization and scientific accuracy of future QRA.

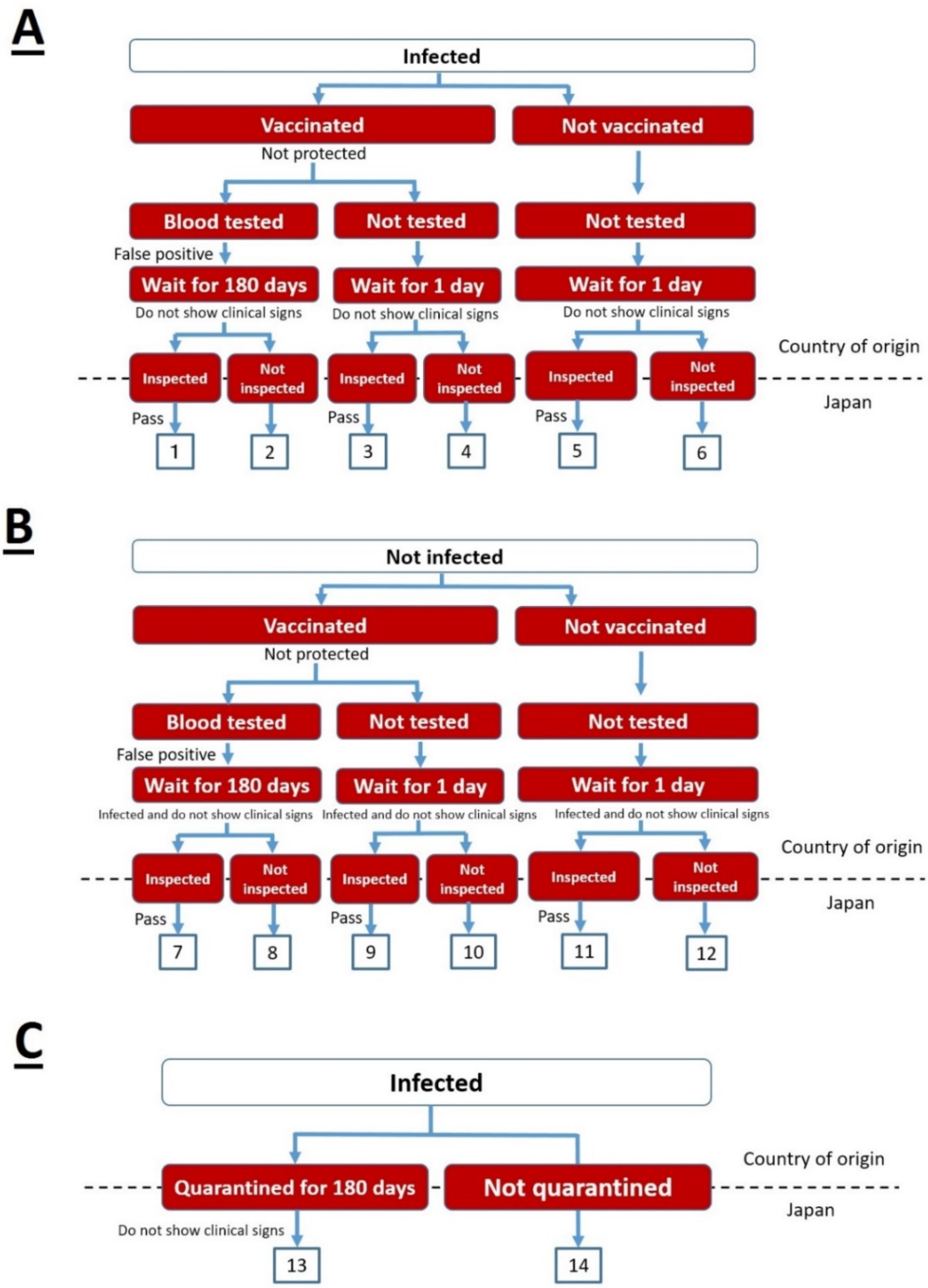
Finally, the annual probability of rabies introduction through the importation via USFJ (mean $P_{usfj,worldwide}$ is 5.45 X 10^{-6}) is only 3.7-fold lower than the risk through the importation via AQS (mean $P_{aqs,worldwide}$ is 2.02 X 10^{-5}). It was concluded that this risk must not be overlooked and further QRA would help reduce the uncertainty of the results in this study. In the current model, the parameters used for this risk pathway are largely based on the assumption that all animals imported via USFJ would undergo a quarantine of 180 days. Detailed information including the actual implementation of the import regime by USFJ and the level of compliance are warranted for a more accurate risk assessment.

5. Conclusions

The risk of rabies introduction into Japan through the importation of dogs and cats is very low. The current import regime will maintain this level of risk, even if the import level and rabies prevalence in the world increase considerably in the future. However, non-compliance or smuggling activities could substantially increase the risk of rabies introduction. The immense potential for policy amendment to promote compliance is demonstrated in various scenario analyses highlighting that the waiting period and the required number of vaccinations could be reduced. Nonetheless, serological testing should not be ceased. These evidence-based recommendations would guide policy decisions strengthening the current rabies prevention system in Japan.

6. Figures and tables

Fig 1.1 Scenario trees showing the 14 risk pathways of rabies introduction into Japan

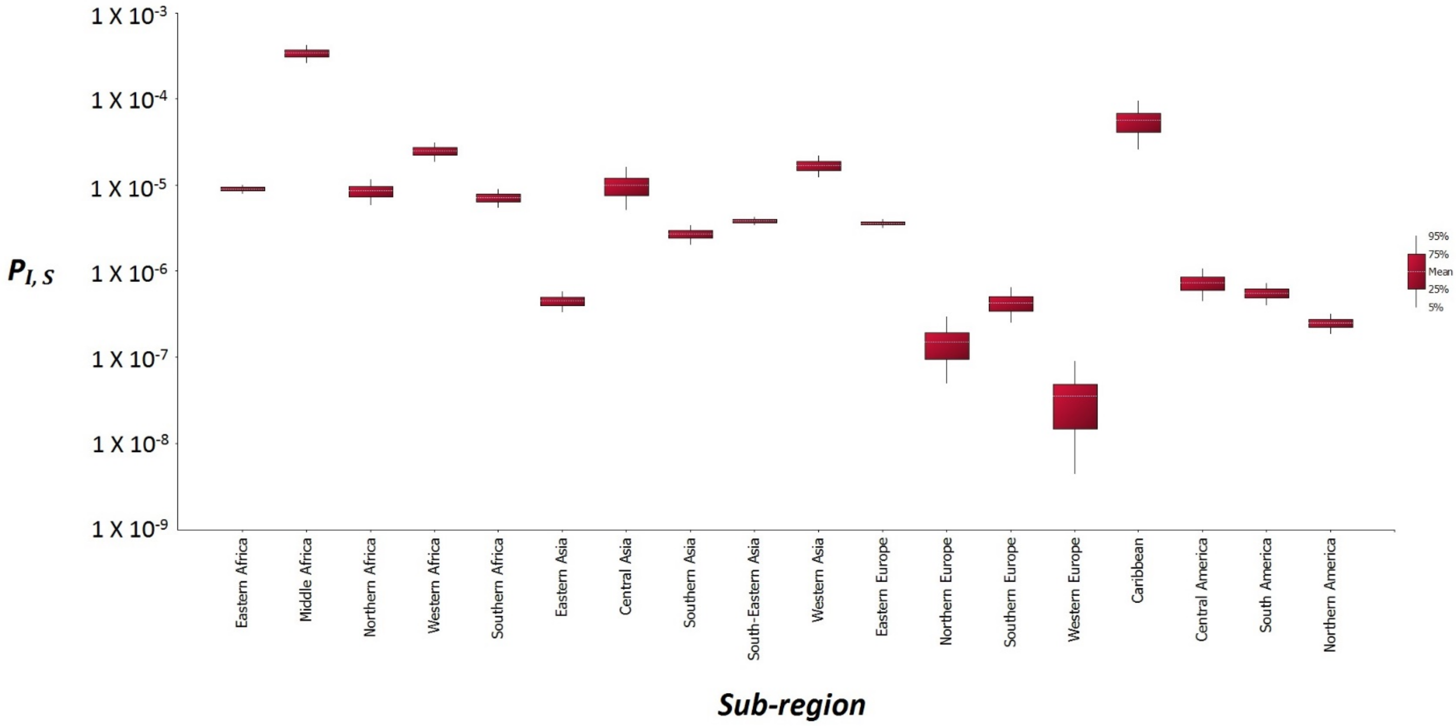


A: Rabies introduction through importation via Animal Quarantine Service (AQS) assuming the animal is infected before first vaccination

B: Rabies introduction through importation via AQS assuming the animal is infected during the waiting period

C: Rabies introduction through importation via United States Force Japan assuming the animal is infected before quarantine

Fig. 1.2 Probability that an animal from a sub-region (*s*) is incubating rabies ($P_{I, S}$)



The number of rabies cases was assumed to be zero (hence a zero $P_{I, S}$) for the following sub-regions: Australia/New Zealand, Melanesia, Micronesia and Polynesia.

Fig. 1.3 Maximum annual number of dogs and cats imported to Japan during 2010 to 2013 through the Animal Quarantine Service (above) and United States Force Japan (bottom) from each sub-region, denoted as $N_{aqs,s}$ and $N_{usfj,s}$, respectively

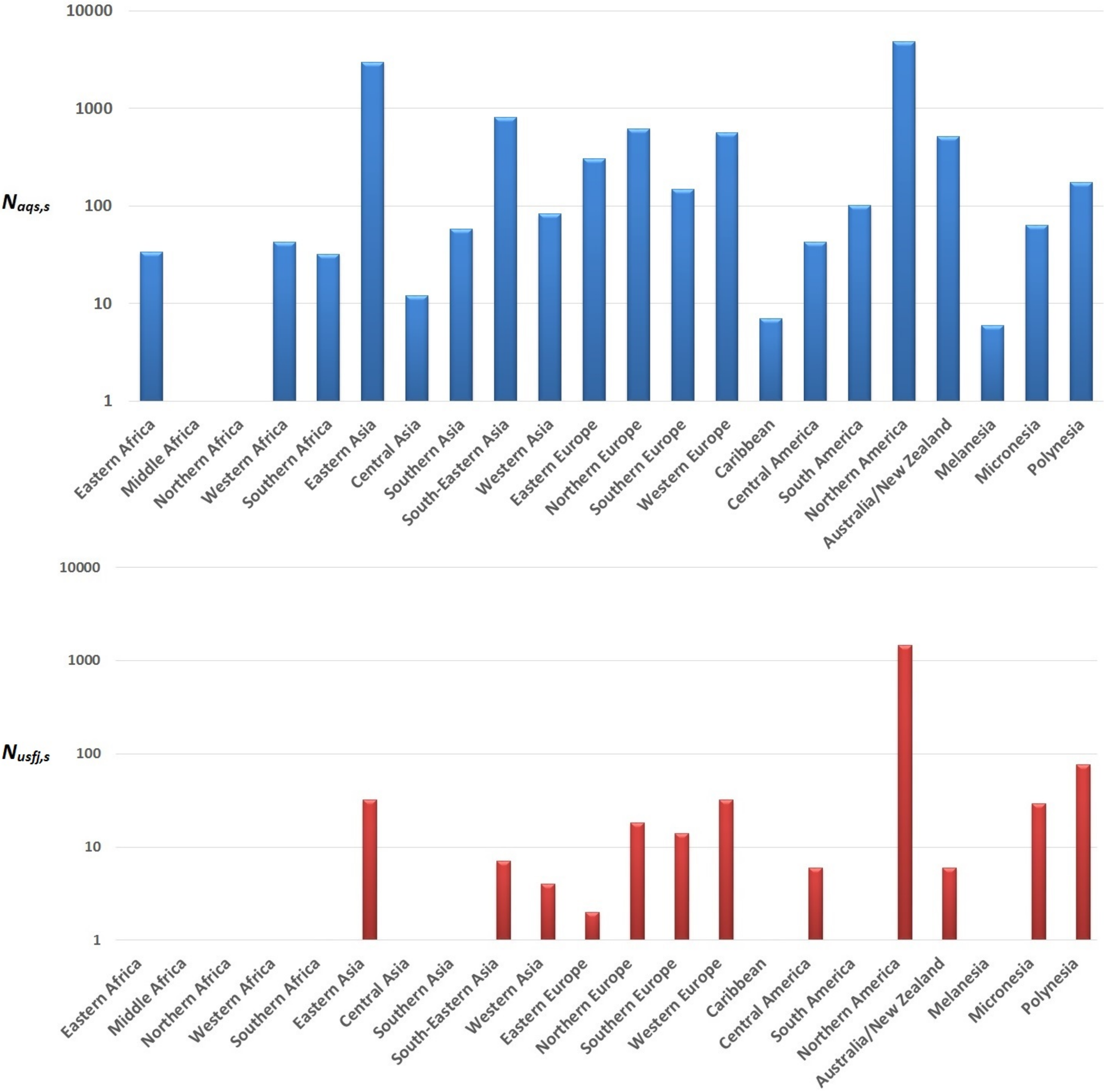
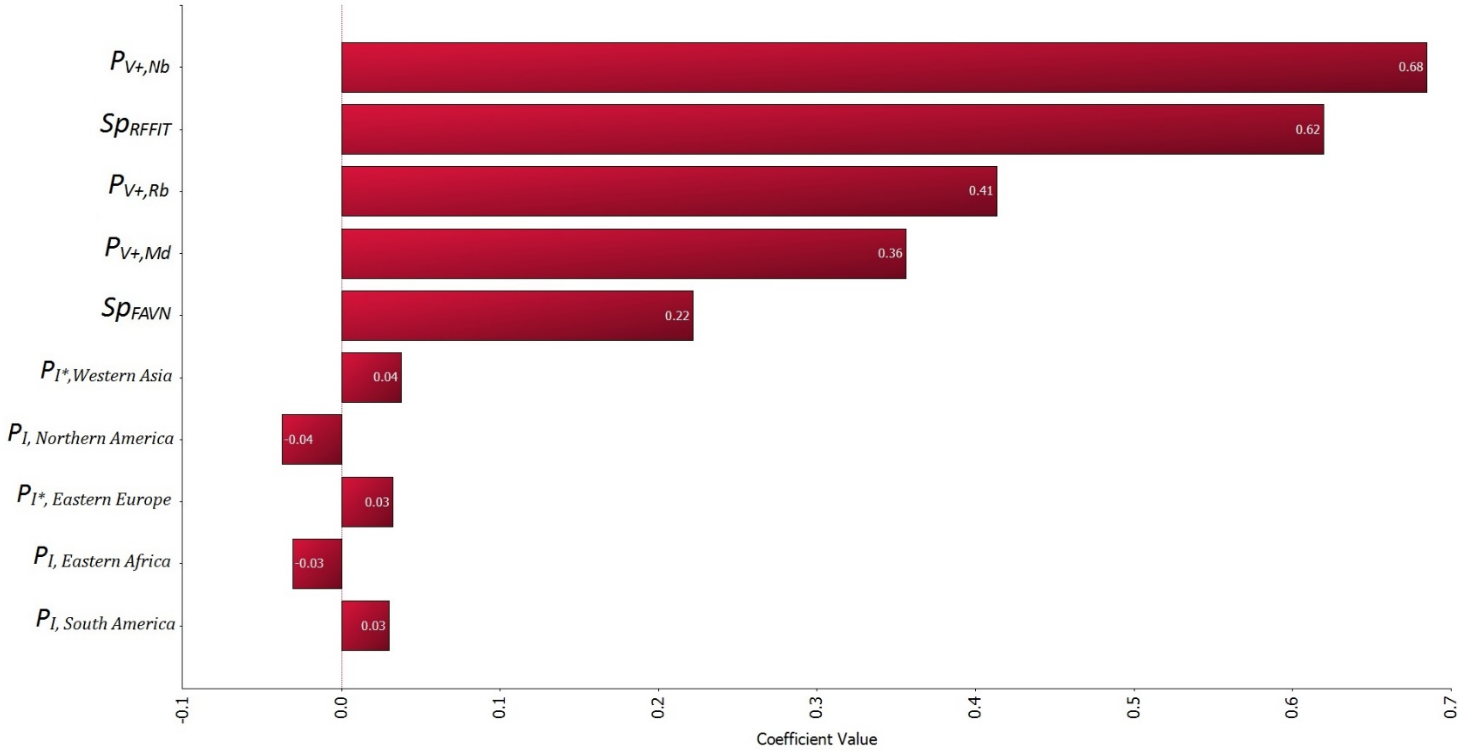
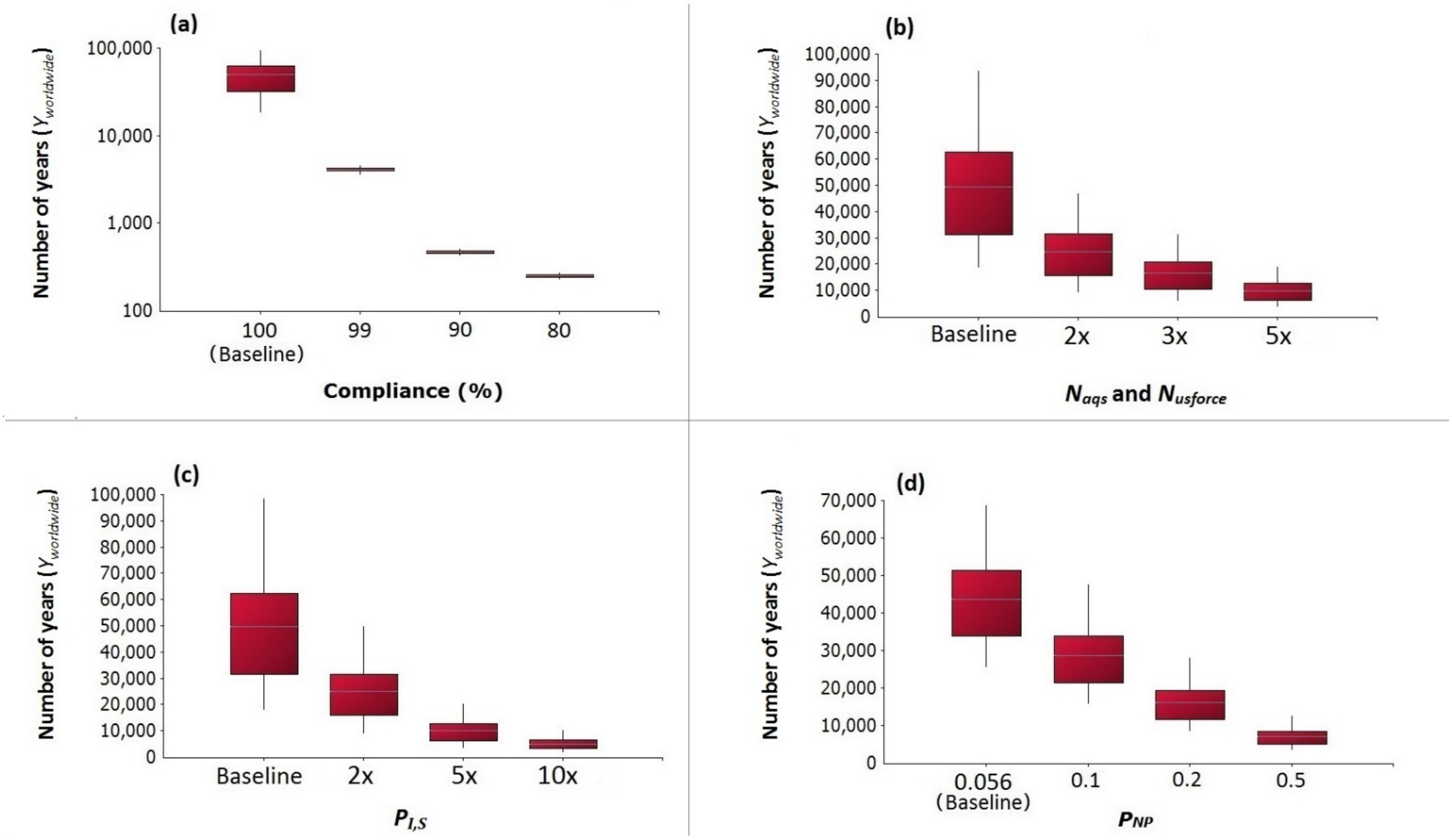


Fig. 1.4 Tornado graph illustrating the result of sensitivity analysis



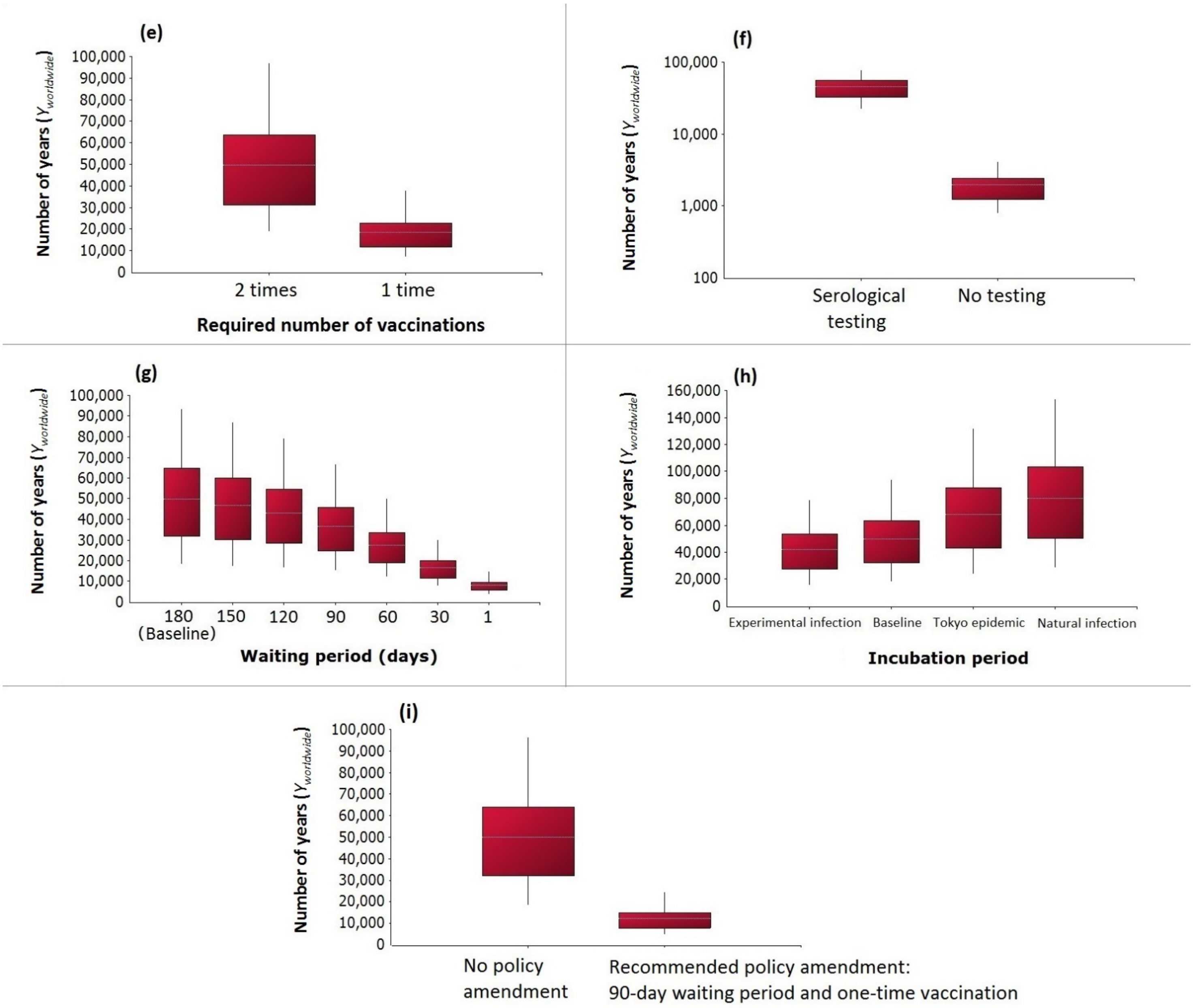
All model input parameters are ranked by Spearman's correlation coefficient according to their contributions to the variance of model output $Y_{worldwide}$. The 10 most correlated input parameters are shown in this figure. The top five most correlated parameters include $P_{V+,Nb}$, Sp_{RFFIT} $P_{V+,Rb}$, $P_{V+,Md}$ and Sp_{FAVN}.

Fig. 1.5 (a–d) Scenario analysis depicting the effects of tested scenarios on the number of years until the introduction of a rabies case $Y_{worldwide}$



For each box-whisker plot, the white dotted line indicates the mean; the length of the box indicates the inter-quartile range; the whiskers indicate the 5th percentile and the 95th percentile respectively. For Fig. 1.5a, a base-10 log scale was used for the Y axis. For Fig. 1.5d, a fixed value of 0.056 was used as the baseline.

Fig. 1.5 (e–i) Scenario analysis depicting the effects of tested scenarios on the number of years until the introduction of a rabies case $Y_{worldwide}$



For Fig. 1.5f, a base-10 log scale was used for the Y axis.

Table 1.1 List of countries/territories (a total of 147) with exportation of dogs and/or cats through AQS and/or USFJ into Japan during 2010–2013

Region	Sub-region	Country/Territory
Africa	Eastern Africa	Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mozambique, Rwanda, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
	Middle Africa	Cameroon, Gabon
	Northern Africa	Algeria, Egypt, Libyan Arab Jamahiriya, Morocco, Sudan, Tunisia
	Western Africa	Benin, Burkina Faso, Ghana, Guinea, Niger, Nigeria, Senegal, Sierra Leone
	Southern Africa	Namibia, South Africa
Asia	Eastern Asia	China, China/Hong Kong SAR, China/Macao SAR, China/Taiwan, Mongolia, Republic of Korea
	Central Asia	Kazakhstan, Kyrgyzstan, Tajikistan, Uzbekistan
	Southern Asia	Afghanistan, Bangladesh, Bhutan, India, Iran (Islamic Republic of), Nepal, Pakistan, Sri Lanka
	South-Eastern Asia	Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand, Vietnam
	Western Asia	Azerbaijan, Bahrain, Georgia, Israel, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Turkey, United Arab Emirates, Yemen
Europe	Eastern Europe	Belarus, Bulgaria, Czech Republic, Hungary, Poland, Romania, Russian Federation, Slovakia, Ukraine
	Northern Europe	Denmark, Estonia, Faeroe Islands, Finland, Ireland, Latvia, Lithuania, Norway, Sweden, United Kingdom of Great Britain
	Southern Europe	Bosnia and Herzegovina, Canary Islands, Croatia, Greece, Italy, Malta, Melilla, Portugal, San Marino, Serbia, Slovenia, Spain
	Western Europe	Austria, Belgium, France, Germany, Luxembourg, Monaco, Netherlands, Switzerland
Latin America and Caribbean	Caribbean	Cayman Islands, Cuba, Dominican Republic, Puerto Rico
	Central America	Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama
	South America	Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Paraguay, Peru, Uruguay, Venezuela (Bolivarian Republic of)
North America	Northern America	Canada, United States of America (mainland)
Oceania	Australia/New Zealand	Australia, New Zealand
	Melanesia	Fiji, New Caledonia, Papua New Guinea
	Micronesia	Guam, Marshall Islands, Micronesia (Federated States of), Nauru, Northern Mariana Islands, Palau
	Polynesia	French Polynesia, Samoa, Tonga, United States of America/Hawaii

Table 1.2 An alphabetical list of parameters and quantities used in the model

I_j	Annual incidence of dog and cat rabies in exporting country *j*
$I_j^{(max)}$	Maximum annual incidence of dog and cat rabies in exporting country *j*
$I_j^{(year)}$	Annual incidence of dog and cat rabies in exporting country *j* in a specific year (2010, 2011, 2012, 2013)
IP	Incubation period of rabies in dogs and cats (days)
I_s	Maximum annual incidence of dog and cat rabies in sub-region *s*
j	Exporting country
$N_{aqs,s}$	Maximum annual number of dogs and cats imported from sub-region *s* through Animal Quarantine Service during 2010 to 2013
$N_{companion,s}$	Companion dog and cat population in sub-region *s*
$N_{usfj,s}$	Maximum annual number of dogs and cats imported from sub-region *s* by United States Force Japan during 2010 to 2013
$P_{aqs,r}$	Annual probability of importing at least one infected dog or cat through Animal Quarantine Service from region *r*
$P_{aqs,worldwide}$	Annual probability of importing at least one infected dog or cat through Animal Quarantine Service from the world
$P_{I,S}$	Probability that an animal from a sub-region (*s*) is incubating rabies
$P_{I',S}$	Daily probability of an animal becoming infected with rabies in sub-region *s*
$P_{I*,S}$	Probability that an animal becomes infected during the waiting period in sub-region *s*
P_{Md+}	Probability that a Madivak-vaccinated animal acquires an antibody titre ≥0.5 IU/ml
P_{Nb+}	Probability that a Nobivak-vaccinated animal acquires an antibody titre ≥0.5 IU/ml
P_{NP}	Probability that an animal is not protected against rabies after two-time vaccination
P_{Rb+}	Probability that a Rabisin-vaccinated animal acquires an antibody titre ≥0.5 IU/ml
$P_{usfj,worldwide}$	Annual probability of importing at least one infected dog or cat by United States Force Japan from the world
P_V	Probability that an animal is vaccinated (compliance parameter)
$P_{worldwide}$	Annual probability of importing at least one infected dog or cat from the world
$R_{aqs,\ s}$	Probability of infection in a single dog or cat imported through Animal Quarantine Service from sub-region *s*
$R_{s,pathway}$	Probability of rabies introduction from sub-region *s* through a specific pathway (*1, 2, 3,…, 14*)
$R_{usfj,\ s}$	Probability of infection in a single dog or cat imported through United States Force Japan from sub-region *s*
s	Sub-region
Sp_{FAVN}	Specificity of Fluorescent Antibody Virus Neutralization
Sp_{RFFIT}	Specificity of Rapid Fluorescent Focus Inhibition Test
T	Exposure time in the exporting country
$Y_{worldwide}$	The number of years until the introduction of a rabies case into Japan
λ_S	Maximum number of unobserved rabies cases at a particular instant of time in sub-region *s*

Table 1.3 List of scenarios that were tested in scenario analysis and the modified parameter values under each scenario

Parameter	Scenario	Value	Comments
Compliance parameters (P_V , P_{ST}, P_C)	1	100% (baseline)	To assess the effect of reduced compliance. If 100% compliance is not observed, the waiting period is assumed to be 1 day.
	2	99%	
	3	90%	
	4	80%	
Annual number of imports (N_{aqs} and N_{usfj})	1	Baseline	To assess the effect of an increased level of importation
	2	2-fold increase	
	3	3-fold increase	
	4	5-fold increase	
Probability that the animal is incubating rabies ($P_{I,S}$)	1	Baseline	To assess the effect of an increased number of rabies cases in all exporting countries
	2	2-fold increase	
	3	5-fold increase	
	4	10-fold increase	
Probability that a vaccinated animal is not protected (P_{NP})	1	0.056 (baseline)	To assess the effect of a vaccine with poor efficacy being used in the exporting country
	2	0.1	
	3	0.2	
	4	0.5	
	1	0.056 (two-time vaccination)	To assess the effect of the required number of rabies vaccination being reduced due to policy amendment
	2*	0.19 (one-time vaccination)	
Probability that an unprotected animal passes serological testing (P_{ST+})	1	0.031 (Current regime)	To assess the effect of compulsory serological testing is abandoned due to policy amendment
	2	1 (Removal of testing)	
Waiting period in exporting countries	1	180 days (baseline)	To assess the effect if the waiting period is reduced due to policy amendment
	2	150 days	
	3	120 days	
	4	90 days	
	5	60 days	
	6	30 days	
	7	1 day	
Incubation period (*IP*)	1	Lognormal (23.7 , 15) (experimental infection)	To assess the effect if a different probability distribution of *IP* is input into the model
	2	Lognormal (27.3 , 20.2) (Tokyo epidemic)	

	3	Lognormal (35 , 36.8) (baseline)	
	4	Lognormal (39.7 , 41.9) (natural infection or naturally-acquired cases)	
Waiting period and required number of vaccination	1	No policy amendment (baseline)	To highlight to decision makers the potential for policy amendment recommended by the author
	2	Recommended policy amendment: 90-day waiting period and one-time vaccination	

* The P_{NP} for this scenario is given by $\frac{(1-P_{Rb+})+(1-P_{Md+})+(1-P_{Nb+})}{3}$

Table 1.4 Probability of infection in a single dog or cat imported into Japan (*R*) from each sub-region or region

	Region	Sub-region	R_S	R_R	$R_{aqs,worldwide}$ / $R_{usj,worldwide}$	$R_{worldwide}$
AQS	Africa	Eastern Africa	1.72E-8 (4.37E-9, 4.04E-8)	2.77E-8 (4.6E-9, 4.6E-9)	1.62E-9 (5.76E-12, 7.14E-9)	2.16E-9 (6.65E-11, 6.48E-9)
		Middle Africa	6.48E-7 (1.65E-7, 1.53E-6)			
		Northern Africa	1.59E-8 (4.3E-9, 3.74E-8)			
		Western Africa	4.67E-8 (1.19E-8, 1.1E-7)			
		Southern Africa	1.35E-8 (3.42E-9, 3.17E-8)			
	Asia	Eastern Asia	8.45E-10 (2.15E-10, 1.99E-9)	2.93E-9 (2.39E-10, 1.21E-8)		
		Central Asia	1.75E-8 (4.44E-9, 4.13E-8)			
		Southern Asia	5.09E-9 (1.3E-9, 1.2E-8)			
		South-Eastern Asia	7.32E-9 (1.86E-9, 1.73E-8)			
		Western Asia	3.17E-8 (8.06E-9, 7.47E-8)			
	Europe	Eastern Europe	6.91E-9 (1.75E-9, 1.59E-8)	1.44E-9 (1.23E-11, 8.42E-9)		
		Northern Europe	2.3E-10 (5.69E-11, 5.33E-10)			
		Southern Europe	7.78E-10 (1.96E-10, 1.81E-09)			
		Western Europe	3.27E-11 (7.25E-12, 7.88E-11)			
	Latin America and Caribbean	Caribbean	9.55E-8 (2.41E-8, 2.25E-7)	5.44E-9 (2.85E-1, 4.89E-9)		
		Central America	1.34E-9 (3.39E-10, 3.16E-9)			
		South America	1.04E-9 (2.63E-10, 2.43E-9)			
	North America	Northern America	4.69E-10 (1.19E-10, 1.11E-9)	4.69E-10 (1.19E-10, 1.11E-9)		
USFJ	Africa	Eastern Africa	8.76E-8 (7.78E-8, 9.78E-8)	6.97E-8 (5.39E-8, 8.72E-8)	4.04E-9 (1.74E-9, 3.39E-9)	
		Middle Africa	3.35E-6 (2.61E-6, 4.17E-6)			
		Northern Africa	8.36E-8 (5.75E-8, 1.14E-7)			
		Western Africa	2.42E-7 (1.84E-7, 3.07E-7)			
		Southern Africa	6.97E-8 (5.39E-8, 8.72E-8)			

	Asia	Eastern Asia	4.39E-9 (3.29E-9, 5.63E-9)	2.46E-8 (3.38E-9, 1.6E-7)		
		Central Asia	9.79E-8 (5.1E-8, 1.57E-7)			
		Southern Asia	2.63E-8 (2.01E-8, 3.33E-8)			
		South-Eastern Asia	3.74E-8 (3.34E-8, 4.16E-8)			
		Western Asia	1.65E-7 (1.22E-7, 2.12E-7)			
	Europe	Eastern Europe	3.51E-8 (3.15E-8, 3.88E-8)	2.54E-9 (6.94E-11, 5.81E-9)		
		Northern Europe	1.47E-9 (4.9E-10, 2.87E-9)			
		Southern Europe	4.2E-9 (2.5E-9, 6.29E-9)			
		Western Europe	3.43E-10 (4.33E-11, 8.78E-10)			
	Latin America and Caribbean	Caribbean	5.49E-7 (2.58E-7, 9.27E-7)	8.45E-8 (4.53E-9, 6.08E-7)		
		Central America	7.17E-9 (4.44E-9, 1.04E-8)			
		South America	5.41E-9 (3.93E-9, 7.07E-9)			
	North America	Northern America	2.44E-9 (1.84E-9, 3.11E-9)	2.44E-9 (1.84E-9, 3.11E-9)		

Values are presented in: Mean (5th percentile, 95th percentile); E-n refers to multiplying by 10^{-n}. The number of rabies cases was assumed to be zero for the following sub-regions: Australia/New Zealand, Melanesia, Micronesia and Polynesia. The R_S for all these sub-regions were therefore assumed to be zero.

Table 1.5 Annual probability of importing at least one infected dog or cat (*P*) from each sub-region or region

	Region	Sub-region	P_S	P_R	$P_{aqs,worldwide}$ / $P_{usfj,worldwide}$	$P_{worldwide}$
AQS	Africa	Eastern Africa	5.82E-7 (1.45E-7, 1.37E-6)	3.02E-6 (7.43E-7, 7.12E-6)	2.02E-5 (5.15E-6, 4.65E-5)	2.57E-5 (1.06E-5, 5.22E-5)
		Western Africa	2E-6 (4.94E-7, 4.71E-6)			
		Southern Africa	4.3E-7 (1.06E-7, 1.01E-6)			
	Asia	Eastern Asia	2.51E-6 (6.23E-7, 5.9E-6)	1.16E-5 (2.86E-6, 2.72E-5)		
		Central Asia	2.1E-7 (5.18E-8, 4.96E-7)			
		Southern Asia	2.94E-7 (7.31E-8, 6.9E-7)			
		South-Eastern Asia	5.95E-6 (1.47E-6, 1.4E-5)			
		Western Asia	2.62E-6 (6.48E-7, 6.15E-6)			
	Europe	Eastern Europe	2.09E-6 (5.31E-7, 4.8E-6)	2.37E-6 (6.02E-7, 5.43E-6)		
		Northern Europe	1.43E-7 (3.53E-8, 3.31E-7)			
		Southern Europe	1.15E-7 (2.9E-8, 2.68E-7)			
		Western Europe	1.84E-8 (4.08E-9, 4.43E-8)			
	Latin America and Caribbean	Caribbean	6.67E-7 (1.67E-7, 1.57E-6)	8.29E-7 (2.07E-7, 1.94E-6)		
		Central America	5.73E-8 (1.41E-8, 1.34E-7)			
		South America	1.05E-7 (2.58E-8, 2.46E-7)			
	North America	Northern America	2.27E-6 (5.59E07, 5.35E-6)	2.27E-6 (5.59E-7, 5.35E-6)		
USFJ	Africa	Southern Africa	6.97E-8 (5.38E-8, 8,72E-8)	6.97E-8 (5.38E-8, 8.72E-8)	5.45E-6 (4.51E-6, 6.51E-6)	
	Asia	Eastern Asia	1.41E-7 (1.05E-7, 1.8E-7)	1.06E-6 (8.88E-7, 1.26E-6)		
		South-Eastern Asia	2.62E-7 (2.34E-7, 2.91E-7)			
		Western Asia	6.59E-7 (4.9E-7, 8.48E-7)			

	Europe	Eastern Europe	7.01E-8 (6.3E-8, 7.76E-8)	1.66E-7 (1.3E-7, 2.07E-7)		
		Northern Europe	2.65E-8 (8.82E-9, 5.17E-8)			
		Southern Europe	5.88E-8 (3.46E-8, 8.81E-8)			
		Western Europe	1.1E-8 (1.39E-9, 2.81E-8)			
	Latin America and Caribbean	Caribbean	5.49E-7 (2.58E-7, 9.27E-7)	5.92E-7 (2.97E-7, 9.65E-7)		
		Central America	4.3E-8 (2.67E-8, 6.26E-8)			
	North America	Northern America	3.56E-6 (2.68E-6, 4.55E-6)	3.56E-6 (2.68E-6, 4.55E-6)		

Values are presented in: Mean (5th percentile, 95th percentile); E-n refers to multiplying by 10^n. There was no import of dogs or cats into Japan during 2010 to 2013 from the following sub-regions: Middle Africa and Northern Africa (via AQS); Eastern Africa, Middle Africa, Northern Africa Western Africa, Central Asia, Southern Asia and South America (via USFJ). The number of rabies cases was assumed to be zero for the following sub-regions: Australia/New Zealand, Melanesia, Micronesia and Polynesia. The P_S for all these sub-regions were therefore assumed to be zero.

Table 1.6 Number of years until the introduction of a rabies case into Japan (*Y*) from each sub-region or region

	Region	Sub-region	Y_S	Y_R	$Y_{aqs,worldwide}$ / $Y_{usfj,worldwide}$	$Y_{worldwide}$
AQS	Africa	Eastern Africa	2.72E+6 (7.3E+5, 6.89E+6)	5.26E+5 (1.4E+5, 1.35E+6)	7.8E+4 (2.15E+4, 1.94E+05)	4.94E+4 (1.92E+4, 9.46E+4)
		Western Africa	7.92E+5 (2.12E+5, 2.02E+6)			
		Southern Africa	3.69E+6 (9.86E+5, 9.39E+6)			
	Asia	Eastern Asia	6.32E+5 (1.69E+5, 1.61E+6)	1.37E+5 (3.67E+4, 3.49E+5)		
		Central Asia	7.61E+6 (2.01E+6, 1.93E+7)			
		Southern Asia	5.39E+6 (1.45E+6, 1.37E+7)			
		South-Eastern Asia	2.26E+5 (7.14E+4, 6.77E+5)			
		Western Asia	6.05E+5 (1.62E+5, 1.54E+6)			
	Europe	Eastern Europe	7.54E+5 (2.08E+5, 1.88E+6)	6.65E+5 (1.84E+5, 1.66E+6)		
		Northern Europe	1.12E+7 (3.02E+6, 2.82E+7)			
		Southern Europe	1.38E+7 (3.73E+6, 3.44E+7)			
		Western Europe	9.3E+7 (2.25E+7, 2.45E+8)			
	Latin America and Caribbean	Caribbean	2.39E+6 (6.36E+5, 5.99E+6)	1.91E+6 (5.16E+5, 4.83E+6)		
		Central America	2.78E+7 (7.48E+6, 7.11E+7)			
		South America	1.52E+7 (4.06E+6, 3.87E+7)			
	North America	Northern America	6.99E+5 (1.87E+05, 1.79E+6)	6.99E+5 (1.87E+05, 1.79E+6)		
USFJ	Africa	Southern Africa	1.47E+7 (1.15E+7, 1.86E+7)	1.47E+7 (1.15E+7, 1.86E+7)	1.86E+5 (1.54E+5, 2.22E+5)	
	Asia	Eastern Asia	7.31E+6 (5.56E+6, 9.5E+6)	9.53E+5 (7.96E+5, 1.13E+6)		
		South-Eastern Asia	3.84E+6 (3.44E+6, 4.28E+6)			
		Western Asia	1.56E+6 (1.18E+6, 2.04E+6)			

	Europe	Eastern Europe	1.43E+7 (1.29E+7, 1.59E+7)	6.13E+6 (4.82E+6, 7.7E+6)		
		Northern Europe	5.09E+7 (1.93E+7, 1.12E+8)			
		Southern Europe	1.85E+7 (1.13E+7, 2.9E+7)			
		Western Europe	2.49E+8 (3.56E+7, 7.18E+8)			
	Latin America and Caribbean	Caribbean	2.12E+6 (1.08E+6, 3.87E+6)	1.92E+6 (1.03E+6, 3.36E+06)		
		Central America	2.49E+7 (1.6E+7, 3.75E+7)			
	North America	Northern America	2.88E+5 (2.2E+5, 3.73E+5)	2.88E+5 (2.2E+5, 3.73E+5)		

Values are presented in: Mean (5th percentile, 95th percentile); E+n refers to multiplying by 10^n. There was no import of dogs or cats into Japan during 2010 to 2013 from the following sub-regions: Middle Africa and Northern Africa (via AQS); Eastern Africa, Middle Africa, Northern Africa Western Africa, Central Asia, Southern Asia and South America (via USFJ). The number of rabies cases was assumed to be zero for the following sub-regions: Australia/New Zealand, Melanesia, Micronesia and Polynesia. The Y_S for all these sub-regions were therefore assumed to be zero.

Study 2

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

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Summary

Historical reviews indicate that the illegal landing of dogs from Russian fishing boats in the ports of Hokkaido occurred frequently especially in the late 1990s and this could potentially be a source of rabies introduction into Japan. The method of scenario tree modelling was used and the following entry and exposure pathway was considered the most likely route of rabies entry: a rabies-infected dog arriving on a Russian fishing boat lands in a port of Hokkaido in Japan, it becomes infectious, contacts and infects a susceptible domestic animal (companion dog, stray dog or wildlife). Input parameter values were based on surveys of Russian fishermen, expert opinion and scientific data from the literature. At present (2006–2015), the probability of the introduction of rabies as a result of one Russian fishing boat arriving at a port of Hokkaido is 8.33×10^{-10} (90% Prediction Interval (PI): $7.15 \text{ X } 10^{-11} – 5.34 \times 10^{-9}$), while this probability would have been 7.70×10^{-9} (90% PI: $6.40 \times 10^{-10} – 4.81 \times 10^{-8}$) in the past (1998–2005). Under the current situation (average annual number of boat arrivals is 1,106), rabies would enter Japan every 1,084,849 (90% PI: 169,215 – 20,188,348) years, while the disease would have been introduced every 18,309 (90%PI: 2,929 – 220,048) years in the past (average annual number of boat arrivals is 7,092). The risk of rabies introduction has decreased 59-fold due to both the effective control of the issue of illegal landing of dogs and the decline in the number of Russian boat arrivals. Control efforts include

education of Russian fishermen, establishment of warning signs, daily patrols and regular port surveillance of potential dog landing activity. Although the current risk of rabies introduction is very low to negligent, control measures against the illegal landing of dogs must be maintained. Further risk management measures, such as the management of wildlife from the port area and regular monitoring of the rabies situation in Russia (particularly the easternmost regions), can be established to strengthen the current rabies prevention system in Hokkaido.

1. Introduction

Although Japan has the geographical advantage of being isolated by the sea, it is subject to considerable movements of ships and boats which could potentially be a source of rabies introduction as suspected in the cases in Bali and Flores in Indonesia (Susetya et al. 2008; Putra et al. 2013; Townsend et al. 2013). Renowned for its fishing industry, Hokkaido is an island in northernmost Japan with large amount of boat visits every day. Furthermore, Hokkaido shares a close maritime border with Russia where animal rabies is widespread, especially in the western regions such as Belgorad Oblast, Yaroslavl Oblast, Kirov Oblast and Republic of Tartarstan (FSVPS 2015; Makarov & Vorob'ev 2004). Like many European countries where sylvatic (wildlife) rabies predominates, wild carnivores, particularly red foxes and racoon dogs, have remained the main reservoirs of the rabies virus in Russia (though pet animals, mainly dogs and cats, and farm animals are also affected by the disease) (Metlin 2008). Likewise, the Sakhalin fox (*Vulpes vulpes schrencki*; a sub-species of red fox) is a wild animal abundant in Hokkaido and the presence of such wildlife may serve as a reservoir of rabies should the disease be introduced into Japan.

Based on Japan Coast Guard (JCG) (2016), there have been substantial numbers of

Russian boats arriving at the 12 major ports of Hokkaido especially in the late 1990s (Fig. 2.1). These boats arriving from Russia are usually small commercial fishing boats carrying sea products such as crab and sea urchin for sale; they are generally 30 to 35 metres in length, 100 to 200 tons in weight and can accommodate 10 to 15 people. In accordance with the Rabies Prevention Law, any dog from a ship or boat is prohibited from landing in Japan without undergoing a six-month quarantine period at the animal quarantine station managed by AQS; alternatively, the dog could enter and be landed in Japan by following the standard import regime (in place since November 2004) which consists of identification with microchip, two-time rabies vaccination, antibody level titration and a 180-day waiting period in the country of origin (Takahashi-Omoe et al. 2008; Kamakawa et al. 2009). However, many Russian fishermen who bring their dogs while sailing often ignored these rules and allowed their dogs out to roam freely in the port area (Ogawa 2000; MHLW 2002). According to past surveys at Port of Wakkanai in 1997 and 1999, 60% of Russian fishing boats had dogs on board (*n*=108); 34% of the fishermen of these boats admitted that they would take their dogs out of the boat (*n*=65) with 99% of them knowing that the landing of dogs in the port area is illegal without a permit (*n*=108) (Ogawa, 2000). Since the early 2000s, massive control efforts against this problem have been in place including education of Russian fishermen using information pamphlets, establishment of warning signs, daily patrols and regular port surveillance (MAFF 2010; MHLW 2002). In particular, port surveillance is conducted regularly in each month involving whole-day monitoring of the presence of dogs on Russian fishing boats and should any illegal landing of dogs be noticed, warning would be given to the fisherman.

This study aimed to quantitatively assess the risk of the introduction of rabies into Japan through the illegal landing of dogs from Russian fishing boats in the ports of Hokkaido. Through such risk analysis, the present study evaluates the current rabies prevention system against the illegal landing of dogs and thereby gives evidence-based recommendations regarding which control measures should be maintained, intensified or discontinued.

2. Material and methods

2.1 Assessment framework and parameter estimation

The current risk assessment was performed based on the World Organisation for Animal Health (OIE) framework of risk analysis (OIE 2018a). The following entry and exposure pathway was considered the most likely route of rabies introduction: a rabies-infected dog arriving on a Russian fishing boat lands in a port of Hokkaido in

Japan, it becomes infectious, contacts and infects a susceptible domestic animal (companion dog, stray dog or wild animal). A stochastic Monte Carlo model was developed based on the generic rabies risk assessment framework developed by Ward and Hernández-Jover (2015) with specific modifications to accommodate the local conditions in Japan.

The parameter values input into the model were based on the following sources:

1. Survey conducted at the Port of Wakkanai and data from regular port surveillance conducted at the Port of Hanasaki;
2. Elicitation of expert opinion;
3. Scientific data from literature reviews of previous rabies quantitative risk assessments.

Current survey of Russian fishermen was conducted by the author at the Port of Wakkanai for one week during 8 to 15 July 2015. The paper questionnaire was first written in English and then translated into Russian; it included a series of closed questions to obtain information on whether a dog is present on the fishing boat and whether the fisherman would land the dog in the port area. Eighteen captains of Russian fishing boats were interviewed during the survey period. To collect expert opinion, five staff members from three local shipping agencies with extensive field experience in providing logistics services for Russian fishing boats were also interviewed. Each shipping agency was asked independently via paper questionnaire to infer the probability of contact between a landed Russian dog and domestic animals. Finally, field observation at the port was also undertaken to validate the findings from survey and expert opinion, for example whether a dog would actually land in the port area when the fisherman provided a “no” answer in the questionnaire, and when a low contact probability is inferred, whether this expert opinion is appropriate judging from actual field situation.

Another investigation trip was taken at Port of Hanasaki in Nemuro during 9 to 11 November 2015. Data collected from regular port surveillance during 2002 to 2015 (until October) was provided by the Nemuro city government and this serves as the survey information on Port of Hanasaki. Elicitation of expert opinion (five experts from three shipping agencies) and field observation were conducted in the same manner as in Wakkanai. The Port of Wakkanai and Port of Hanasaki were selected as investigation sites because these two ports had the largest number of Russian fishing boat arrivals during 1998 to 2015, a total of 23,996 and 15,180, respectively (Fig. 2.1). The locations of the 12 major ports Hokkaido are shown in Fig. 2.2.

2.2 Scenario tree

The scenario tree depicting the risk pathway leading to the introduction of rabies into Japan is shown in Fig. 2.3. The parameter values input into each node of the scenario tree are listed in Table 2.1. To assess the periodic variation in the risk of rabies introduction, some input variables are divided into two time periods, present situation (2006–2015) and past situation (1998–2005), based on data in the corresponding period.

The scenario tree includes a total of eight nodes. Nodes 1 to 5 represent the entry pathways, and Nodes 6 to 8 represent the exposure pathways:

Node 1. The probability that a dog is present on a Russian fishing boat (*P_presence*) – at Port of Wakkanai, 12 dogs were present on 18 fishing boats based on the current survey (there was one boat with two dogs on board and this was counted as 2 in the numerator) while 65 dogs were present on 108 fishing boats based on the past survey (Ogawa 2000); at Port of Hanasaki, 59 dogs were present on 1,218 fishing boats based on surveillance data during 2006 to 2015 while 198 dogs were present on 1,420 fishing boats during 2002 to 2005.

Node 2. Proportion of different origins of Russian dogs (*P_origin*) – the origin of the dog is based on the origin of the fishing boat from a particular administrative division of Russia. It is important to consider the specific origin of the dog for an accurate estimation of the probability that a dog is infected with rabies (Node 3) because the rabies situation varies widely in each administrative division of Russia and is much more severe in the west. At Port of Wakkanai, nine fishing boats with a dog on board all came from the Sakhalin island, Sakhalin Oblast based on current survey (*n*=12; three boats are with unknown specific origin because the fishermen refused to disclose personal information) while the origins of Russian fishing boats included Sakhalin Oblast and also Primorsky Krai (*n*=30) based on past survey (Ogawa 2000); at Port of Hanasaki, all the fishing boats originated from Kunashir Island, Sakhalin Oblast based on surveillance data (*n*=257) and expert opinion. Both Sakhalin Oblast and Primorsky Krai are located in the easternmost area of Russia where the rabies situation is not very severe (especially when compared with western regions).

Node 3. The probability that the dog is infected with rabies (*P_infected*) – this is calculated based on the maximum annual incidence of rabies cases in dogs ($Incidence_{max}$) in Sakhalin Oblast (zero case) and Primorsky Krai (two cases) during 2005–2015 (for three boats with unknown specific origin, *Incidence* $_{max}$ of the whole Russia was considered) (FSVPS 2015; OIE WAHIS Interface). This calculation method is based on a number of rabies quantitative risk assessments (Jones 2005; Kamakawa et al. 2009; Goddard et al. 2012) and is used because of two reasons: 1) the incidence provides a direct estimate of the probability or risk of a disease (Thrusfield 2008) and 2) by considering the maximum reported cases, the effect of under-reporting would be taken into account to a certain extent and also the worst case scenario would be addressed.

The incubation period of rabies is highly variable depending on a number of factors including virus strain, number of virus particles transmitted, site of exposure (proximity to the brain), immunological status of the host and nature of the wound. (Tojinbara et al. 2015). For dogs and cats, the incubation period is most frequently within two weeks and three months and is usually less than six months (CPSPH 2012). Tojinbara et al. (2015) have recently estimated an incubation period with a mean of 27.3 days and a standard deviation of 20.2 days based on 98 rabies cases in dogs and cats from the 1948–1954 Tokyo epidemic. In the current model, the incubation period in dogs is estimated to follow lognormal distribution with a mean of 34 days (*Incubation* $_{mean}$) with a standard deviation of 31 days by bootstrapping six scientific data sets based on the method described in Goddard et al. (2012).

The maximum number of unobserved rabies cases on a particular day (α) is given by: $Incidence_{max} \times Incubation_{mean} / 365$. Assuming that new rabies cases follow a Poisson process, gamma distribution is used to describe the uncertainty of the Poisson mean: $\lambda \sim \text{Gamma}(\alpha+1, 1/t)$, where t refers to exposure time of 1 day in the current calculation (Vose, 2008). *P_infected* is then given by dividing λ by the estimated companion dog population in Sakhalin Oblast and Primorsky Krai, which are estimated to be 42,557 and 167,202, respectively (12,500,000 for Russia) (FEDIAF 2012; FSSS, 2011).

Node 4. Probability of illegal landing of dog (*P_landing*) – this node represents the probability that the dog leaves the boat and lands in the port area. According to past surveys at Port of Wakkanai (*n*=65) (Ogawa 2000), this probability is estimated to be 34%. In terms of current situation, no fishermen acknowledged that they would land their dogs (*n*=12) in the port area and no event of illegal dog landing was observed by the author during the survey period. This finding was validated by expert opinion agreeing that the issue has been largely minimised in recently years. At Port of Hanasaki, the illegal landing of three dogs was observed during 2006 to 2015 (until

October) based on surveillance data (*n*=59) and these cases all happened during 2006 to 2008. Port surveillance data before 2006 is incomplete, therefore the *P_landing* (past situation) for Port of Hansaki is also based on past survey results at Port of Wakkanai.

Node 5. The probability of infectiousness (*P_infectious*) – it is assumed in this model that a rabid dog showing clinical signs (whether in furious or paralytic form) will not board a Russian fishing boat. Therefore, this node accounts for the conditional probability $P(A|B)$ where probability B describes the first condition where the rabies-incubating Russian dog does not exhibit signs prior to sailing, and probability A describes the second condition where the dog becomes infectious (able to infect other animals with rabies) after landing. $P(B)$ is calculated by estimating the value of a risk-output equation where the incubation period is greater than the period between exposure to rabies and sailing ($T_{exposure}$). Assuming that a dog in Russia is constantly exposed to the risk of contracting rabies since birth, $T_{exposure}$ is modelled using uniform distribution assigning equal probability to a random value between zero (infected on the day of sailing) and the age of the dog (infected on the day of birth). The age of the dog is modelled using the data of dogs living at different ages from the life table of insured dogs with an estimated mean of 2,800 days (Inoue et al. 2015). $P(A)$ is then calculated by the equation where the sum of $T_{exposure}$ and the sailing time ($T_{sailing}$) is greater than the latent period. The mean $T_{sailing}$ is 10 hours for Port of Wakkanai and 7 hours for Port of Hanasaki based on survey and expert opinion. Latent period refers to the time from infection and infectiousness and depending on the disease, it can be shorter than the incubation period which is the time between infection and clinical onset of the disease. In the case of rabies, the infectious period for dogs is considered by OIE (2018b) to start 10 days before the first apparent clinical signs (See Node 7 for more details). Overall, *P_infectious* is given by *P (A* and *B) / P (B)*.

Node 6. The probability of contact with a susceptible domestic animal (companion dog, stray dog or wild animal) after landing (*P_contact*) – the expert opinions were collected using the four-step interval elicitation procedure, where the expert is asked to provide a lower limit, upper limit and best guess with a self-assigned confidence level. This method is used as opposed to the three-point elicitation method to minimise overconfidence in the interval judgements of experts (Speirs-Bridge 2010). Five experts from three local shipping agencies at each port were interviewed, with each agency having provided independent opinions, thus creating a total of six sets of individual expert opinion. Each set of expert opinion was transformed into 95% confidence level and modelled using PERT distribution, and all the three sets (for each port) were combined using discrete distribution (Vose 2008).

Node 6a. The probability that a domestic companion dog is vaccinated against rabies (*P_vaccinated*) – the reported vaccination rate averages 70% in Wakkanai and 62% in Nemuro during 2005 to 2014 (data from field investigations). According to Takahashi-Omoe et al. (2008) and expert opinion from local veterinarians in Hokkaido, the actual vaccination coverage is however expected to be much lower than these reported rates due to a large number of unregistered companion dogs. The estimated national registration rate averages 57% during 2005 to 2014 (JPFA 2018; MHLW 2017). The vaccination rates adjusted for registration rate, i.e. 40% in Wakkanai and 35% in Nemuro, are used in the current model to provide a more realistic estimation of the actual vaccination coverage.

Node 6b. The probability that a companion dog vaccinated consistently every year is protected against rabies (*P_protected*) – it is assumed in the current model that stray dogs and wild animals do not have immunity against rabies, while vaccinated companion dogs may be protected depending on the efficacy of the rabies vaccine and the vaccination history. The rabies vaccine used in Japan is prepared from inactivated tissue culture of the RC-HL strain and its efficacy varies with the vaccination history of the dog. For dogs which are vaccinated at least twice (representing consistent vaccination every year), 98.7% (*n*=380) developed an antibody titre greater than or equal to 0.5 international units per ml (IU/ml) which is the OIE standard (Watanabe et al. 2013). Moreover, the *P_protected* is modelled by adjusting the reported efficacy of 98.7% for the specificity of the rapid fluorescent focus inhibition test (estimated mean of 95%) based on the method described in Goddard et al. (2012). Thus, the mean *P_protected* is estimated to be 93%. Finally, the effect of decreased vaccine effectiveness due to owners not vaccinating their dogs regularly every year is tested in scenario analysis.

Node 7. The probability of bite after contact (*P_bite*) – this node accounts for the probability of biting associated with each of the three forms of rabies (pre-clinical, furious and paralytic). A rabies-infected dog can be infectious before the onset of clinical signs and this period of pre-clinical infectious form is considered as 10 days (OIE 2018b). After clinical onset, rabies is frequently manifested as two classic forms, either the furious form or the paralytic form, and death usually occurs within 4 to 13 days (CFSPH 2012). Hence, the whole infectious period (D_{whole}) is considered to be 10 + Uniform (4 , 13) days in the current model. The calculation of *P_bite* thus depends on three factors: the chance of biting (biting is less common in paralytic form than in non-clinical form and furious form), the length of the infectious period and the proportion of each form (100% for non-clinical form; and 25% for furious form and 75% for paralytic form, respectively) (Banyard and Fooks 2011).

Node 8. The probability of transmission of rabies after the bite (*P_transmission*) – the input values were based on Hampson et al. (2009) which estimates a probability of 0.49 with 95% CIs of 0.45 to 0.52.

2.3 Risk estimation and model outputs

The risk of rabies introduction was calculated as follows:

1. The probability of rabies introduction as a result of one Russian fishing boat entering a port of Hokkaido (*P_boat*) is calculated by summing the probability of introduction through a contact with a domestic companion dog vaccinated but not protected; the probability of introduction through a contact with a companion dog not vaccinated; and the probability of introduction through a contact with a stray dog or wild animal:

   P_presence X *P_origin* X *P_infected* X *P_landing* X *P_infectious* X *P_contact_pet* X *P_vaccinated* X (1 – *P_protected*) X *P_transmission* +

   P_presence X *P_origin* X *P_infected* X *P_landing* X *P_infectious* X *P_contact_pet* X

(1 – *P_vaccinated*) X P_transmission +

P_presence X *P_origin* X *P_infected* X *P_landing* X *P_infectious* X (*P_contact_stray* + *P_contact_wildlife*) X *P_transmission*

According to JCG (2016), the annual number of Russian boat arrivals at Port of Wakkanai and Port of Hanasaki averages 309 and 487, respectively, during 2006 to 2015, and 2,613 and 1,289, respectively, during 1998 to 2005. Thus, the *P_boat* for Port of Wakkanai and for Port of Hanasaki are combined together based on a respective weight of 39% and 61% (67% and 33% for past situation);

2. The theoretical number of Russian boat arrivals required to result in one rabies case, given by: Poisson (*P_boat* X N_{median} or $N_{95\%}$), where $N_{95\%}$ and N_{median} refer to the theoretical number of boat arrivals required to bring the 95th percentile of Poisson distribution to one rabies case and the number required to bring the median to one case, respectively;

3. The annual probability that at least one rabies case is introduced, taking into account the actual annual number of Russian boat arrivals (N_{annual}) at all the 12 major ports of Hokkaido; given by: *P_annual* = 1 – (1 – *P_boat*)$^{N\ annual}$, where *N*

$_{annual}$ averages 1,106 during 2006 to 2015 and 7,092 during 1998 to 2005, respectively (JCG, 2016);

4. The number of years for the introduction of one rabies case (Y_{entry}), given by 1 / *P_annual*.

The results of the above simulated model outputs are also divided into two time periods, the current situation (2006–2015) and the past situation (1998–2004), based on the parameters including *P_presence*, *P_landing*, *P_contact* and N_{actual} which have different values under the current situation and the past situation.

2.4 Model implementation

The model was developed in @Risk Version 6.0 (Palisade Corporation) within Microsoft® Excel 2013, and was run with 20,000 iterations using Latin Hybercube sampling for each simulation.

2.5 Sensitivity and scenario analyses

A crude sensitivity analysis was conducted using Spearman's correlation coefficient to rank all the input parameters according to their contributions to the variance in the model output, *P_boat* (current situation), thereby identifying model inputs with most uncertainty (Vose 2008). Advanced sensitivity analysis was then performed using spider plot to illustrate the effects of selected influential input parameters (Vose 2008). To assess the effectiveness of the current rabies prevention system at the ports of Hokkaido, six scenario analyses were conducted testing the effects of changes in *P_presence*, *P_landing*, *P_infected*, *P_contact*, *P_vaccinated* or *P_protection* (Table 2.2). Furthermore, there were occasional reports where a landed Russian dog escapes from the port and enters into the city; while a few Russian fishermen abandoned their dogs in the port (Sato and Sugiyama 2004). Therefore, a scenario analysis was performed to assess the effect of a rabies-infectious Russian dog escaping from the port area and resulting in the direct entry of rabies.

3. Results

The results of simulated model outputs are presented in Table 2.3. The *P_boat* under the current situation (2006–2015) is 8.33×10^{-10} (90% prediction interval (PI): $7.15 \text{ X } 10^{-11} – 5.34 \times 10^{-9}$), while *P_boat* under the past situation (1998–2005) is 7.70×10^{-9} (90% PI: 6.40×10^{-10} to 4.81×10^{-8}) which is 6.14 times higher. Based on the current

P_boat, the 95th percentile and the median of the Poisson distribution would be equal to one rabies case with a number of 90,000,000 and 1,200,000,000 boats arrivals, respectively. The current *P_annual* is 9.22×10^{-7} (90% PI: $7.91 \times 10^{-8} - 5.91 \times 10^{-6}$) while the past *P_annual* is 5.46×10^{-5} (90% PI: $4.54 \times 10^{-6} - 3.41 \times 10^{-4}$). Thus, rabies would be introduced into Japan every 1,084,849 (90% PI: 169,215 – 20,188,348) years, while it would have been introduced every 18,309 (90% PI: 2,929 – 220,048) years in the past, which is 59 times more frequent.

Results of sensitivity analyses are presented in Fig. 2.4 and 2.5. The three most correlated input parameters are *P_landing (Wakkanai), P_infected and P_contact_wildlife (Wakkanai)* which all represent uncertainty. For scenario analysis (Fig. 2.6), increases in *P_infected*, *P_presence*, *P_landing* or *P_contact* all produce an observable increase in *P_boat* (Fig. 2.6a to 2.6e). Importantly, since *P_landing* and *P_contact* are controllable risk factors, the risk of rabies introduction can be effectively reduced when they are well-managed. In contrast, changes in *P_vaccinated* or *P_protected* do not exert any apparent effect on *P_boat* (Fig. 2.6f and 2.5g). For the scenario analysis of dog escape, the risk of rabies introduction would increase considerably with even a 1% of dog escape from $1.63 \text{ X } 10^{-9}$ to $4.03 \text{ X } 10^{-8}$ in terms of median *P_boat* (Fig. 2.6h), and from 553,389 to 22,368 in terms of median Y_{entry}.

4. Discussion

The risk of rabies introduction into Japan through the illegal landing of dogs from Russian fishing boats in the ports of Hokkaido is very low to negligent. The current risk of rabies introduction is lower than the risk in the past, largely attributed to the decreases in the probability of illegal landing of dogs (*P_landing*) and the annual number of boat arrivals (N_{actual}). Although the illegal landing of dogs occurred frequently in the early 2000s, it has been effectively controlled in recent years, for example no such event was observed during the survey period at Port of Wakkanai and the last case at Port of Hanasaki was observed in 2008 based on port surveillance. Thus, current control measures including education of Russian fishermen, establishment of warning signs, daily patrols and regular port surveillance must be maintained at the same level given their effectiveness. Moreover, the annual number of Russian fishing boat arrivals at the 12 major ports of Hokkaido has decreased from 9,456 in 1998 to 676 in 2015 (JCG 2016) (Fig. 2.1). The number of Russian boat arrivals was substantial during the late 1990s driven by poaching and smuggling activities; however, it has gradually declined over the past decade, particularly following the Russo-Japanese agreement on the prevention of poaching and smuggling (MFAJ 2012).

The *P_presence* based on current survey at Port of Wakkanai (estimated mean of 0.65) is fairly close to the *P_presence_past* (estimated mean of 0.60), suggesting that the behaviour of some Russian fishermen introducing their dogs while sailing has not changed, although few of them would take their dogs out of the boat now. This situation is on the other hand different in Port of Hanasaki where a dog present on a Russian fishing boat was last observed in 2013 based on port surveillance.

In terms of the probability of contact between a Russian dog and domestic animals (*P_contact*), the values inferred by the experts (from each port) are variable but their opinions are consistent, all agreeing that the current risk of contact is low. For both ports, the *P_contact_stray* and *P_contact_pet* are low and have decreased when compared with past situation, largely due to reinforced stray dog control and the fact that dog owners would not walk their dogs near the port area, especially since the risk of contact with a Russian dog has now been well communicated. During the one week survey period at Port of Wakkanai, there were neither stray dogs nor pet dogs (introduced by local owners) observed near the port area. However, the presence of Sakhalin fox was sighted and the inferred *P_contact_wildlife* is relatively high because of the abundance of this wildlife. If a Sakhalin fox is infected by a rabid Russian dog, spillover (cross-species transmission) of the rabies virus is said to occur; however, long-term establishment in a secondary species, i.e. the domestic population of Sakhalin fox, is not easily achieved unless cross-species adaptation of the rabies virus occurs (Mollentze et al. 2014). Nonetheless, the management of wild animals around the port area can further strengthen the current rabies prevention system in Wakkanai. Lastly, the risk of contact at Port of Wakkanai is considered to be generally lower than that at Port of Hanasaki due to the establishment of fences and security guards, and this difference is also reflected in the values of *P_contact* inferred by the two groups of experts.

As mentioned, there were occasional incidents where a landed Russian dog escapes from the port area. During the investigation at Port of Wakkanai, it was observed that some large-breed dogs, such as Siberian Husky, were left alone on the boats tethered by metal chain, while some fishermen allowed their dogs roam freely in the boat. Based on these findings, a rabies-infected Russian dog escaping from the port area is considered as a potential pathway for the permanent release of rabies. The scenario analysis of this pathway revealed that the risk of rabies introduction would increase drastically, highlighting the importance of management systems including fences and security guards (in preventing dog escape) and warning systems including patrol and port surveillance (in notifying the incident) . Another major concern for dogs escaping from the port area is the risk to human health. At Port of Wakkanai in 2005, four people were bitten by illegally landed dogs from Russian fishing boats and presumably received post exposure prophylaxis (NIID 2007).

In scenario analysis (Fig. 2.6f and 2.6g), changes in vaccination rate (*P_vaccinated*) and changes in vaccine efficacy (*P_protection*) do not exert an observable effect on the risk of rabies introduction, mainly due to a low contact probability between a Russian dog and a domestic companion dog (*P_contact_pet*). Importantly, under the scenario where *P_vaccinated* is set as zero representing the abolition of the mandatory vaccination policy, there is only a negligible increase in the risk of rabies introduction (median *P_boat*: 1.78×10^{-9}) when compared with the baseline (median *P_boat*: 1.66×10^{-9}). These results suggest that the policy of domestic dog vaccination may not be contributing effectively to the Japanese rabies prevention system in terms of reducing the risk of rabies introduction through the illegal landing of dogs from Russian boats (provided that the risk of contact with domestic companion dogs is well managed). The feasibility of maintaining the current policy of annual rabies vaccination of domestic dogs will be critically assessed through benefit-cost analysis in Study 5.

Finally, it should be noted that the results of the current study could be generalised to similar situations of rabies introduction in other ports in Japan. Nonetheless, readers should bear certain factors in mind, for example there are other types of ships/boats at other ports, e.g. illegal landing of dogs from Russian cargo ships has been reported in the Port of Fushiki at Toyama; the origin of the ship/boat must also be considered where many ships/boats also come from South Korea, Republic of Liberia and China (JCG 2016). Overall, it is expected based on the results of the current study that the risks of rabies introduction through the illegal landing of dogs (or even other animals such as cat) from boats/ships at other ports in Japan would also be very low.

When performing risk assessment, it is good practice to separate variability and uncertainty where variability refers to inherent stochastic nature while uncertainty refers to lack of precise knowledge; this is important because uncertainty can be reduced in future assessment by research whereas variability cannot be further reduced (Voss 2008). Our current model simulated both uncertainty and variability (randomness) together, sampling from the distributions reflecting the uncertainty of the input variables and from probability distributions reflecting variability. To assess whether uncertainty or variability dominates the current model, we ran second-order modelling with 250 iterations (representing variability) and 500 simulations (representing uncertainty) (Cummins et al. 2008; Vose 2008), and confirmed that uncertainty dominates variability by a factor of 1.34 in the current model (Fig. 2.7). This is mainly attributed to the uncertainties in *P_landing (Wakkanai)*, *P_infected* and *P_contact_wildlife (Wakkanai)* as indicated in the sensitivity analysis.

5. Conclusions

The risk of rabies introduction identified in this study is very low to negligent and the current risk has decreased 59-fold due to both the effective control of the problem of illegal landing of dogs and the decline in the number of Russian fishing boat arrivals. Thus, current control measures including education of Russian fishermen, establishment of warning signs, daily patrols and regular port surveillance should be maintained. Furthermore, scenario analysis revealed that the policy of mandatory domestic dog vaccination does not contribute effectively to Japan's rabies prevention system under rabies-free situation. Finally, further risk management measures, such as the removal of wildlife from the port area in Wakkanai and regular monitoring of the rabies situation in Russia (particularly the easternmost regions), can be established to strengthen the current rabies prevention system in Hokkaido.

6. Figures and tables

Fig. 2.1 Annual number of Russian fishing boat arrivals at the 12 major ports of Hokkaido 1998–2015 based on official data from Japan Coast Guard

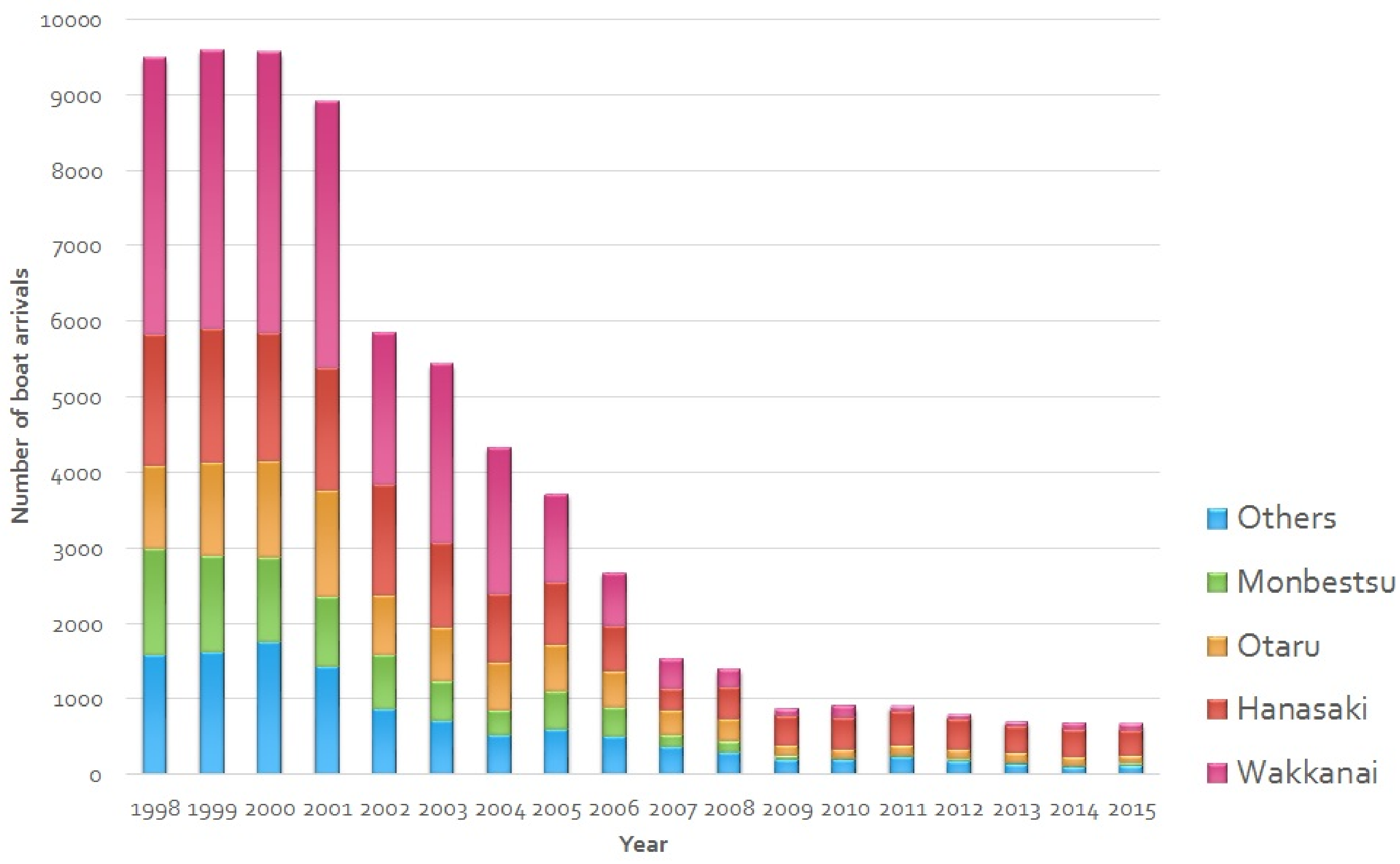
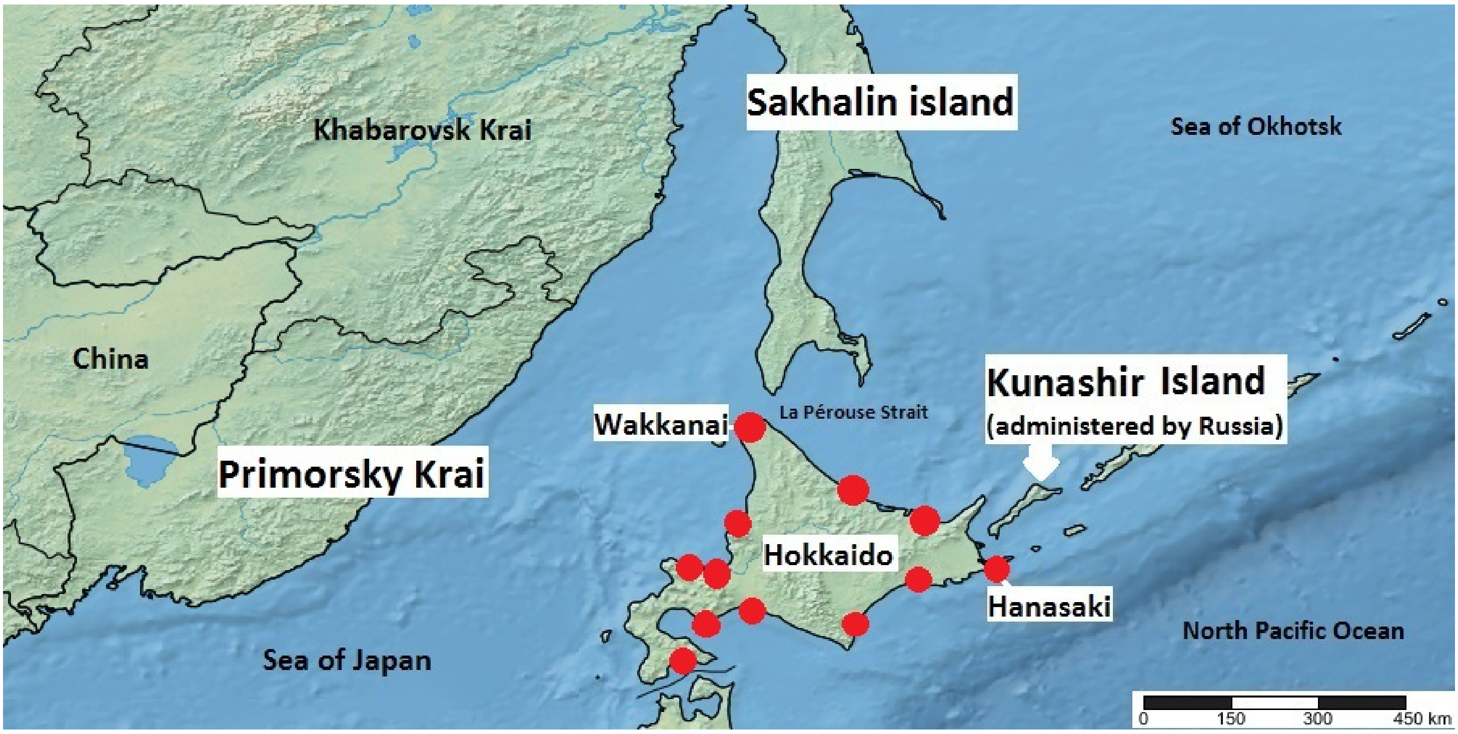
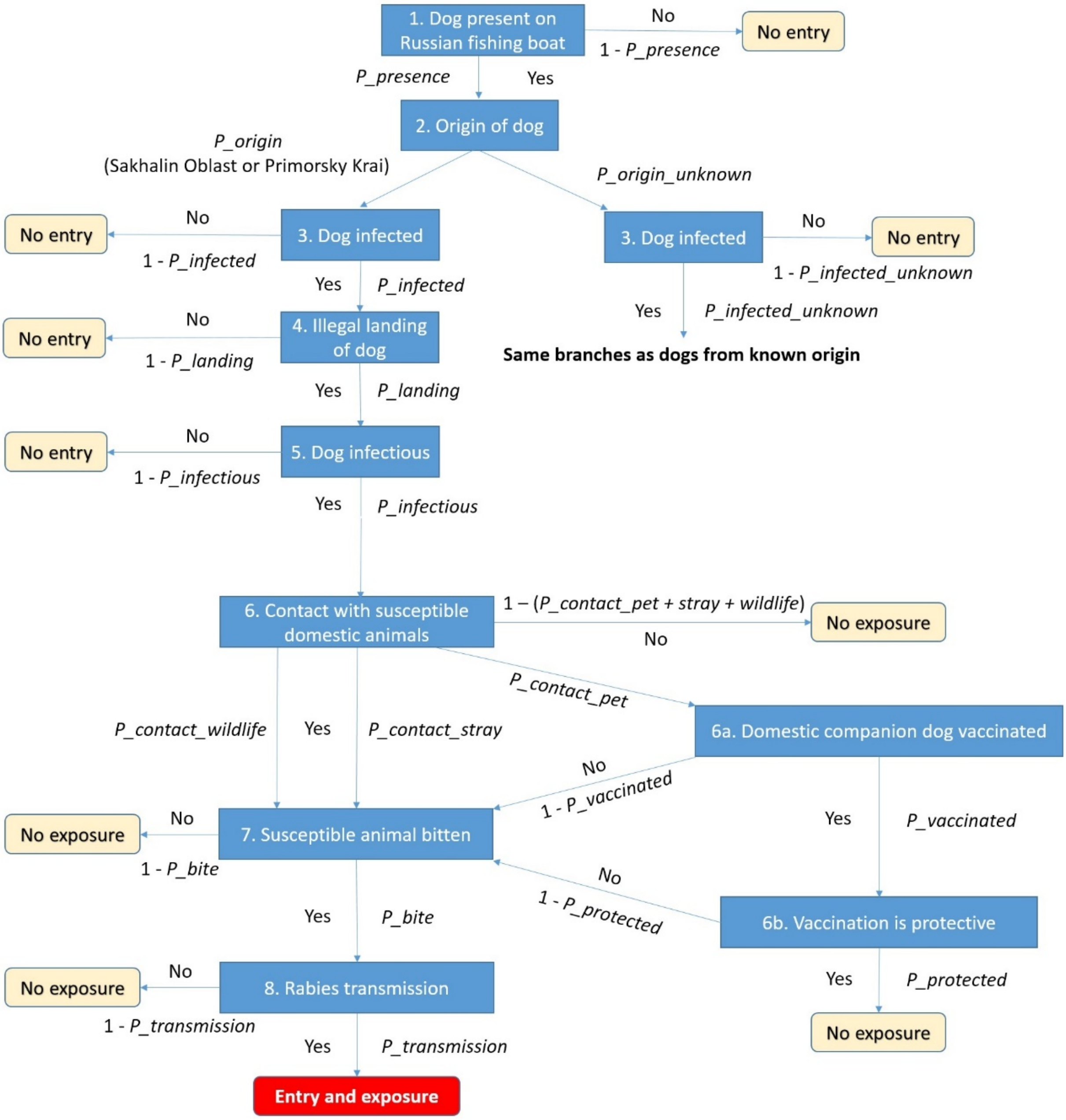


Fig. 2.2 Geographical situation between Hokkaido and easternmost Russia



The red circles indicate the locations of the 12 major ports of Hokkaido. Port of Wakkanai and Port of Hanasaki were the two chosen investigation sites.

Fig. 2.3 Scenario tree depicting the risk pathway of rabies introduction used in the current model



P_boat = $P\_presence \times P\_origin \times P\_infected \times P\_landing \times P\_infectious \times P\_contact\_pet \times P\_vaccinated \times (1 - P\_protected) \times P\_transmission$

$+$

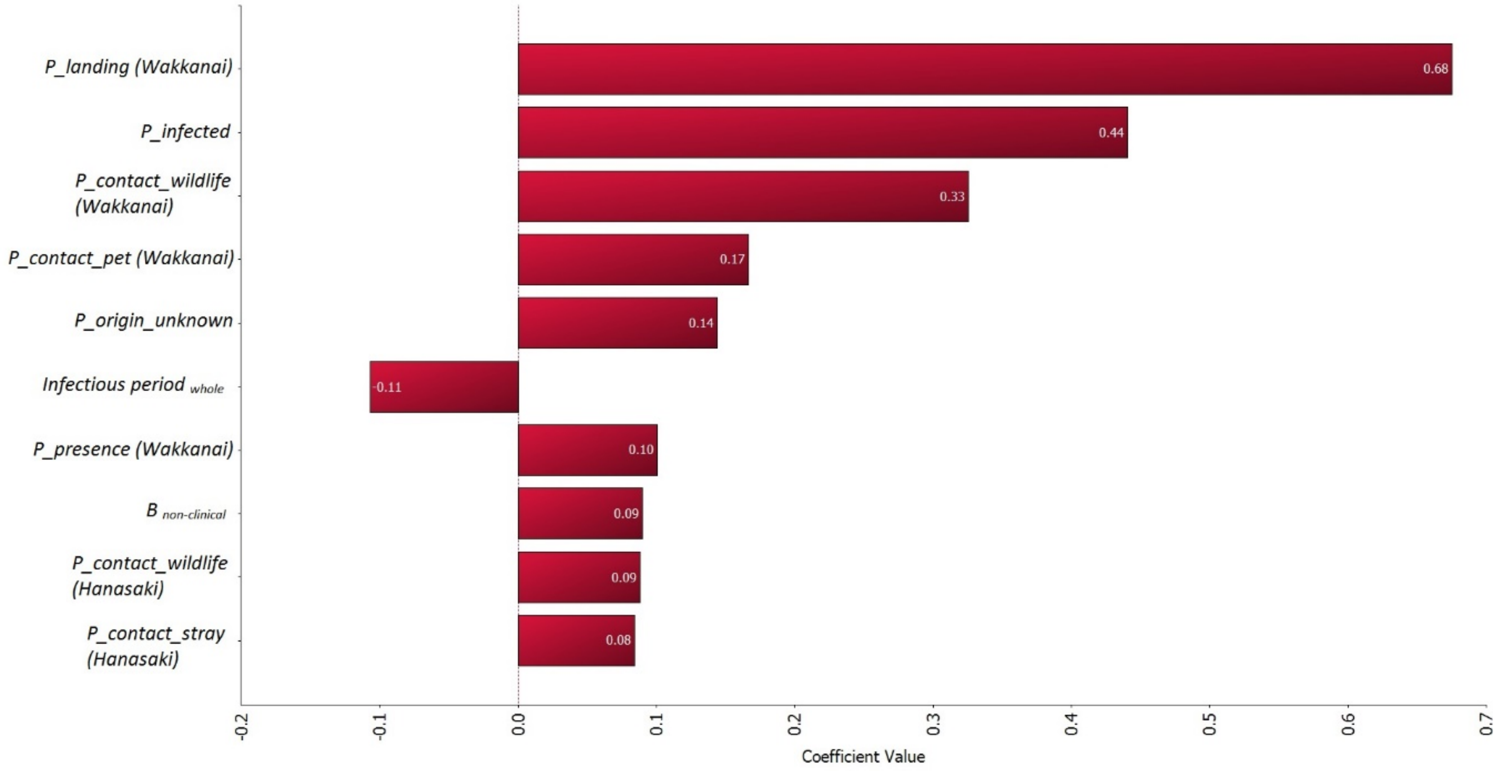
$P\_presence \times P\_origin \times P\_infected \times P\_landing \times P\_infectious \times P\_contact\_pet \times (1 - P\_vaccinated) \times P\_transmission$

$+$

$P\_presence \times P\_origin \times P\_infected \times P\_landing \times P\_infectious \times (P\_contact\_stray + P\_contact\_wildlife) \times P\_transmission$

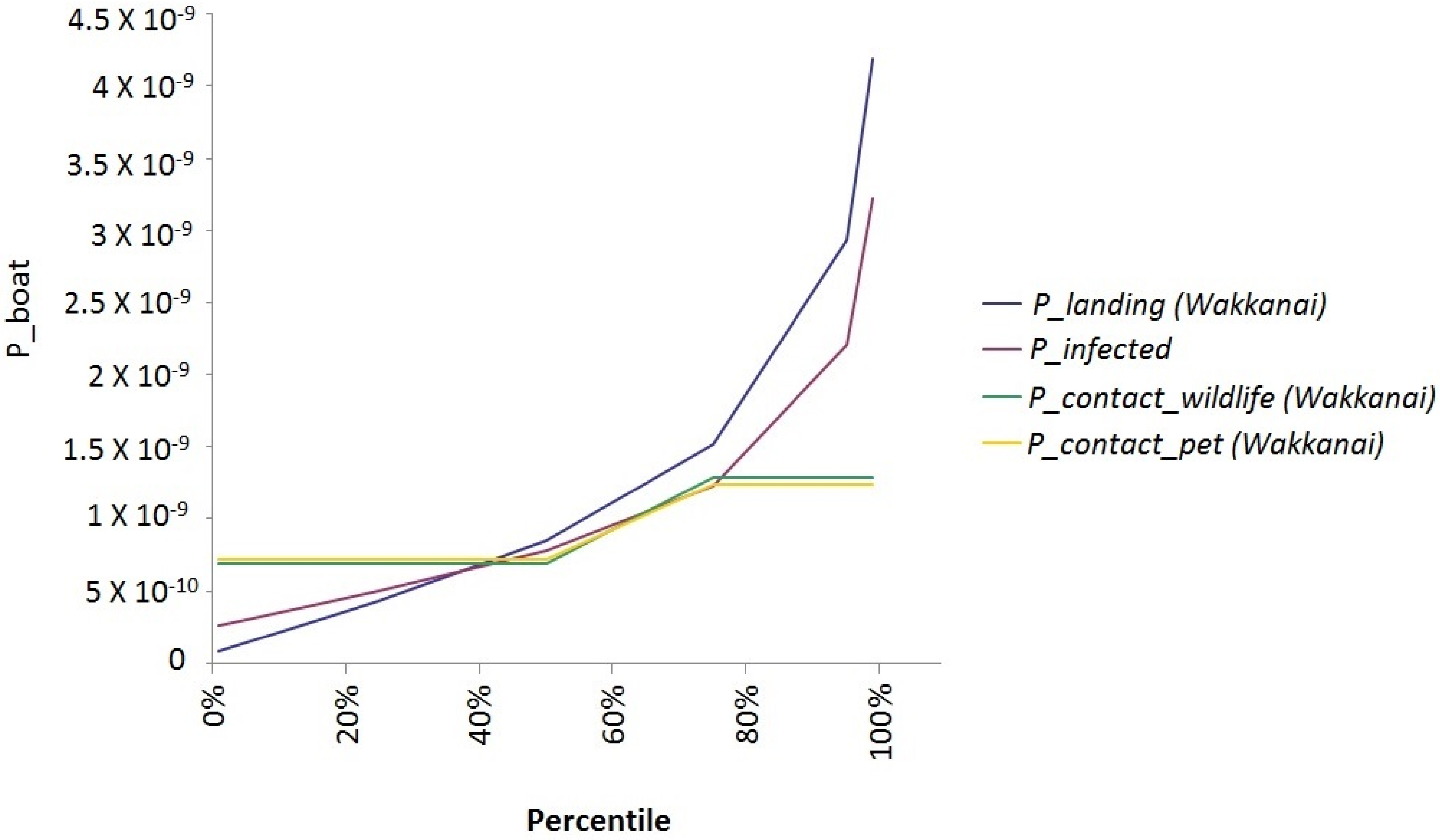
The calculation formula of *P_boat* is shown under the scenario tree. *P_boat* represents the probability of rabies introduction into Japan through the arrival of one Russian fishing boat at a port of Hokkaido.

Fig. 2.4 Tornado graph illustrating the result of sensitivity analysis. All model input parameters are ranked by Spearman's correlation coefficient according to their contributions to the variance of model output *P_boat* (current situation)



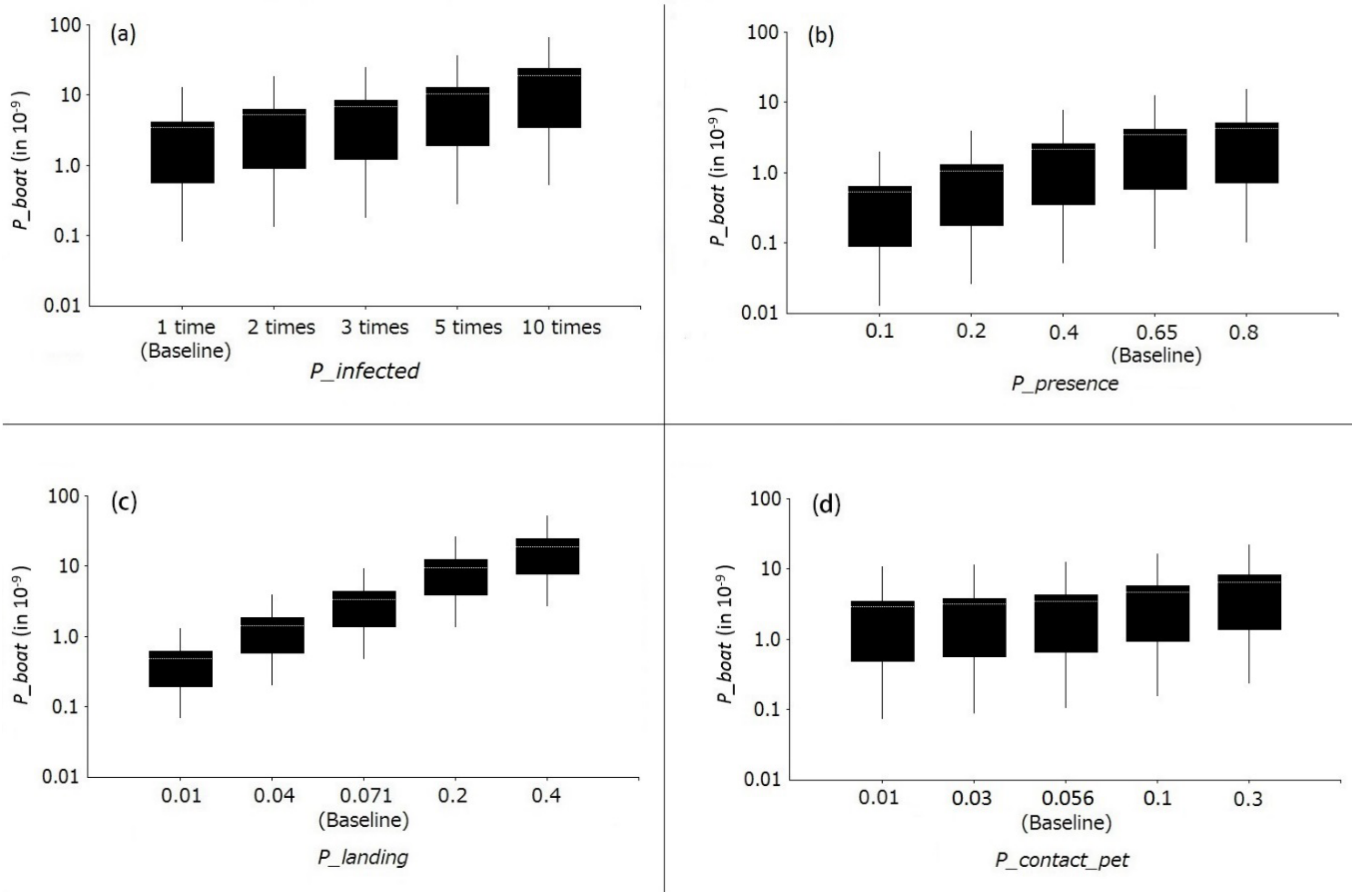
The 10 most correlated input parameters are shown in this figure. The three most correlated input parameters are *P_landing (Wakkanai)*, *P_infected* and *P_contact_wildlife (Wakkanai)* which all represent uncertainty.

Fig. 2.5 Spider plot depicting the effects of selected parameters under different input distribution percentiles on the median of *P_boat*



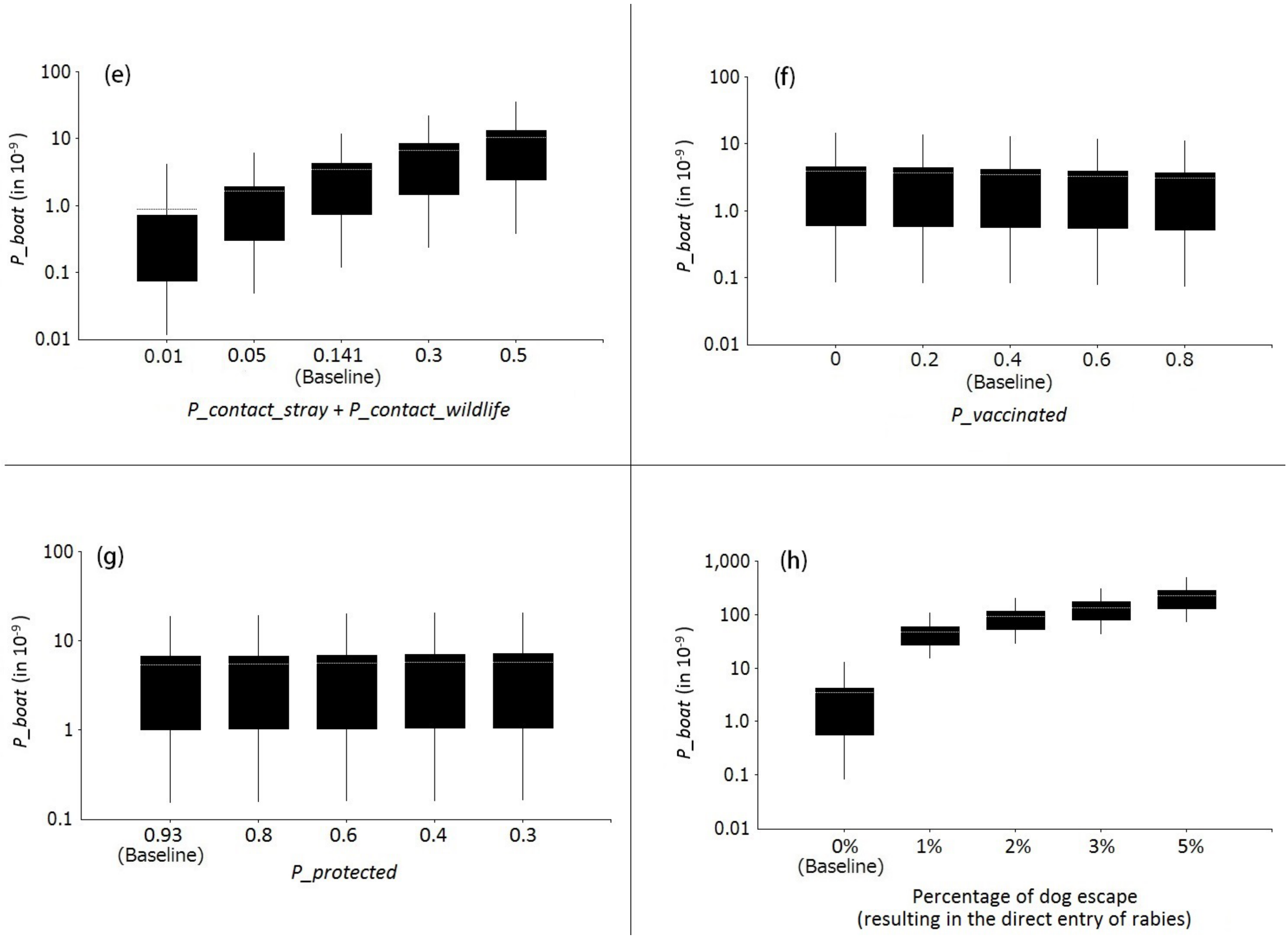
P_landing is the most influential parameter with the steepest spider line.

Fig. 2.6 (a–d) Scenario analysis showing the effects of tested scenarios on the risk of rabies introduction, as represented by *P_boat*



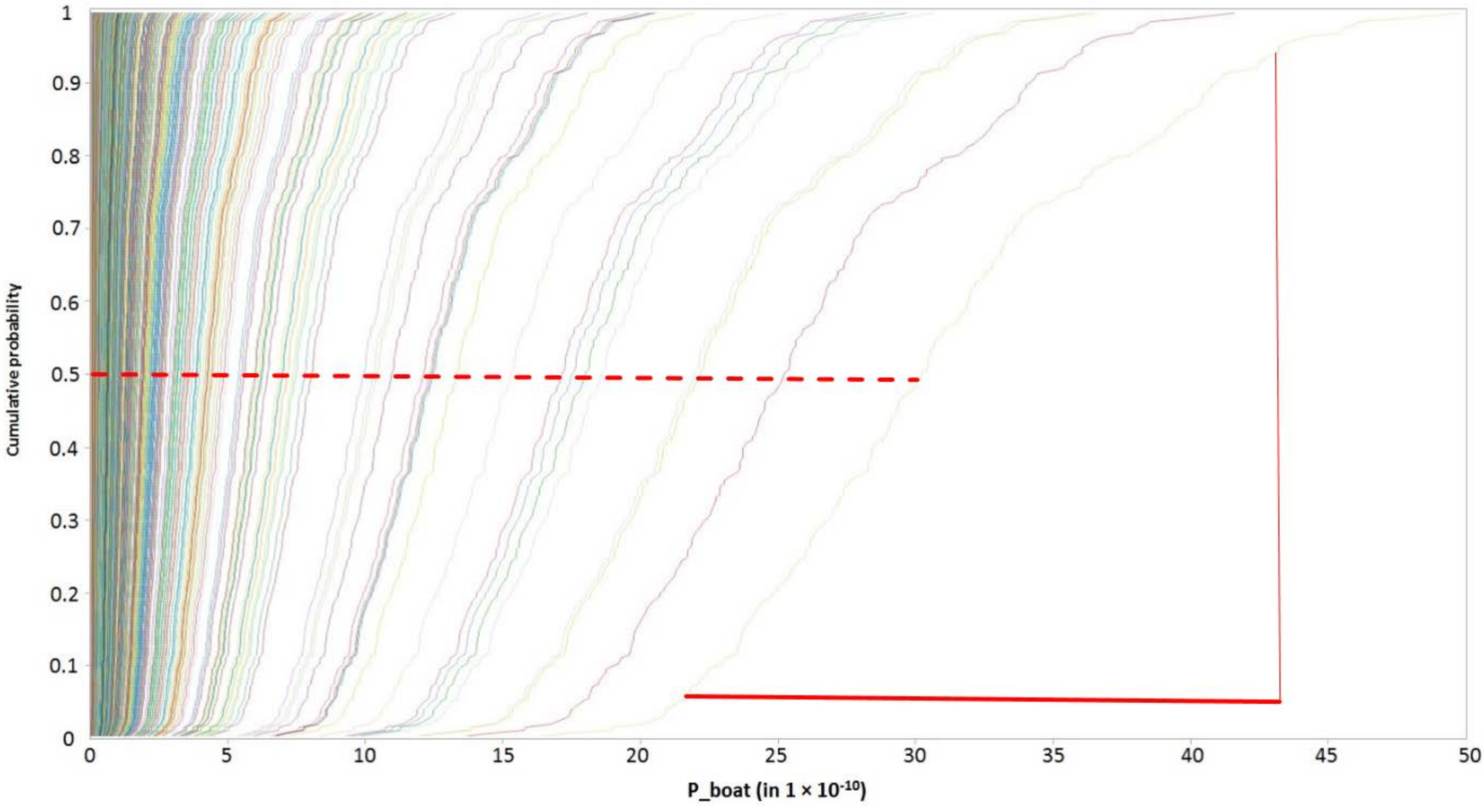
For each box-whisker plot, the width of the box indicates the inter-quartile range; the dotted white line indicates the mean; the ends of the whiskers indicates the 5th percentile and the 95th percentile respectively. Changes in the values of *P_infected*, *P_presence* and *P_landing* all produce an observable increase or decrease in *P_boat*. Importantly, since *P_landing* and *P_contact* are controllable risk factors, the risk of rabies introduction can be effectively reduced when they are well-managed.

Fig. 2.6 (e–h) Scenario analysis showing the effects of tested scenarios on the risk of rabies introduction, as represented by *P_boat*



Changes in the values of *P_contact_stray + P_contact_wildlife* or the percentage of dog escape all produce an observable increase or decrease in *P_boat*. However, changes in *P_vaccinated* or *P_protected* do not exert any apparent effect on *P_boat*, as illustrated by the approximately same height position of the five box-whisker plots in the corresponding graph.

Fig. 2.7 Second-order cumulative probability plot illustrating the result of second order modelling



Uncertainty (horizontal dashed line) is dominating over variability (horizontal solid line) by a factor of 1.34.

Table 2.1 List of model input parameters and their estimated values under model simulation

Parameter	Notation	Node[1]	Input values (in distribution or fixed value)[2]	Estimated mean (90% PI)[2]	Nature of uncertainty	Data source[2]
Probability that at least one dog is present on the Russian fishing boat (current situation)	*P_presence*	1	Beta (12 + 1 , 18 –12 + 1)	0.65 (0.47 – 0.78)	Uncertainty	Current survey (*n*=18)
			Beta (59 + 1 , 1218 –59 + 1)	0.049 (0.039 – 0.060)		Surveillance data (*n*=1218)
Probability that at least one dog is present on the Russian fishing boat (past situation)	*P_presence_past*	1	Beta (65 + 1 , 108 –65 + 1)	0.60 (0.52 – 0.68)	Uncertainty	Survey by Ogawa (2000) (*n*=65)
			Beta (198 + 1 , 1420 – 198 + 1)	0.14 (0.13 – 0.16)		Surveillance data (*n*=198)
Proportion of different origins of dogs (current situation)	*P_origin* (Sakhalin Oblast or Primorsky Krai) *P_origin_unknown* (for Port of Wakkanai only)	2	Beta (9 + 1 , 12 – 9 + 1) Beta (3 + 1 , 12 – 3 + 1)	71% (51% – 89%) 29% (11% – 49%)	Uncertainty	Current survey (*n*=12)
			100%	n/a[3]	Fixed value	Surveillance data of this study (*n*=59)
Proportion of different origins of dogs (past situation)	*P_origin_past* (Sakhalin Oblast or Primorsky Krai)	2	100%	n/a	Fixed value	Survey by Ogawa (2000) (*n*=30)
			100%	n/a		Surveillance data (*n*=198)
Probability of dog being infected with rabies	*P_infected* *P_infected_unknown*	3	Gamma (0.19 + 1 , 1) / (42,557 + 167,202) Gamma (119.46 + 1 , 1) / 12,500,000	5.8 X 10^{-6} (4.3 X 10^{-7} – 1.6 X 10^{-5}) 9.6 X 10^{-6} (8.2 X 10^{-6} – 1.1 X 10^{-5})	Uncertainty	FSSS, 2011; FEDIAF, 2012; OIE WAHIS Interface
Probability of illegal landing (current	*P_landing*	4	Beta (0 + 1 , 12 – 0 + 1)	0.071 (0.0039 – 0.21)	Uncertainty	Current survey (*n*=12)

situation)			Beta (3 + 1 , 59 – 3 + 1)	0.066 (0.023 – 0.12)		Surveillance data (*n*=59)
Probability of illegal landing (past situation)	*P_landing_past*	4	Beta (22 + 1 , 65 – 22 + 1)	0.34 (0.25 – 0.44)	Uncertainty	Survey by Ogawa (2000) (*n*=65)
Mean incubation period (days)	$Incubation_{mean}$	5	Parametric bootstrap on data sets	34.63 (95% CI: 30.33 – 39.44)	Uncertainty	Committee of Inquiry on Rabies 1971; Fekadu et al. 1982; Foggin 1988; Advisory Group on Quarantine 1998; Bingham 1999; Fooks et al. 2008
Standard deviation of incubation period (days)	$Incubation_{stdev}$	5	Parametric bootstrap on data sets	31.12 (95% CI: 24.43 – 38.49)	Uncertainty	Same as above
Incubation period (days)	*Incubation*	5	Lognormal ($Incubation_{mean}$, $Incubation_{stdev}$)	34.63 (95% CI: 30.33 – 39.44)	Variability	n/a
Latent period (days)	*Latent*	5	IF (*Incubation* – 10 < 0, 0, *Incubation* – 10)	24.63 (95% CI: 20.33 – 29.44)	Variability and uncertainty	OIE 2018b
Period between exposure to rabies and sailing (days)	$T_{exposure}$	5	Uniform (0 , *X*) *X* is the age of the dog in days (estimated mean is 2,800)	1,400 (62 – 3,282)	Variability	Inoue et al. 2015
Sailing time (days)	$T_{sailing}$	5	Lognormal (10.40 , 1.02) / 24	0.43 (95% CI: 0.40 – 0.47)	Variability	Current survey

			Uniform (6 , 8) / 24	0.29		Expert opinion
Probability that dog does not show clinical signs prior to sailing	*P (B)*	5	IF (*Incubation* > $T_{exposure}$, 1, 0)	0.028139 0.028016	Fixed value	n/a
Probability that dog becomes infectious after landing	*P (A)*	5	IF ($T_{exposure}$ + $T_{sailing}$ > Latent, 1, 0)	0.977 0.981	Fixed value	n/a
Probability that dog does not show clinical signs prior to sailing and becomes infectious after landing	*P (A* and *B)*	5	IF (AND (*P (A)*, *P (B)*, 1, 0)	0.008148 0.008251	Fixed value	n/a
Probability of infectiousness	*P_infectious*	5	*P (A* and *B)* / *P (B)*	0.2896 0.2945	Fixed value	n/a
Probability of contact with a susceptible animal after landing (current situation)	*P_contact_pet* *P_contact_stray* *P_contact_wildlife*	6	Refer to 2.1 Scenario Tree *Node 6.* for use of distributions	0.056 (0.00027 – 0.23) 0.0010 (0.00023 – 0.0019) 0.14 (0.032 – 0.28) 0.11 (0.00044 – 0.49) 0.11 (0.00044 – 0.50) 0.13 (0.00044 – 0.63)	Uncertainty	Expert opinion

Probability of contact with a susceptible animal after landing (past situation)	*P_contact_pet_past* *P_contact_stray_past* *P_contact_wildlife_past*	6	Refer to 2.1 Scenario Tree *Node 6.* for use of distributions	0.17 (0.00035 – 0.60) 0.0010 (0.00023 – 0.0019) 0.10 (0.022 – 0.23) --- 0.24 (0.00058 – 0.51) 0.33 (0.00059 – 0.70) 0.17 (0.00058 – 0.52)	Uncertainty	Expert opinion
Probability that companion dog is vaccinated against rabies	*P_vaccinated*	6a	0.40 --- 0.35	n/a --- n/a	Fixed value	MHLW 2017; JPFA 2018
Specificity of rapid fluorescent focus inhibition test	*Sp_RFFIT*	6b	Beta (92.97 , 5.132)	0.95 (0.91 – 0.98)	Uncertainty	Cliquet at al. 1998; Goddard et al. 2012
Probability that rabies vaccination is protective	*P_protected*	6b	Beta (355+1 , 380–355+1)	0.93 (0.87 – 0.97)	Uncertainty	Watanabe et al. 2013
Chance of biting a susceptible animal	$B_{non-clinical}$ $B_{furious}$ $B_{paralytic}$	7	Uniform (0.31 , 0.7) Uniform (0.71 , 1) Uniform (0.05 , 0.3)	0.51 0.86 0.18	Variability	Author's assumption based on Ward & Hernández-Jover 2015
Infectious period (days)	$D_{non-clinical}$ $D_{furious}$	7	10 Uniform (6 ,	n/a 9.5	Variability	CFSPH 2012; OIE 2018b

	$D_{paralytic}$ D_{whole}		13) Uniform (4 , 11) 10 + Uniform (4 , 13)	7.5 18.5		
Probability of bite post contact	*P_bite*	7	$B_{non\text{-}clinical}$ X 100% X ($D_{non\text{-}clinical}$ / D_{whole}) + $B_{furious}$ X 25% X ($D_{furious}$ / D_{whole}) + $B_{paralytic}$ X 75% X ($D_{paralytic}$ / D_{whole})	0.44 (0.30 – 0.62)	Variability	Banyard & Fooks 2011
Probability of transmission after a bite	*P_transmission*	8	Uniform (0.45 , 0.52)	0.49	Variability	Hampson et al. 2009

[1] Node of the scenario tree shown in Fig. 1

[2] Where there are two rows divided by a dashed line, the information in the upper row represent Port of Wakkanai and the lower row represent Port of Hanasaki

[3] Not applicable

Table 2.2 List of scenario analyses performed and the modified parameter values under each scenario

Parameter	Scenario	Value*	Purpose
P_infected	1	Current level (baseline)	If rabies continues to spread in western regions in Russia, the rabies situation in the east would also deteriorate. This scenario analysis assesses the effect of future increase in the number of rabies cases in Russia.
	2	2 times	
	3	3 times	
	4	5 times	
	5	10 times	
P_presence	1	0.05	To assess the effect if the number of dogs present on Russian fishing boats increases or decreases. The baseline of 0.65 refers that there are on average 65 dogs on 100 Russian boats.
	2	0.2	
	3	0.4	
	4	0.65 (baseline)	
	5	0.8	
P_landing	1	0.01	To assess the effect if the number of illegally-landed Russian dogs increases or decreases. The baseline of 0.071 refers that there are on average 7 dogs being landed out of 100 dogs present on Russian fishing boats.
	2	0.04	
	3	0.071 (baseline)	
	4	0.02	
	5	0.04	
P_contact_pet	1	0.01	To assess the effect if the contact probability between a Russian dog and a domestic companion dog increases or decreases. The baseline of 0.056 refers that there are on average 6 Russian dogs which would contact a companion dog out of 100 landed Russian dogs.
	2	0.03	
	3	0.056 (baseline)	
	4	0.15	
	5	0.3	
P_contact_stray + *P_contact_wildlife*	1	0.01	To assess the effect if the contact probability between a Russian dog and a stray dog or wild animal increases or decreases. The baseline of 0.141 refers that there are on average 14 Russian dogs which would contact a stray dog or wild animal out of 100 landed Russian dogs.
	2	0.05	
	3	0.141 (baseline)	
	4	0.3	
	5	0.5	
P_vaccinated	1	0	To assess the effect if the rabies vaccination rate increases or decreases. The baseline of 0.4 refers that there are on average 40 dogs vaccinated against rabies out of 100 domestic companion dogs. Scenario 1 represents the abolition of the mandatory vaccination policy.
	2	0.2	
	3	0.4 (baseline)	
	4	0.6	
	5	0.8	
P_protected	1	0.93 (baseline)	To assess the effect of decreased vaccine efficacy due to owners not vaccinating their dogs regularly every year. The baseline of 0.93 refers that there are on average 93 dogs
	2	0.8	
	3	0.6	

	4	0.4	protected against rabies when vaccinated (regularly every year) out of 100 companion dogs.
	5	0.3	
Percentage of dog escape (resulting in the direct entry of rabies)	1	0% (baseline)	To assess the effect if a rabies-infectious Russian dog escapes from the port and results in the direct entry of rabies. A value of 1% refers that there is 1 dog escaping from the port area out of 100 Russian dogs present on fishing boats.
	2	1%	
	3	2%	
	4	3%	
	5	5%	

*The baseline value is based on the estimated mean of the input parameter (current situation) for Port of Wakkanai

Table 2.3 Results of simulated model outputs and information on the number of Russian fishing boat arrivals

Model parameters	Current situation (2006-2015)	Past situation (1998-2005)
*P_boat**	8.33×10^{-10} ($7.15 \text{ X } 10^{-11} – 5.34 \times 10^{-9}$)	7.70×10^{-9} ($6.40 \times 10^{-10} – 4.81 \times 10^{-8}$)
$N_{95\%}$**	90,000,000	7,000,000
N_{median}**	1,200,000,000	90,000,000
N_{actual}***	1,106	7,092
*P_annual**	9.22×10^{-7} ($7.91 \times 10^{-8} – 5.91 \times 10^{-6}$)	5.46×10^{-5} ($4.54 \times 10^{-6} – 3.41 \times 10^{-4}$)
Y_{entry}*	1,084,849 (169,215 – 20,188,348)	18,309 (2,929 – 220,048)

* *P_boat*, *P_annual* and Y_{entry} are presented as: Median (90% prediction interval). *P_boat* refers to the probability of rabies introduction as a result of one Russian fishing boat entering a port of Hokkaido. *P_annual* refers to the annual probability that at least one rabies case is introduced, taking into account the reported annual number of Russian boat arrivals. Y_{entry} refers to the number of years for the introduction of one rabies case.

** $N_{95\%}$ and N_{median} refer to the theoretical number of boat arrivals required to bring the 95th percentile of Poisson distribution to one rabies case and the number required to bring the median to one case, respectively

*** N_{actual} refers to the actual average annual number of Russian boat arrivals at the 12 major ports of Hokkaido based on reported data from Japan Coast Guard (2016)

Study 3

Evaluating the contact rate between companion dogs during dog walking and the practices towards potential cases of rabies among dog owners in Japan

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Summary

This study aimed to examine the habits of dog walking in Japan using an internet survey of insured dog owners. 96.4% of the respondents (*n*=1,151) reported that they would take their dogs for a walk and they most frequently walk their dogs once or twice a day (75.9%) for 30 minutes to 1 hour (83.1%). The probability of a companion dog having contact with other dogs during dog walking was estimated to be 0.83 (95% confidence interval [CI]: 0.81 – 0.85) and the associated daily contact rate was estimated using log-normal distribution with a mean of 2.73 (95%CI: 2.42–3.11) and a standard deviation (SD) of 6.39 (95% CI: 5.18 – 7.84). Multiple linear regression revealed that the contact rate is mainly influenced by the social behaviour of the owner and to a lesser degree by his/her demographic characteristics including the area of residence, the breed size of dog and the age of the owner. In addition, ten Likert items measured on a 5-point scale were designed to assess the practices towards potential cases of rabies among dog owners. The respondents (*n*=972) achieved a mean score of 2.99 (out of a full score of 4) with a SD of 0.90 in responding to situations related to dog bite incidents and injury from stray cat scratches during dog walking. They achieved a higher score in responding to situations related to sighting a stray or wild animal during dog walking and situations related to non-specific clinical signs of rabies and bite injuries from stray dogs or wild animals during dog walking with a mean

of 3.70 (SD=0.58) and 3.84 (SD=0.34), respectively. The level of best practice was also proved to be significantly associated with the demographic characteristics of the dog owner.

1. Introduction

Dog walking is a purposeful physical activity which provides health benefits both to the owner and the dog (Lentino et al. 2012). In Japan, the companion dog population is estimated to be 8.9 million and about 13% of the households own at least one dog; the most popular dog breeds are small-breed dogs such as miniature dachshund, Chihuahua, toy poodle and shiba-inu (JPFA 2018). Various studies both in Japan and overseas have examined the epidemiology of dog walking and its associated health benefits, while recent studies have focussed on the interaction and contact rate between domestic dogs with particular reference to rabies (Oka & Shibata 2009; Hidano et al. 2012; Christian et al. 2013; Laager et al. 2018).

Although the risks of re-introduction of rabies into Japan have been quantitatively assessed as very low in Studies 1 and 2, the field experiences in Western Europe demonstrated that incursion of travel-associated rabies into a rabies-free country is indeed possible, particularly due to illegal importation of pets (Ribadeau-Dumas et. 2016). In 2008, France experienced a rabies outbreak involving three pet dogs where the primary case was illegally introduced from Morocco by a dog owner and eventually led to two local secondary cases (Allibert et al. 2008). Thus, one can reasonably anticipate that a rabies incursion into Japan would follow the above scenario and the behaviour of local dog owners would play an important role in influencing how the disease might spread in the domestic dog population (Kadowaki et al., 2018).

Indeed, the knowledge, awareness and practices (KAP) of the community, particularly the most at-risk populations such as dog owners, is a key determinant in the success of rabies prevention and control (WHO 2018). Public education campaigns on canine rabies have sought to promote KAP in terms of responsible dog ownership, awareness to report a suspected case, dog bite prevention and prompt first aid after potential exposure (Matibag et al. 2009; Wu et al. 2016). A number of studies have identified the considerable gaps in KAP of the community in rabies-endemic countries (Davlin et al. 2014; Sambo et al. 2014; Tschopp et al. 2016). In Japan, it has been highlighted that the public KAP towards rabies is at a suboptimal level since the disease has not occurred in the country for almost 60 years except for two imported human cases in 2006 (Kashino et al. 2014).

The current study aimed to examine the habits of dog walking in Japan with emphasis on evaluating the contact rate between companion dogs during dog walking and the practices towards potential cases of rabies among dog owners. The scientific information provided by this study will be useful in the following ways: 1) facilitating future research to improve the current understanding of the extent of a potential canine rabies outbreak in Japan; 2) guiding public education campaigns to address the gaps in KAP of Japanese dog owners and 3) refining the national contingency plan in response to a canine rabies incursion.

2. Materials and methods

2.1 Survey design and data collection

An online multiple-choice questionnaire written in Japanese was created using Google Docs (Google Inc., California, U.S.) and distributed nationally to 208,509 insured dog owners of Anicom Insurance Inc. on 7 April 2017. A total of 1,151 valid responses were received during 7 April 2017 and 17 May 2017, giving a response rate of 0.55%. Responses from 46 prefectures of Japan were received except from Yamagata Prefecture. The structure of the questionnaire and summary information on the responses are summarised in Table 3.1.

The types of data obtained from the questionnaire of insured dog owners and the associated model output, i.e. daily contact rate among companion dogs during dog walking and the level of best practice from dog owners towards potential cases of rabies, are depicted in Fig. 3.1.

2.2 Estimation of the daily contact rate between companion dogs during dog walking ($N_{contact}$)

The current survey revealed that 96.4% of the surveyed dog owners in Japan (*n*=1151) would take their dogs for a walk (Table 3.1, Q2c). Note that dog owners in Japan are obliged to keep their dogs under effective control in public places, e.g. using a lead, in accordance with the Act on Welfare and Management of Animals and the Basic Guidelines on the Care and Keeping of Companion Animals (published by Ministry of the Environment). The $N_{contact}$ was estimated by considering how frequently the companion dog would be walked by its owner each day (Q3a), how frequently out of 10 walks it would contact at least one other dog during a walk (Q3e) and how many dogs on average it would contact during that single walk (Q3f). The definition of contact was defined as when a dog comes close (within one metre) to another dog and has the chance to touch and interact with that dog. Responses in interval were converted into a fixed mean value, e.g. a dog that is walked by its owner 5–6 times a week corresponds to a frequency of 5.5 times a week and hence a daily frequency of 0.79; thus, a dog that is walked by its owner 5–6 times a week, contacts at least one dog in 1–2 walks per 10 walks and for each walk contacts 1–2 dogs on average would have a $N_{contact}$ of 0.79 X 0.15 X 1.5 = 0.18.

Moreover, $N_{contact}$ was modelled using probability distribution according to the method of maximum likelihood estimation (MLE) described in Tojinbara et al. (2015). The probability of a companion dog having a contact with other dogs during dog walk ($P_{contact}$) was first considered because 16.6% of the responses (n=1,108) had a zero $N_{contact}$, i.e. owners answered that their dogs never contact another dog during dog walking. The $P_{contact}$ was modelled using beta distribution assuming a non-informative prior. A log-normal distribution was then used to estimate the non-zero $N_{contact}$ ($N_{contact,>0}$) since log-normal distribution had the best fit when compared to gamma distribution and Weibull distribution based on Akaike information criterion (AIC).

2.3 Analysis of log-transformed $N_{contact}$ ($N_{contact,log}$) using multiple linear regression

Since $N_{contact}$ was highly positively skewed, i.e. a mean of 2.08 (standard error of 0.11), a median of 0.68 and a range between 0 and 38.5, a log-transformation was carried out by adding 0.01 to all the values of $N_{contact}$ such that the zero values could also be transformed. This improved the frequency distribution of $N_{contact}$ as $N_{contact,log}$ had a mean of -0.67 (standard error of 0.06), a median of -0.38 and a range between -4.61 and 3.65. The potential predictors of $N_{contact,log}$ were then considered in terms of gender, age and household status of the owner, number of owned dogs, breed size of the dog, duration of the walk, nature of the walk (whether it is social or not), whether the walk is during peak hours or not and companion dog density of the prefecture where the owner lives. Prefectural companion dog density was calculated by dividing the estimated number of companion dog, i.e. official number of registered dogs adjusted for the estimated registration rate, by the estimated inhabitable area in the prefecture (MHLW 2017; JPFA 2018). Thus, the prefectural companion dog density (dogs/km^2) was estimated with a mean of 102 with a standard error of 17 and a median of 69; and it is highest in Tokyo, i.e. 652 dogs/km^2, and lowest in Hokkaido, i.e. 17 dogs/km^2.

After initial screening with simple linear regression, three predictors including gender and household status of the owner and the number of owned dogs were excluded from the final multiple regression because no statistically-significant associations between these predictors and $N_{contact}$ (at p<0.1) could be observed. Hence, six predictors including age of the owner, breed size of the dog, duration and nature of the walk, whether the walk is during peak hours and prefectural companion dog density were included in the final model (p<0.05 was considered significant) after assessing the goodness of fit of the model based on AIC.

2.4 Likert items assessing the practices towards potential cases of rabies among dog

owners

Ten Likert items measured on a 5-point scale (0 = strongly disagree, 1 = disagree, 2 = neutral, 3 = agree and 4 = strongly agree) were designed to assess the practices towards potential cases of rabies (Table 3.2). Each item included an example of best practice such as “If my dog starts to show any of the following signs: abnormal sound in barking, abnormal licking of water, restlessness and biting with no provocation, I should stop bringing my dog for a walk and take immediate actions such as bringing it to the vet for check-up” and “If my dog bites another dog in the street, I should take immediate actions such as bringing my dog to the vet for check-up and/or reporting this incident to the animal welfare centre or local health centre”. Respondents with better knowledge and awareness of rabies were expected to provide a response towards strong agreement, i.e. a score towards 4, and vice versa. Item responses were grouped into constructs using principle component analysis (PCA) with varimax rotation and after assessing internal consistency based on Cronbach’s α, i.e. inter-correlation among responses within each construct. The mean score of the responses of each construct was then calculated for further regression analysis in the same manner mentioned above.

2.5 Statistical analysis and model implementation

Collected survey data was organised in Microsoft Excel 2016 for statistical analysis using the SPSS ver. 23 (IBM Corp., Armonk, NY, USA). @RISK ver. 7.5.1 (Palisade Corp., Ithaca, NY, USA) was used for the modelling of probability distribution.

3. Results

3.1 Estimation of the probability of a companion dog having a contact with other dogs during dog walking ($P_{contact}$) and the associated (non-zero) daily contact rate ($N_{contact,>0}$)

Results on the estimation of $P_{contact}$ and $N_{contact,>0}$ are summarised in Table 3.3 and Fig. 3.2. In terms of the whole Japan, $P_{contact}$ was estimated to be 0.83 (95% confidence interval [CI]: 0.81 – 0.85) and the log-normal distribution of $N_{contact,>0}$ was estimated with a mean of 2.73 (95%CI: 2.42–3.11) and a SD of 6.39 (95% CI: 5.18 – 7.84). This means that a companion dog in Japan would have an 83% chance of contacting another dog during dog walking and would contact on average 2.73 other dogs on a daily basis. In terms of regional differences, the contact frequency is highest in Keihin where the $P_{contact}$ was estimated as 0.87 (95%CI: 0.85 – 0.90) with a mean $N_{contact>0}$ of 3.21 (95% CI: 2.74 – 3.75); while it is lowest in Chugoku and Shikoku where the $P_{contact}$ was estimated as 0.80 (95%CI: 0.65 – 0.89) with a mean $N_{contact>0}$ of 1.35 (95% CI: 0.75 – 2.22).

3.2 Predictors of log-transformed $N_{contact}$ ($N_{contact,log}$)

Results of the multiple linear regression assessing the association between $N_{contact,log}$ and significant predictors are shown in Table 3.4. In the final model, owners who reported a social walk had the strongest positive effect (β=0.48) on $N_{contact,log}$, followed by owners who reported a mixed type of walk, i.e. sometimes social and sometimes private (β=0.39), a walk during peak hours (β=0.15), duration of the walk (β=0.12), companion dog density of the prefecture where the owner lives (β=0.10), owners having a non-small breed dog (β=0.08) and age of the owner (β=0.05).

3.3 Predictors of the responses to the Likert items assessing the practices towards potential cases of rabies

Responses to the Likert items assessing the practices towards potential cases of rabies and the results of principle component analysis (PCA) are presented in Table 3.2. The respondents (*n*=972) achieved a mean score of 2.99 with a standard deviation (SD) of 0.90 in responding to situations related to dog bite incident and injury from stray cat scratches during dog walking (Construct #1). In comparison, they achieved a higher score in responding to situations related to sighting a stray or wild animal during dog walking (Construct #2) and situations related to non-specific clinical signs of rabies and bite injury from stray dog or wild animals during dog walking (Construct #3) with a mean of 3.70 (SD=0.58) and 3.84 (SD=0.34), respectively. It should be noted that 98.5% of the respondents (*n*=949) have never sighted a stray dog during dog walking, while 91.2% of them (*n*=965) have never sighted a wild animal (Table 3.1, Q3). Using Construct #1 as the dependent variable indicating the level of best practice among the respondents (since it has the highest internal consistency, i.e. Cronbach's α=0.79), multiple linear regression revealed that older dog owners (β=0.14) and those who live outside the Kansai region (β=0.10) had a higher level of best practice, while owners with a medium- or large-breed dog had a lower level of best practice when compared to owners with a small-breed dog (β=-0.09) (Table 3.5).

3.4 Use of dog identification equipment and viewpoint towards dog rabies vaccination

71% of the surveyed dog owners (*n*=1,137) reported that their dogs are equipped with registration tag, rabies vaccination tag, microchip or a combination of these identification equipment (Table 3.1, Q4a). Owner compliance to the current dog rabies vaccination policy appears to be influenced by various factors including concerns over the dog's health (e.g. vaccine-associated adverse event), opportunity cost of time and the false security that rabies will not occur in Japan (Table 3.1, Q4d). In addition, 88.8%

of the respondents (*n*=640) supported the amendment of the current vaccination policy to one that requires less frequent boosters and 57.9% of them (*n*=997) agreed that the current price of single vaccination could be reduced (Table 3.1, Q4e & f).

4. Discussion

The current study explored the habits of dog walking among Japanese owners through a national internet survey, with particular focus on evaluating the contact rate between companion dogs and the practices towards potential cases of rabies. The proportion of dog owners who would walk their dogs was 96% in the current survey, while it was reported to be 64% and 90%, respectively, in two previous Japanese studies (note that those two studies conducted an internet survey of general dog owners in Japan instead of insured dog owners) and ranged from 69% to 80% in overseas studies in Taiwan, United States (US) and Australia (Ham & Epping 2006; Cutt et al. 2008; Hidano et al. 2012; Oka and Shibata 2012; Liao et al. 2018). Furthermore, the surveyed dog owners most frequently walk their dogs once or twice a day (75.9%) for 30 minutes to 1 hour (83.1%) and this result is consistent with that in Oka & Shibata (2012). In contrast, the national internet survey conducted annually by Japan Pet Food Association (JPFA) reported that only 30% of the dog owners (*n*=1039) walk their dogs at least once every day and 46% of them would walk for at least 30 minutes, while a previous US study reported that only 42.3% of the dog owners would walk for over 30 minutes in one day (Ham & Epping 2006; JPFA 2017). Based on the current survey, the average dog walking time per week was estimated to be 453 minutes (SD: 348 minutes), while it was reported to be 214 minutes (SD: 190 minutes) by Oka & Shibata (2012) and 232 minutes (SD: 211 minutes) by Liao et al. (2018). Direct comparisons of results with the other studies mentioned above should be interpreted with caution because of the differences in study location, survey methodology and assessment instrument, e.g. the current study estimated the dog walking time per week based on surveyed information reported in intervals which could have resulted in over-estimation. In addition, a previous Australian survey in 1998 reported results with striking differences where only 41% of the owners (n=410) walked their dogs, with an average time of 57 minutes per week (Bauman et al. 2001), suggesting that the behaviour of dog owners who walk their dogs may have changed over time. Nevertheless, it appears that the respondents in the current survey were more likely to walk their dogs for a relatively long period of time; this could be due to selection bias where a survey of insured dog owners is inherently biased towards owners who presumably provide better veterinary care to their dogs.

Moreover, the current study estimated the probability of a companion dog having a contact with other dogs during dog walking and the associated daily contact rate in normal circumstances. It should be noted that the contact rate between companion dogs is expected to increase considerably on special occasions, e.g. when the dog is brought to a dog park (known as dog run in Japan; dog runs are generally not at walking distance from homes and an entrance fee may be charged), dog café or dog hotel where it becomes off the lead. In this regard, the regression model captured the effect of owner behaviour on the contact rate between companion dogs during dog walking, revealing that the contact rate ($N_{\text{contact,log}}$) is mainly influenced by whether the owner intends to engage in a social walk or not (Table 3.4). Although to a much lesser degree, the $N_{\text{contact,log}}$ is also influenced by the companion dog density in the prefecture where the owner resides, as reflected in the differences in $N_{\text{contact,>0}}$ between the six respective regions in Japan. In addition, the $N_{\text{contact,log}}$ was higher in medium and large-breed dogs than in small-breed dogs, which is consistent with the results by Hidano et al. (2012). As mentioned above, the likely scenario for a rabies incursion into Japan would be via importation of an infected pet dog and hence the disease is expected to initially spread in the local companion dog population. Therefore, information regarding the contact rate between companion dogs provided by this study should serve as the basis for further research, particularly simulation model which predicts the potential outcomes of a rabies outbreak in the domestic companion dog population in Japan. Similarly, recent Australian studies on rabies have focused on investigating the roaming behaviour and contact rate in free-ranging dogs, particularly community dogs in the Aboriginal communities in Northern Australia (Dürr & Ward 2014; Sparkes et al. 2014, 2016; Molloy et al. 2017).

The data of the current study was based on an internet survey of insured dog owners from Anicom Insurance Inc. in Japan. It is estimated that approximately 10% of the companion dogs in Japan are insured for veterinary care; 507,375 dogs were insured by Anicom in 2016, representing 5% of the estimated companion dog population (*n*=9,878,000), and it has been reported that more than half of the insured dogs in Japan is covered by Anicom (Inoue et al 2015; Anicom 2018; JPFA 2018). Although the response rate to the current survey is very low which could create nonresponse bias, the responses appear representative of the present situation of dog ownership in Japan as depicted by the JPFA survey, e.g. 76.7% of the respondents own only one dog, while this was reported as 70.2% in the 2017 JPFA survey (*n*=1250); ownership of small-breed dogs accounted for 82.2% of the respondents, while this was reported as at least 73.2% in the JPFA survey (JPFA 2018). Nonetheless, the inherent selection bias mentioned above is evident in certain results of the current survey: 1) up to 93.2% of the respondents vaccinate their dogs against rabies every year (note that dog owners in Japan are obliged to register and vaccinate their dogs (starting from 91-day old) against rabies every year in accordance with the Rabies Prevention Law enacted since 1950), in contrast to an estimated national vaccination rate of 46.7% in 2016 based on adjusting the official vaccination rate of 71.4% reported by MHLW for an estimated dog registration rate of 65.3% reported by JPFA; 2) at least 87.9% of the respondents attend veterinary clinic for rabies vaccination of their dogs, whereas it has been reported that about 47.2% to 48.6% of owners would attend the vaccination campaign organised by Japan Veterinary Medical Association (JVMA) and 3) 67.3% of the respondents have microchipped their dogs, whereas this was reported to be only 14.9% in the 2017 JPFA survey (MHLW 2017; JPFA 2018). Overall, one can reasonably expect that insured dog owners in Japan have responsible dog ownership, e.g. they are very compliant with vaccinating their dogs against rabies as mentioned above and it can be assumed that the majority of them would have also registered their dogs; nevertheless, it appears that they prefer microchipping their dogs and therefore are not as compliant with the Japan-specific rules of dog identification as only 35.4% and 38.6% of the respondents reported that they would equip their dogs with a registration collar tag and a tag certifying rabies vaccination, respectively (Table 3.1 Q4a). It should be noted that dog microchipping is commonly compulsory in overseas countries (and territories) such as Australia, United Kingdom and Hong Kong.

Therefore, it is highly warranted to review the current Japan-specific rules of dog identification and consider adopting compulsory dog microchipping (which also facilitates storage of the dog's data such as rabies vaccination history) in the future, which is now an international standard on dog identification, particularly in terms of identifying stray, lost and abandoned dogs. Lastly, it is useful to conduct a more in-depth survey of the general dog owners in Japan on their habits of dog ownership and walking and compare the results with those of the current study.

Assessment of the practices towards potential cases of rabies during dog walking revealed satisfactory results as the respondents achieved an average score ranging from 2.99 (Construct #1) to 3.84 (Construct #3) out of a total score of 4 (Table 3.2). Again, such satisfactory results might be partly attributed to the inherent selection bias where insured dog owners are presumed to have better veterinary knowledge and awareness. In particular, dog owners with a higher level of best practice were significantly associated with increased age, living outside the Kansai region and owning small-breed dog(s) (Table 3.5). Probable reasons for dog owners from Kansai region having a lower level of best practice may include potential differences in the levels of knowledge and awareness towards rabies and their personality traits (e.g. Kansai people are well known for their perceived character of being friendly and passionate).

It should also be noted that the fitted regression model has a very low predictive power, indicating a high degree of variability in the Likert item responses. Since the current study did not directly assess the knowledge and awareness towards rabies among the respondents, it is highly warranted to conduct a more general KAP survey of Japanese dog owners in the future and investigate into other underlying factors influencing the differences in KAP among the community.

In terms of the best practice for dog owners to facilitate early detection of a rabies incursion into Japan, it shall involve, as described in the designed Likert items, reporting to the animal welfare centre or local health centre if the dog bites another dog/a person in the street and/or immediately bringing the unwell dog to see a vet once it develops clinical signs suspicious of rabies. From the current survey results it can be deduced that the probability of a Japanese dog owner following the best practice mentioned above would be approximately 0.75 (based on the average score in Construct #1 which is 3 out of 4). According to the simulation model by Kadowaki et al. (2018), if the probability of an owner releasing a rabid dog increased from 0.5 to 0.9 (corresponding to a decrease in the probability of best practice from 0.5 to 0.1), the number of rabies cases in an outbreak would increase 2.4-fold from 4.7 to 11.3. In addition, it would be beneficial to conduct further research to assess the KAP of doctors and veterinarians in Japan towards rabies, thus identifying any gaps and areas of concern that should be addressed in future continuous professional training (Hennenfent et al. 2018).

5. Conclusions

The current internet survey of insured dog owners in Japan illustrated that the contact rate between companion dogs during dog walking is mainly influenced by the behaviour of the dog owner, specifically whether he/she wants to engage in a social walk or not, and to a lesser degree by his/her demographic characteristics including area of residence, breed size of dog(s) owned and age. Assessment of the practices towards potential cases of rabies revealed satisfactory results and the level of best practice was also proved to be significantly associated with the demographic characteristics of the dog owner mentioned above.

6. Figures and tables

Fig. 3.1 Conceptual diagram depicting the data obtained from questionnaire of insured dog owners and the associated model output, i.e. daily contact rate among companion dogs during dog walking (A) and the level of best practice from dog owners towards potential cases of rabies

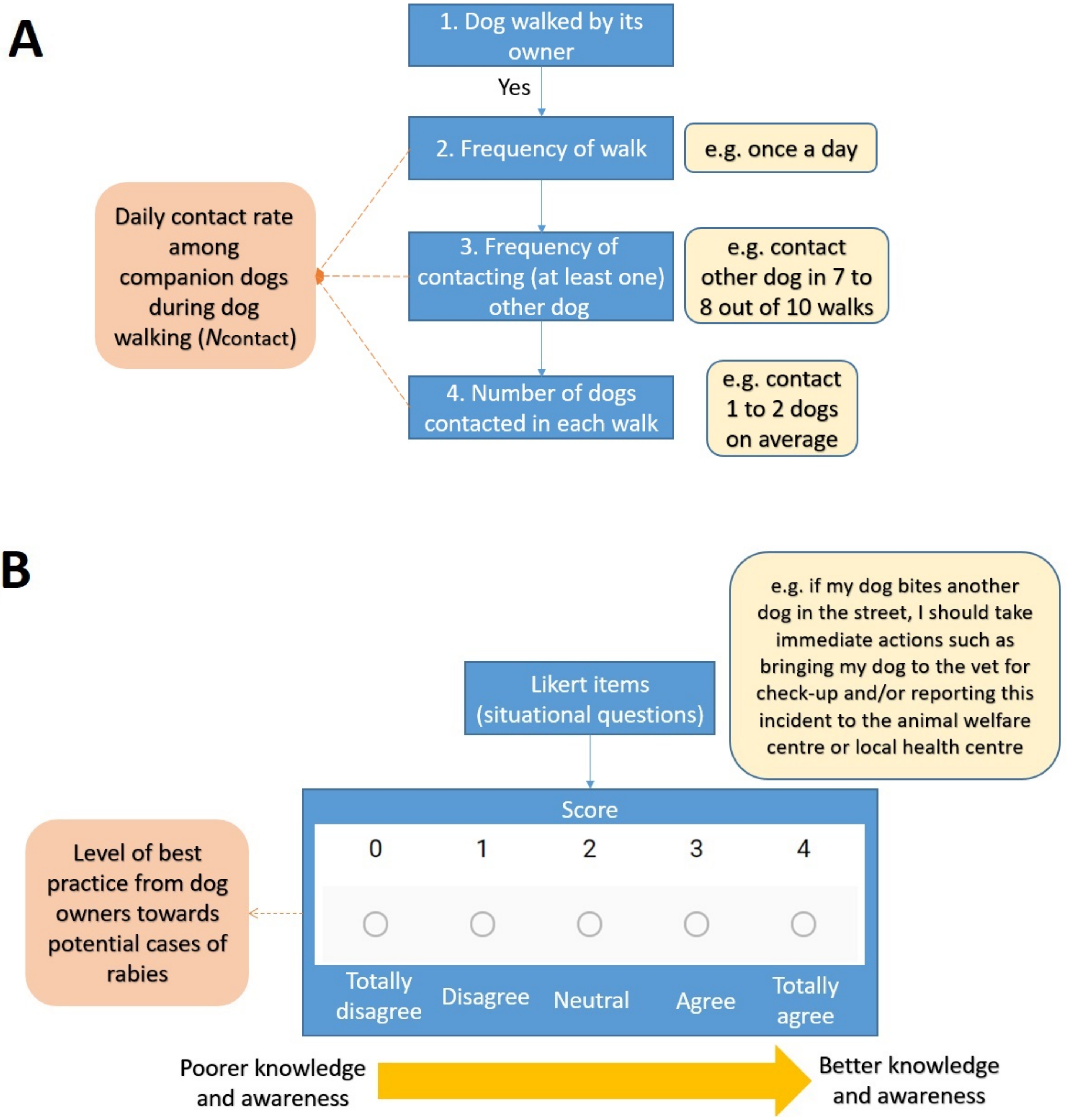


Fig. 3.2 Frequency distribution of the non-zero daily contact rate ($N_{contact,>0}$; in blue colour) between companion dogs during dog walking in Japan fitted with a log-normal distribution (in red colour) with a mean of 2.73 (95% CI: 2.42 – 3.11) and a standard deviation of 6.39 (95% CI: 5.18 – 7.84)

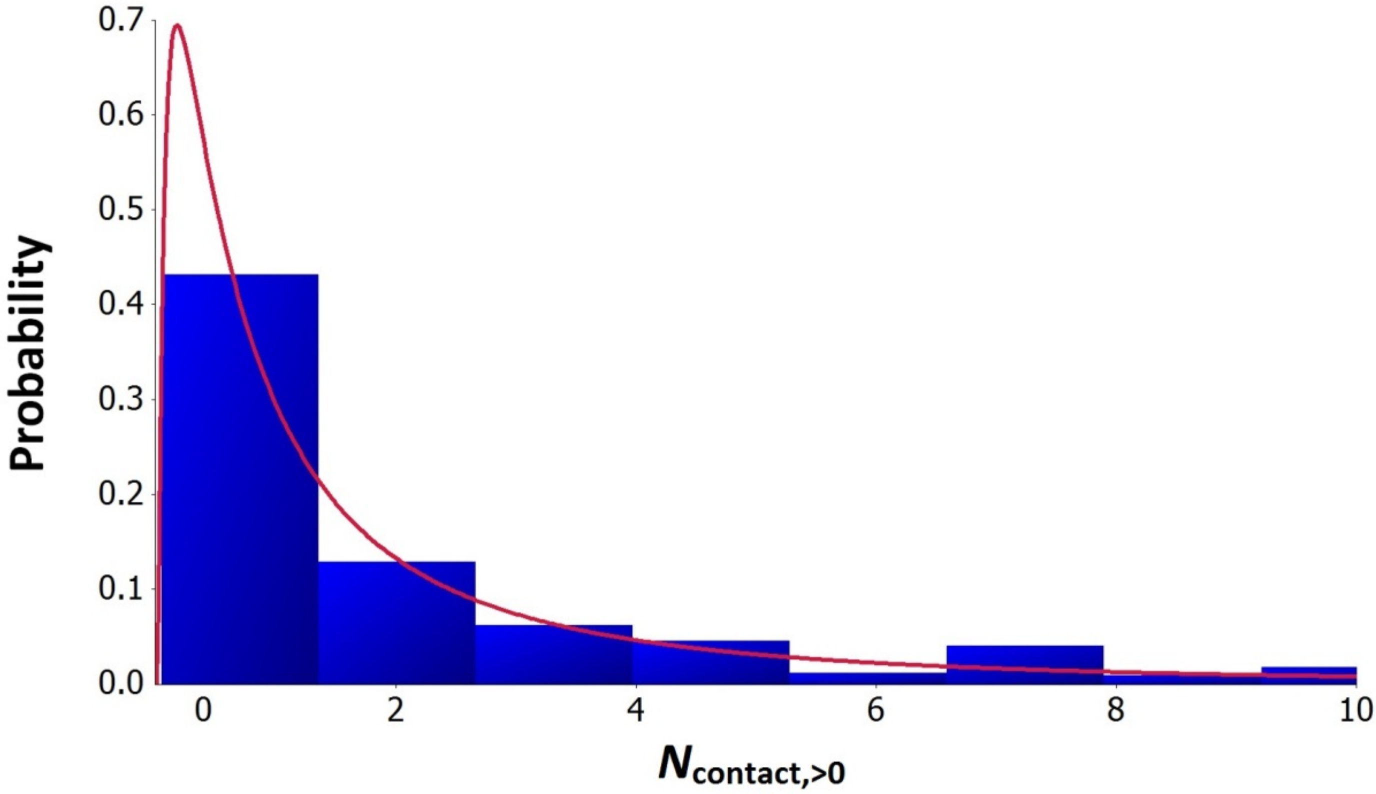


Table 3.1 Summary information on the valid responses (*n*=1,151) to the online questionnaire distributed to insured dog owners of Anicom Insurance Inc. during 7 April 2017 and 17 May 2017

Q1. Demographics	
a) Gender (*n*=1,150)	➢ Male: 25.8% ➢ Female: 74.2%
b) Age (*n*=1,143)	➢ <20s: 0.3% ➢ 20s: 2.4% ➢ 30s: 10.1% ➢ 40s: 30.3% ➢ 50s: 35.8% ➢ 60s: 16.9% ➢ ≥70s: 4.2%
c) Household status (*n*=1,146)	➢ Single (living alone): 8.9% ➢ Multiple (at least 2 persons): 91.1%
d) Region of residence (*n*=1,151)	➢ Hokkaido, Tohoku and Kitakanto: 8.9% ➢ Keihin: 52.0% ➢ Koshinestsu, Hokuriku and Chubu: 13.7% ➢ Kansai: 15.6% ➢ Chugoku and Shikoku: 3.9% ➢ Kyushu and Okinawa: 5.8%

Q2. Dog ownership and living style of the dog(s)	
a) Number of dogs owned (*n*=1,150)	➢ 1 dog: 76.7% ➢ 2 dogs: 18.8% ➢ 3 dogs: 2.8% ➢ 4 dogs or more: 1.7%
b) Breed size (*n*=1,135) *Breed groups were classified as follows- small: weight of <10 kg and withers height (WH) of <40 cm; medium: weight of 10 to 20 kg and WH of 40–50 cm; large: weight of >20 kg and WH of >50 cm	➢ Small: 82.2% ➢ Medium: 6.9% ➢ Large: 8.7% ➢ Mixed (when owner has at least two dogs which are in different size groups): 2.2%
c) Living style (*n*=1,150)	➢ Always indoor (i.e. the owner never brings the dog outside for a walk): 3.6% ➢ Indoor (and outdoor during walking): 92.5% ➢ 50% indoor + 50% outdoor, i.e. stay in the backyard or a confined space: 1.7% ➢ 50% indoor + 50% outdoor, i.e. allowed to roam freely: 1.4% ➢ Always outdoor and allowed to roam freely: 0.9%

Q3. Dog walking	
a) How often do you walk your dog? (*n*=1,109)	➢ Once a day: 31.4% ➢ Twice a day: 44.5% ➢ Three times a day: 7.2% ➢ Four times or more a day: 1.7% ➢ Five to six times a week: 2.8% ➢ Three to four times a week: 4.5% ➢ One to two times a week: 7.8%
b) At what time do you walk your dog? (*n*=1,110)	➢ Peak hours (6–9 am and/or 3–6 pm): 74.6% ➢ Non-peak hours: 25.4%
c) What is the average duration of each walk? (*n*=1,106)	➢ 15 minutes or less: 10.8% ➢ 30 minutes: 52.2% ➢ 1 hour: 30.9% ➢ 1 hour and 30 minutes: 4.3% ➢ 2 hours or more: 1.7%
d) How would you describe the nature of the walk? (*n*=1,097)	➢ Non-social (i.e. I walk my dog privately): 42.3% ➢ Social (i.e. I walk my dog to the park or places where I can meet my friends, etc.): 24.2% ➢ Mixed (i.e. sometimes social and sometimes non-social): 33.5%
e) How frequently (out of 10 walks) would your dog contact* (at least one) other dog in the street? (*n*=1,108) *Definition of contact here refers to the situation where your dog come close (within one metre) with another dog and has the chance to touch and interact with that dog. Please do not consider dogs that you see far way across the street.	➢ Never*: 16.6% ➢ 1–2 walks per 10 walks: 26.2% ➢ 3–4 walks per 10 walks: 19.1% ➢ 5–6 walks per 10 walks: 15% ➢ 7–8 walks per 10 walks: 12.4% ➢ 9–10 walks per 10 walks: 10.7% *Respondents who answered “never” here were directed to answer Q4 to complete the questionnaire, i.e. skipping Q3f–h.
f) For each walk, how many other dogs on average would your dog come into contact*? (*n*=925) *For example, your dog meets and contacts 1 dog on your way to the park, and then it plays with 2 other dogs at the park, the total number of contact would be 3.	➢ 1–2 dogs: 62.7% ➢ 3–4 dogs: 27.8% ➢ 5–6 dogs: 6.5% ➢ 7–8 dogs: 1.8% ➢ 9–10 dogs or more: 1.2%
g) How often do you sight a stray dog during a dog walk? (*n*=949)	➢ Never: 98.5% ➢ 1–2 walks per 10 walks: 1.4% ➢ 7–8 walks per 10 walks: 0.1%

h)	How often do you see a wild animal, e.g. fox and racoon dog, during a dog walk? (*n*=965)	➢ Never: 91.2% ➢ 1–2 walks per 10 walks: 8.3% ➢ 3–8 walks per 10 walks: 0.5%

Q4. Use of dog identification equipment and viewpoint towards dog rabies vaccination		
a)	Which of the following identification equipment does your dog wear? (*n*=1,137)	➢ Registration tag only: 3.8% ➢ Registration tag and microchip: 2.1% ➢ Registration tag and rabies vaccination tag: 12.5% ➢ Registration tag, rabies vaccination tag and microchip: 17% ➢ Microchip only: 26.6% ➢ Rabies vaccination tag and microchip: 9.1% ➢ None: 29%
b)	Do you vaccinate your dog against rabies? (*n*=1,142)	➢ Yes and every year: 93.2% ➢ Yes but not every year: 4% ➢ No: 2.8%
c)	Where do you attend for your dog's rabies vaccination? (*n*=1,117)	➢ Annual vaccination campaign: 8.6% ➢ Veterinary clinic: 87.9% ➢ Not fixed (sometimes campaign and sometimes clinic): 3.5%
d)	What is the reason you do not vaccinate your dog against rabies? (*n*=67)	➢ I think rabies vaccination is not necessary in Japan because the disease has not occurred in the country for many years: 22.4% ➢ I think rabies vaccination is not necessary for my dog, e.g. I do not walk my dog very often so the risk of contracting the disease is low: 4% ➢ My dog is not healthy for vaccination because it has long-term illness or other relevant medical conditions, e.g. experience of vaccine-associated adverse event: 68.7% ➢ A combination of the above reasons: 6%
e)	Considering the average price of a single rabies vaccination is ¥3304 (including the price of a certification tag) in Japan, what do you think is a reasonable/affordable price if the current price could be reduced? (*n*=997)	➢ The current price is fair: 42.1% ➢ ¥2000: 26.9% ➢ ¥1000: 19.8% ➢ ¥500: 3.5% ➢ Free: 7.7%
f)	If the current annual rabies vaccination policy could be amended to one with less frequent booster requirement, e.g. every 3 years, do you think it is a good idea? (*n*=640)	➢ Yes: 88.8% ➢ No: 11.3%

Table 3.2. Responses to the Likert items assessing the practices towards potential cases of rabies among dog owners (*n*=972)

Information is presented in terms of the mean and standard deviation of the responses to each item, their respective factor loadings[2] based on principle component analysis (PCA), internal consistency of the responses within each construct based on Cronbach's α and the total variance explained by each construct.

Likert items[1]	Mean	Standard deviation	Factor loadings		
			#1	#2	#3
<u>Construct #1: Responding to situations related to dog bite incident and injury from cat scratches during dog walking (Cronbach's α=0.79)</u>	2.99	0.90			
If my dog bites another dog in the street[3], I should take immediate actions such as bringing my dog to the vet for check-up and/or reporting this incident to the animal welfare centre or local health centre	2.73	1.23	0.84		
If my dog bites a person in the street[3], I should take immediate actions such as bringing my dog to the vet for check-up and/or reporting this incident to the animal welfare centre or local health centre	2.92	1.21	0.85		
If I am bitten by another pet dog in the street[3], I should take immediate actions such as seeing a doctor for check-up	3.28	1.01	0.73		
If I am scratched by a stray cat[3], I should take immediate actions including seeing a doctor for check-up	3.02	1.12	0.63		
<u>Construct #2: Responding to situations related to sighting a stray or wild animal during dog walking (Cronbach's α=0.64)</u>	3.70	0.58			
If I see a stray dog, I should not approach the animal, touch it or feed it	3.69	0.82		0.77	
If I see a wild animal such as fox or racoon dog, I should not approach the wild animal, touch it or feed it	3.92	0.46		0.71	
If I see a stray cat, I should not approach the	3.48	0.94		0.77	

wild animal, touch it or feed it					
<u>Construct #3: Responding to situations related to non-specific clinical signs of rabies and bite injury from stray dog or wild animals during dog walking (Cronbach's α=0.54)</u>	3.84	0.34			
If my dog starts to show any of the following signs: abnormal sound in barking, abnormal licking of water, restlessness and biting with no provocation, I should stop bringing my dog for a walk and take immediate actions such as bringing it to the vet for check-up	3.71	0.63			0.77
If I am bitten by a stray dog[3], I should take immediate actions such as seeing a doctor for check-up	3.89	0.43			0.53
If I am bitten by a wild animal such as fox or racoon dog[3], I should take immediate actions such as seeing a doctor for check-up	3.93	0.31			0.79
Total variance explained			24.7%	17.6%	16.4%

[1] Responses were measured on a 5-point Likert scale, i.e. 0 = strongly disagree, 1 = disagree, 2 = neutral, 3 = agree and 4 = strongly agree.

[2] The factor loadings of a principle component analysis (PCA) with varimax rotation are presented. Only factor loadings >|0.45| are shown, as this stands for 20% (or more) overlapping variance among the factors (Tabachnick & Fidell, 2013).

[3] The wound sustained has tiny bleeding

Table 3.3 Estimation of the probability of a companion dog having a contact with other dogs during dog walking ($P_{contact}$) and the associated (non-zero) daily contact rate ($N_{contact,>0}$) in Japan and the respective six regions

Region	$P_{contact}$*	Parameters of the fitted log-normal distribution of $N_{contact,>0}$**	
		Mean***	Standard deviation***
Japan (whole country)	0.83 (0.81 – 0.85)	2.73 (2.42 – 3.11)	6.39 (5.18 – 7.84)
Hokkaido, Tohoku and Kitakanto	0.81 (0.73 – 0.88)	1.66 (1.07 – 2.47)	3.58 (1.77 – 6.81)
Keihin	0.87 (0.85 – 0.90)	3.21 (2.74 – 3.75)	7.52 (5.71 – 9.81)
Koshinestsu, Hokuriku and Chubu	0.80 (0.73 – 0.86)	1.74 (1.29 – 2.36)	3.44 (2.07 – 5.75)
Kansai	0.77 (0.70 – 0.83)	3.12 (2.21 – 4.33)	7.92 (4.39 – 14.10)
Chugoku and Shikoku	0.80 (0.65 – 0.89)	1.35 (0.75 – 2.22)	2.56 (0.99 – 5.94)
Kyushu and Okinawa	0.77 (0.65 – 0.85)	2.29 (1.37 – 3.58)	4.67 (2.01 – 9.68)

*95% confidence interval was estimated using beta distribution assuming a non-informative prior

**Log-normal distribution was fitted by setting a minimum $N_{contact,>0}$ value of 0.01

***Estimated mean (95% confidence interval) are presented

Table 3.4 Association of the log-transformed daily contact rate between companion dogs during a walk ($N_{contact,log}$) with significant predictors including nature and duration of the walk, whether the walk is during peak hours, companion dog density of the prefecture where the owner lives, breed size of the dog and age of the owner modelled by multiple linear regression

Independent variables	Coefficient (B)	Standard error of B	Standardised coefficient (β)
Nature of the walk			
Social	2.36	0.14	0.48***
Mixed, i.e. sometimes social, sometimes private	1.76	0.12	0.39***
Private (reference)	0.00	-	-
Whether the walk is during peak hours (6–9 am and/or 3–6 pm)			
Yes	0.72	0.12	0.15***
No (reference)	0.00	-	-
Duration of the walk (hours)	0.60	0.15	0.11***
Companion dog density of the prefecture where the owner lives (number of dogs per km²)	0.001	0.0002	0.09***
Breed size of the dog(s)			
Medium breed, large breed or a combination of breed sizes (owners with at least two dogs)	0.41	0.14	0.08**
Small breed (reference)	0.00	-	-
Age of the owner (years)	0.11	0.05	0.05*
Constant	-3.62	0.26	0.00***
Model statistics	F (7, 1074) = 86.06, p = <0.0001; adjusted R^2 = 0.36		

*p<0.05

**p<0.001

***p<0.0001

Table 3.5 Association of the level of best practice towards potential cases of rabies among Japanese dog owners with significant predictors including age and region of residence the owner and breed size of the dog(s) modelled by multiple linear regression

Independent variables	**Coefficient (B)**	**Standard error of B**	**Standardised coefficient (β)**
Age of the owner (years)	0.12	0.03	0.14**
Region of residence			
Other regions, i.e. Hokkaido, Tohoku, Kitakanto, Keihin, Koshinestsu, Hokuriku and Chubu, Chugoku, Shikoku, Kyushu and Okinawa	0.25	0.08	0.10*
Kansai (reference)	0.00	-	-
Breed size of the dog(s)			
Medium breed, large breed or a combination of breed sizes (for owners with at least two dogs)	-0.20	0.07	-0.09*
Small breed (reference)	0.00	-	-
Constant	2.51	0.13	0.00**
Model statistics	F (3, 957) = 13.36, p = <0.0001; adjusted R^2 = 0.034		

*p<0.001

**p<0.0001

Study 4

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 meta-analysis

This study has been published in Preventive Veterinary Medicine, vol. 147, pp. 172–177, https://doi.org/10.1016/j.prevetmed.2017.09.007

Summary

Japan is one of the few rabies-free countries or territories which still implement the policy of mandatory vaccination of domestic dogs. Under the Rabies Prevention Law enacted since 1950, pet owners in Japan are obliged to vaccinate their dogs every year. However, the national vaccination rate is estimated to average 43% over the past decade. Given this low owner compliance, there is debate over whether or not the mandatory vaccination policy should be maintained and if it were to be maintained, whether the yearly booster requirement is necessary or not. Data on 144 companion dogs vaccinated with the Japanese rabies RC-HL strain vaccine was analysed using multiple logistic regression. An extensive literature review was conducted and five previous vaccination studies were selected for meta-analysis. Results of logistic regression indicate that the proportion of dogs having a satisfactory antibody level lasting for 12 months ($P\_protected_{12}$) with only one vaccination was 74.7% (95% prediction interval (PI): 51.4% – 90.5%). By contrast, $P\_protected_{12}$ for dogs vaccinated 2–4 times and 5 times or more was estimated as 96.6% (95%PI: 83.1% – 99.3%) and 98.7% (95%PI: 96.9% – 99.6%), respectively. Moreover, *P_protected* for 36 months would drop to 33.4% (95%PI: 11.4% – 71.6%) for dogs vaccinated only once, while it would be 83.0% (95% PI: 39.4% – 97.1%) and 93.0% (95%PI: 59.7% – 99.2%) for dogs vaccinated 2–4 times and 5 times or more, respectively. The pooled *P_protected* for at

least 12 months from meta-analysis was estimated as 83.8% (95%CI: 66.1% – 97.5%) for dogs vaccinated only once, while it was estimated as 94.7% (95%CI: 87.7% – 99.1%) for dogs vaccinated at least twice. Therefore, the yearly booster requirement of the current mandatory vaccination policy in Japan is reasonable in terms of its frequency. However, there is potential for future policy amendment to one that requires less frequent boosters, i.e. a booster is required within one year after primary vaccination and then every two to three years.

1. Introduction

Japan is one of the few rabies-free countries or territories which still implement the policy of mandatory vaccination of domestic dogs (Takahashi-Omoe et al. 2008). Under the Rabies Prevention Law enacted since 1950, pet owners in Japan are obliged to vaccinate their dogs every year by attending a veterinary clinic anytime during the year or a vaccination campaign organised by Japan Veterinary Medical Association (JVMA) and prefectural governments during April to June. In the decade 2007–2016, the reported national vaccination rate averages 73.1%, but the actual vaccination coverage is estimated to be 43.2% when adjusted for an average registration rate of 59.2% during the same period (MHLW 2017; JPFA 2018).

The rabies vaccine currently available in Japan is an inactivated cell culture vaccine prepared from the RC-HL strain of rabies virus (hereafter referred to as the Japanese rabies vaccine) (Ito et al. 2001). The efficacy of the Japanese rabies vaccine has already been evaluated in a number of previous studies with general agreement that the current policy of an annual booster is appropriate with the use of this vaccine (Ishikawa et al. 1989; Murakawa et al. 1991; Ezoe et al. 2007a, 2007b; Watanabe et al. 2013; Shiraishi et al. 2014). By contrast, some other rabies vaccines marketed overseas have different recommendations concerning the frequency of booster doses. For example, a booster is recommended one year after primary vaccination and then triennially (e.g. Rabvac® 3, Boehringer Ingelheim Vetmedica, Inc.) or a booster is recommended every 1, 2 or 3 years after primary vaccination (e.g. Rabisin, Merial) (Bahloul et al. 2006; Brown et al. 2016). Time, concern over the dog's health, unawareness of the obligation and the perception that Japan is safe from rabies are influential factors for owner compliance in vaccinating dogs in accordance with their obligation as highlighted in Study 3 and other previous studies (Anonymous 2015, 2016). The current low owner compliance in Japan raises the question as to whether or not the mandatory vaccination policy should be maintained and if it were to be maintained, whether the yearly booster requirement is necessary. The present study aimed to assess the efficacy of the Japanese rabies vaccine for different durations, thereby enabling evidence-based recommendations to be introduced as so potentially to strengthen the current canine rabies prevention system in Japan.

2. Materials and methods

2.1 Data collection

During 2012 to 2015, serum samples of 158 companion dogs were collected during routine rabies vaccination at 15 veterinary clinics situated in Tokyo and run by members of Tokyo Veterinary Medical Association. Summary reports of this survey were published in Japanese in the Tokyo Veterinary Journal (Anonymous 2015, 2016). All these dogs were vaccinated at least once using a commercial Japanese rabies vaccine. Information on age, sex, breed and age of first vaccination of the dog was also collected. Virus neutralisation test (VNT) based on the cytopathic effect using HmLu-1 cells and RC-HL strain of rabies virus was performed to measure the serum antibody level and a titre of ≥1:25 was considered satisfactory (equivalent to the OIE standard of ≥0.5 IU/ml) (Ezoe et al. 2007a, 2007b). We selected data on 144 dogs for the analyses described below based on two criteria: firstly, the total number of vaccinations that the dog has received is known and secondly, the duration between last vaccination and the day of blood collection was at least 12 months (Table 4.1).

2.2 Prediction model using multiple binomial logistic regression

Simple binomial logistic regression was first performed using potential predictors such as the number of vaccinations and age of the dog as independent variables and whether the dog had a satisfactory rabies antibody titre as the dependent variable. Age, sex, weight and breed (breed size and mixed breed or not) of the dog were excluded from the final model since no statistically-significant associations (at $p<0.1$) could be observed (Table 4.2). The Hosmer and Lemeshow goodness-of-fit test was used to decide whether the independent variable to be included in the final model should be continuous or categorical. Thus, the number of vaccinations (categorical: once (reference) vs 2–4 times vs 5 times or more) and duration (in months) since last vaccination were included in the multiple logistic regression model. Age of first vaccination was excluded because it is negatively correlated with the number of vaccinations (rho=-0.553, $p<0.01$), i.e. a dog that started its first vaccination at a younger age was more likely to have received a higher number of vaccinations. Finally, the proportion of vaccinated dogs having a satisfactory antibody level (*P_protected*) was estimated using the following logistic regression equation of the final model:

$$P\_protected = \frac{1}{1+e^{-(\beta_0+\beta_1 * x_{2\text{–}4\ \text{times}}+\beta_2 * x_{\geq 5\ \text{times}}-\beta_3 * x_{\text{months elapsed}})}}$$

where $X_{2\text{–}4\ \text{times}}$ and $X_{\geq 5\ \text{times}}$ can take a value of either 0 or 1 and $X_{\text{months elapsed}}$ can take any value indicating the duration in months since last vaccination; β_0 is the constant and β_1, β_2 and β_3 are the slope coefficients, all of which are modelled with normal distribution using simulation.

All statistical analyses were performed using the SPSS ver. 23 (IBM Corp., Armonk, NY, USA). The final multiple logistic regression model was built in Microsoft Excel 2016 and run with 1000 iterations for each simulation using Latin Hybercube sampling with @RISK ver. 7.5.1 (Palisade Corp.).

2.3 Meta-analysis of past vaccination studies to estimate a pooled P_protected

A systemic search of published literature was conducted on PubMed, Web of Science and J-STAGE (Japan Science and Technology Information Aggregator, Electronic) using the keywords "Japan", "rabies" and "vaccine". A total of 385 article titles (including duplicates) were screened and 11 research articles related to the efficacy of the Japanese rabies vaccine in dogs were identified. Of these, five vaccination studies with information on the efficacy for a 12-month period were selected for meta-analysis (Table 4.3).

An inverse variance heterogenicity (IVhet) model was used for the meta-analysis because it has the advantage of favouring studies with larger sample size while reflecting more uncertainty around the pooled estimate (i.e. a wider 95% confidence interval that retains a correct coverage probability) and therefore it is less likely to result in underestimation of statistical error when compared to the random effects model (Doi et al. 2015). *P_protected* of each vaccination study was double-arcsin transformed to stabilise its variance for the meta-analysis (Barendregt et al 2013). τ^2 (between-study variance), I^2 (proportion of variability in the pooled estimate that is due to τ^2 rather than within-study error) and Cochran's Q test (under the null hypothesis of no heterogeneity) were used to assess study heterogeneity (Higgins

2008; Rücker et al. 2008). Potential publication selection bias was monitored using Doi plot and LFK index. The interpretation of Doi plot is similar to that of funnel plot, where an asymmetrical plot alerts the researcher to suspect publication bias, while a symmetrical one does not. For the LFK index, no asymmetry (hence potential publication bias) is suspected if it is within ±1, while minor asymmetry is suspected if it exceeds ±1 but within ±2 and major asymmetry is suspected if it exceeds ±2. All statistical analyses were performed using MetaXL ver. 5.3 (Epigear International, QLD, Australia).

3. Results

Results of multiple logistic regression are summarised in Table 4.4. When compared to dogs vaccinated only once, dogs vaccinated 2–4 times and those vaccinated 5 times or more had a higher probability of having a satisfactory rabies antibody level with an odds ratio of 9.48 (95%CI: 2.76 – 32.53) and 25.44 (95%CI: 5.14 – 125.99), respectively. The duration in months since last vaccination was negatively associated with the probability of having a satisfactory antibody level with an odds ratio of 0.93 (95%CI: 0.90 – 0.96). The mean proportion of dogs having a satisfactory antibody level lasting for 12 months ($P\_protected_{12}$) with only one vaccination was estimated as 74.7% (95% prediction interval (PI): 51.4% – 90.5%) (Table 4.5 & Fig. 4.1). By contrast, *P_protected*$_{12}$ for dogs vaccinated 2–4 times and 5 times or more was estimated as 96.6% (95%PI: 83.1% – 99.3%) and 98.7% (95%PI: 96.9% – 99.6%), respectively. Moreover, *P_protected* for 36 months would drop to 33.4% (95% PI: 11.4% – 71.6%) for dogs vaccinated only once, while it would be 83.0% (95%PI: 39.4% – 97.1%) and 93.0% (95%PI: 59.7% – 99.2%) for dogs vaccinated 2–4 times and 5 times or more, respectively.

Results of meta-analysis are illustrated in Fig. 4.2. The pooled *P_protected* for at least 12 months was estimated as 83.8% (95%CI: 66.1% – 97.5%) for dogs vaccinated only once, while it was estimated as 94.7% (95%CI: 87.7% – 99.1%) for dogs vaccinated at least twice. Meta-analysis of *P_protected* (1 vaccination) showed mild study heterogenicity while meta-analysis of *P_protected* (at least 2 vaccinations) showed no heterogenicity. No publication bias was suspected in either meta-analysis (Fig. 4.3).

4. Discussion

The current study first evaluated the efficacy of the Japanese rabies vaccine in dogs using logistic regression, revealing that the proportion of dogs reaching a satisfactory antibody level depends on the number of vaccinations and the duration since last vaccination, but is independent of the dog's age, sex, weight and breed (breed size and whether the dog is a mixed breed or not). Such results are mostly consistent with a number of previous studies concerning the efficacy of rabies vaccines marketed overseas, particularly in Europe (Kennedy et al. 2007; Zanoni et al. 2010; Berndtsson et al. 2011; Rota Nodari et al. 2017; Yakobson et al. 2017). These overseas studies further showed that the efficacy of rabies vaccine varied significantly between different brands. In addition, higher success rates of having a satisfactory antibody level were found in certain dog breeds, illustrating either an effect of small size or cross-breeding, or a combination of both; while this could not be demonstrated in the current study.

Meta-analysis of previous vaccination studies was subsequently conducted and the results agree with those of logistic regression, both highlighting that the proportion of dogs having a satisfactory antibody level for at least 12 months with only one vaccination is much lower than that of dogs with at least two vaccinations. Since the late 1980s, Ishikawa et al. (1989) reported that the Japanese rabies vaccine could induce a high booster (anamnestic) response in dogs vaccinated twice within a 12-month interval, while Murakawa et al. (1992) showed that only 60% of the dogs vaccinated once could maintain a satisfactory antibody level for 12 months. There are also studies indicating that the efficacy of the vaccine is relatively low in puppies less than one year old (Shimazaki et al. 2003; Saeki et al. 2015). In addition, the efficacy of the vaccine in cats appeared similar to that in dogs (Ezoe et al. 2007a; Shiraishi et al. 2014).

Although the present study included 144 companion dogs from Tokyo only (one of the 47 prefectures of Japan), the study dog population seems to be representative of the current situation of Japan, as depicted by the annual national online survey conducted by the Japan Pet Food Association, e.g. small breed dogs accounted for 88.2% of the current study dog population, while small breed dogs accounted for at least 80.8% of the survey population (n=1,259); dogs aged seven years or above accounted for 56.7% of the study population, while this age group was 58.6% in the survey population (JPFA 2015; Table 4.1). In contrast, it is difficult to assess whether the study subjects of the previous vaccination studies included in the meta-analysis were representative of the general population of the respective study year because key information such as age and breed of the dogs is not provided (the experimental studies by Ishikawa et al. 1989, Ezoe et al. 2007b and Shiraishi et al. 2014 used Beagle as the subject). Nonetheless, these previous studies provide valuable past data from different prefectures of Japan including Oita, Kumamoto and Chiba (Table 4.3).

Finally, the current study followed the OIE standard using 0.5 IU/ml as a cut-off for a satisfactory antibody level, which is considered a conservative threshold as laboratory dogs with antibody titres ≥0.05 and ≥0.1 IU/ml had a 95% and 100% survival rate, respectively, when challenged with rabies virus (Aubert 1992; Moore & Hanlon 2010).

The results of the present study demonstrate that the current annual rabies vaccination policy in Japan is reasonable in terms of its frequency. There is also a potential for policy amendment to one that requires less frequent boosters given that 83% of the dogs vaccinated twice could theoretically maintain a satisfactory antibody level for three years, i.e. the new policy could require a booster one year after primary vaccination and then every two to three years (Table 4.5 and Fig. 4.1). Considering a puppy which receives its first vaccination at three-month old (to ensure minimal interference from any residual maternal antibodies) and the first booster at one-year old, it could receive a third vaccination at three-year old and complete five vaccinations by seven years of age, after which it could receive a booster every three years, i.e. a sixth vaccination at ten years of age. Such vaccination schedule also applies to any adult dog which is not previously vaccinated; on the other hand, if three years have already passed since the dog was last vaccinated, it would need to receive two rabies vaccination within a one-year period again as a starter course. Relaxing the requirement for re-vaccination could potentially promote greater owner compliance to the mandatory vaccination policy in Japan, particularly from those who worry that their dogs may experience vaccine-associated adverse events (VAAE) as a result of frequent vaccinations. A dog owner survey (*n*=111) conducted by Tokyo Veterinary Medical Association during 2012 to 2015 revealed that the top reasons why owners do not vaccinate their dogs against rabies every year were: firstly, the dog is in a medical condition not suitable for vaccination (32%); secondly, the dog's health deteriorates after vaccination (21%); and thirdly, the time factor of the owner (16%). Thirteen percent of the owners did not know that rabies vaccination is compulsory (Anonymous 2015, 2016).

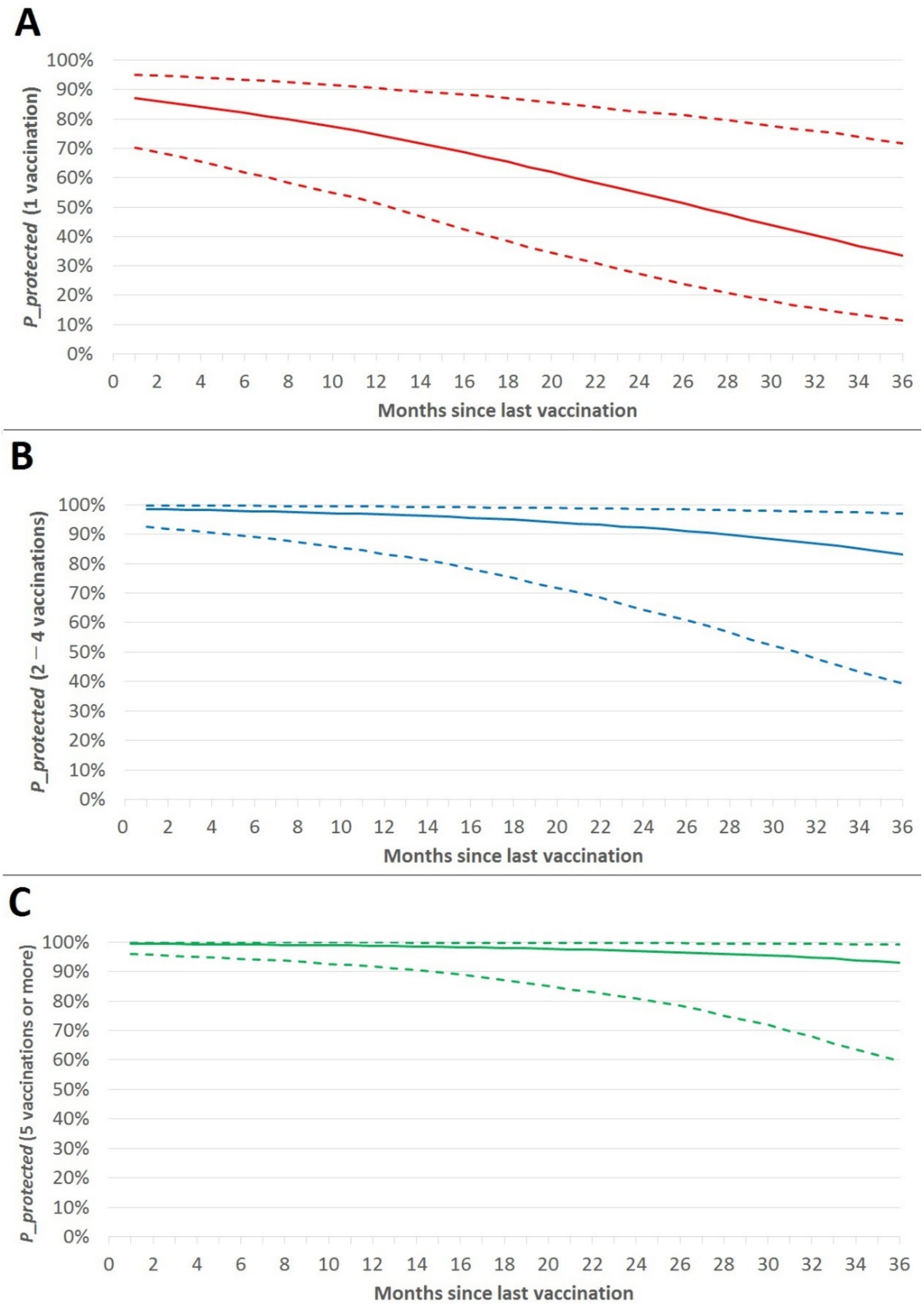
The reason that certain overseas rabies vaccines have less frequent booster requirement is most probably due to the inclusion of adjuvant such as aluminum hydroxide in Rabisin (the Japanese rabies vaccine does not include any adjuvant). Aluminum has been a popular adjuvant for more than 70 years with good safety record and is also used in the development of rabies DNA vaccine for human use (HogenEsch 2013; Garg et al. 2017). The cumulative incidence of vaccine-associated adverse events (VAAE) for the Japanese rabies vaccine was reported as 0.6 per 10,000 vaccinated dogs (based on official report to the National Veterinary Assay Laboratory (NVAL)) and was lower than that of four other combination vaccines (ranged from 1.4 to 4.7 per 10,000 vaccinated dogs) (Gamoh et al. 2008). On the other hand, a survey of 573 veterinary clinics in Japan during 2006–2007 revealed that the incidence of VAAE for non-rabies combination vaccines was up to 62.7 per 10,000 vaccinated dogs, hence indicating that the official data from NVAL is likely to be an under-reporting of the true incidence (Miyaji et al. 2012). Similarly, Moore et al. (2005) estimated that the incidence of VAAE for rabies vaccine in the United States ranged from 0 (dogs weighed >45 kg) to 32.1 (dogs weighed ≥10 kg) per 10,000 dogs vaccinated. These findings highlight that one should exercise a less frequent vaccination regimen whenever possible in an aim to prevent the suffering of companion dogs from VAAE.

5. Conclusions

The efficacy of the Japanese rabies vaccine for a 12-month period is high in dogs vaccinated at least twice, while it is relatively low in dogs vaccinated only once. It can therefore be concluded that the yearly booster requirement of the current mandatory vaccination policy in Japan is reasonable in terms of its frequency. There is also potential for future policy amendment to one that requires less frequent boosters, i.e. a booster is required one year after primary vaccination and then every 2 – 3 years.

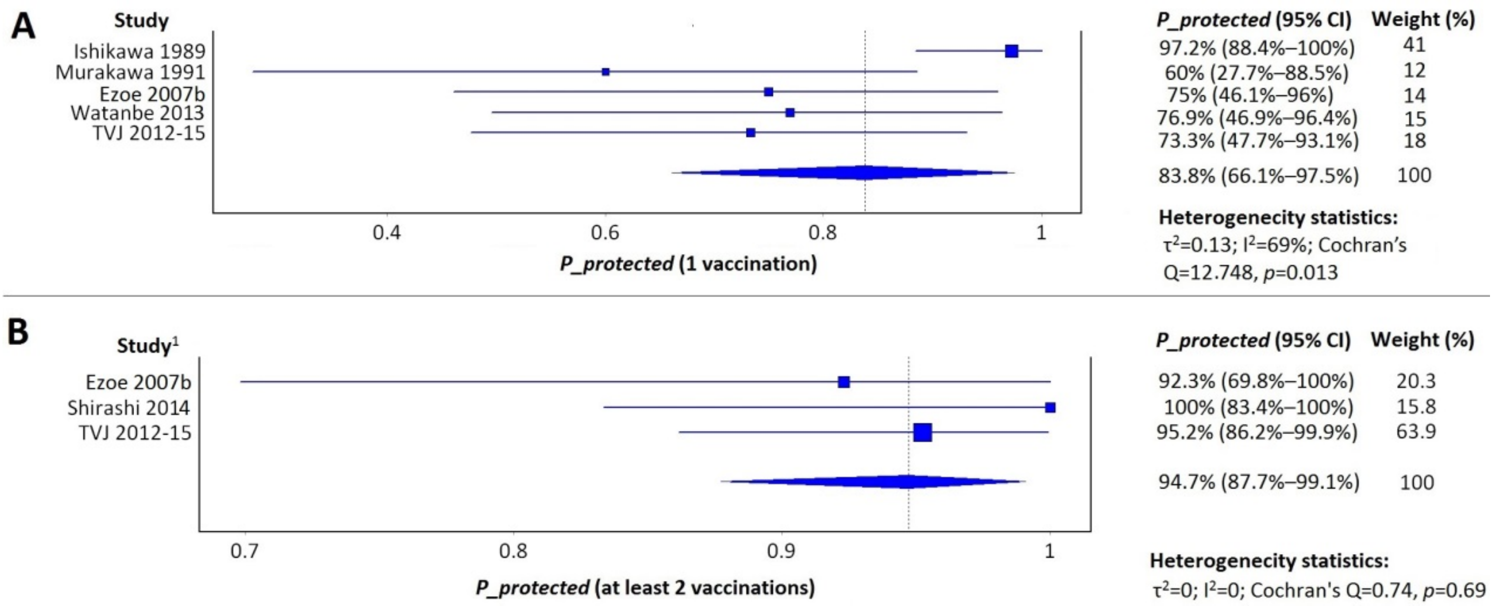
6. Figures and tables

Fig. 4.1 Changes in the proportion of dogs vaccinated with the Japanese rabies vaccine and having a satisfactory antibody level (*P_protected*) during a 3-year period: dogs vaccinated only once (A), dogs vaccinated 2–4 times (B) and dogs vaccinated 5 times or more (C)



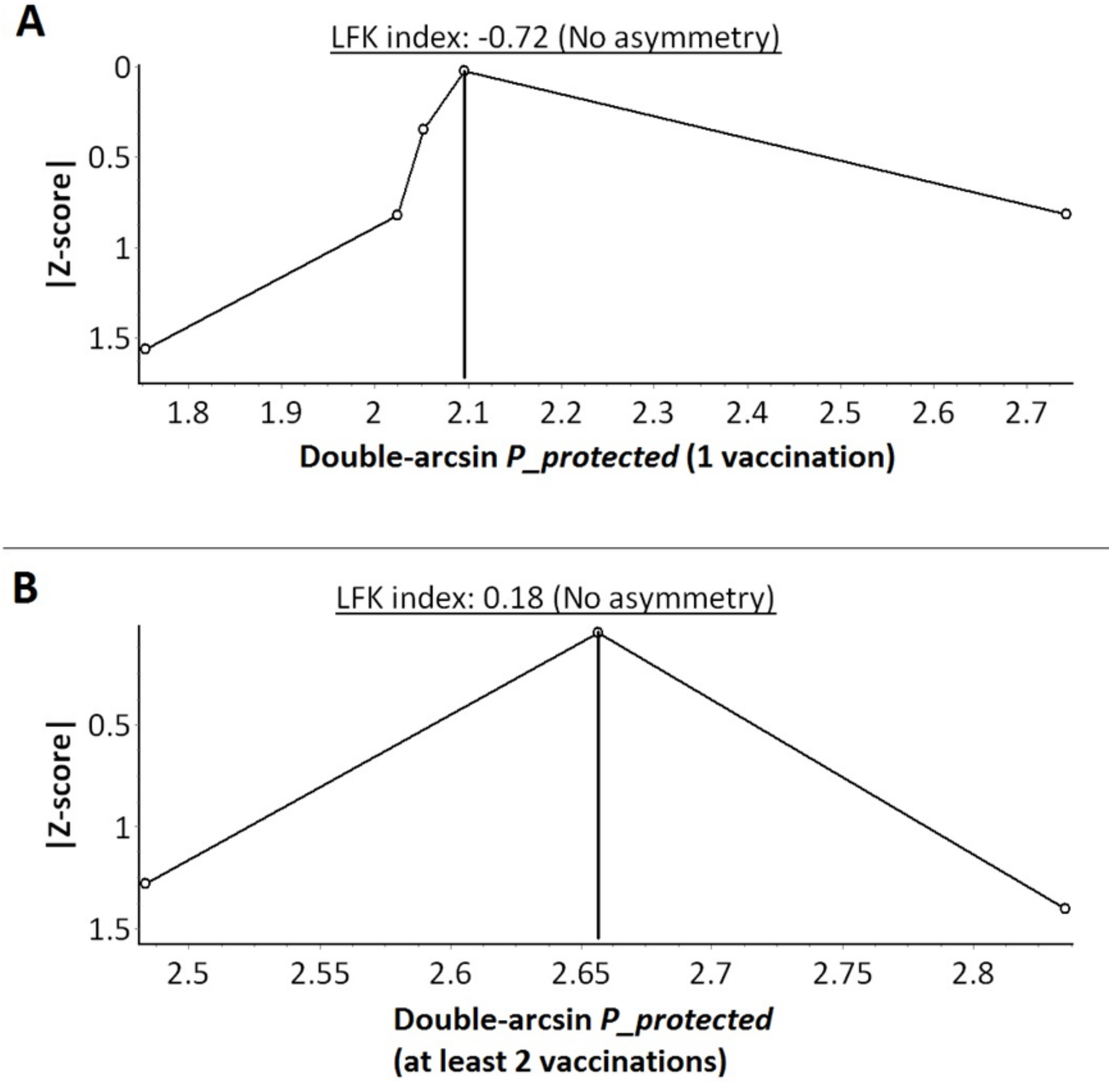
The solid line indicates the median while the dashed lines indicate the 95% prediction interval.

Fig. 4.2 Forest plots of the proportion of dogs vaccinated with the Japanese rabies vaccine and having a satisfactory antibody level for at least 12 months derived from vaccination studies conducted since 1989: dogs vaccinated only once (A) and dogs vaccinated at least twice (B)



[1] Study by Watanabe et al. (2013) was excluded to minimise potential publication bias (see Fig. 4.3)

Fig. 4.3 Doi plots assessing potential publication selection bias within the meta-analysis of *P_protected* (dogs vaccinated only once) (A) and *P_protected* (dogs vaccinated at least twice) (B)



No publication bias is suspected in either meta-analysis as there is no asymmetry of the Doi plot and the LFK index is within ±1.

Table 4.1 Descriptive statistics of the 144 companion dogs which were vaccinated at least once using the Japanese rabies vaccine

Parameter	Distribution
Sex	Male: 26.4%; Male castrated: 20.1%; Female: 20.8%; Female spayed: 29.2%; Unknown: 3.5%
Breed sizes[1]	Small: 88.2%; Medium: 2.1%; Large: 9.7%
Pure breed or mixed breed	Pure breed: 87.5%; Mixed breed: 12.5%
Age (months)	Mean: 105, SD: 46; Range: 16–215
Age of first vaccination (months)	Mean: 46, SD: 42; Median: 29; Range: 11–208
Duration between last vaccination and day of blood collection (months)	Mean: 33, SD: 25; Median: 22; Range: 12–131
Number of vaccinations	Once: 27.1%; 2 to 4 times: 41%; 5 times or more: 31.9%
Proportion with satisfactory neutralizing antibody titer (≥1:25)	Once: 43.6%; 2 to 4 times: 78%; 5 times or more: 93.5%

[1] Breed sizes were classified as follows- small: weight of <10 kg and withers height (WH) of <40 cm; medium: weight of 10 to 20 kg and WH of 40–50 cm; large: weight of >20 kg and WH of >50 cm

Table 4.2 Association between the probability of having a satisfactory rabies antibody level and the dog's age, sex, weight and breed (breed size and mixed breed or not) predicted by simple binomial logistic regression

No statistically-significant associations (at $p<0.01$) could be observed and so these predictors were excluded from the final multiple logistic regression model.

Variable	Coefficient (β)	Standard error of β	Odds ratio	95% CI of odds ratio	*p*-value
Constant	0.87	0.47	-	-	0.063
Age (months)	0.001	0.004	1.00	0.99 – 1.01	0.726
Model statistics	χ^2 (1) = 0.124, p = 0.725; Nagelkerke R^2 = 0.001; Hosmer and Lemeshow test: p = 0.933				

Variable	Coefficient (β)	Standard error of β	Odds ratio	95% CI of odds ratio	*p*-value
Constant	0.85	0.40	-	-	0.03
Sex (categorical variable)					
Female (reference)	0.00	-	1.00	-	-
Female spayed	0.07	0.53	1.07	0.38 – 3.00	0.895
Male	0.18	0.54	1.20	0.41 – 3.48	0.737
Male castrated	0.30	0.59	1.35	0.43 – 4.27	0.613
Model statistics	χ^2 (1) = 0.31, p = 0.958; Nagelkerke R^2 = <0.003; Hosmer and Lemeshow test: p = 1				

Variable	Coefficient (β)	Standard error of β	Odds ratio	95% CI of odds ratio	*p*-value
Constant	1.05	0.27	-	-	<0.0001
Weight (kg)	0.004	0.02	1.00	0.96 – 1.05	0.847
Model statistics	χ^2 (1) = 0.038, p = 0.836; Nagelkerke R^2 = <0.0001; Hosmer and Lemeshow test: p = 0.03				

Variable	Coefficient (β)	Standard error of β	Odds ratio	95% CI of odds ratio	*p*-value
Constant	1.09	0.20	-	-	<0.0001
Breed size (categorical variable)					

Small (reference)	0.00	-	1.00	-	-
Medium	-0.40	1.24	0.67	0.06 – 7.68	0.75
Large	-0.50	0.59	0.61	0.19 – 1.94	0.4
Model statistics	χ^2 (1) = 0.753, p = 0.686; Nagelkerke R^2 = <0.008; Hosmer and Lemeshow test: p = 1				

Variable	Coefficient (β)	Standard error of β	Odds ratio	95% CI of odds ratio	*p*-value
Constant	1.25	0.57	-	-	0.027
Mixed breed or not (categorical variable)					
Pure breed (reference)	0.00	-	1.00	-	-
Mixed breed	0.26	0.60	1.29	0.40 – 4.20	0.669
Model statistics	χ^2 (1) = 0.19, p = 0.66; Nagelkerke R^2 = <0.002; Hosmer and Lemeshow test: p = <0.0001				

Table 4.3 Summary information on six vaccination studies assessing the efficacy of the Japanese rabies vaccine for a (at least) 12-month period selected for meta-analysis

Study title	Study type	Study location	Serological test[1]	*P_protected* (1 vaccination)	*P_protected* (at least 2 vaccinations)
Ishikawa et al. 1989	Experimental	Not mentioned	Virus neutralization test based on cytopathic effect (VNT)	97.2% (*n*=36)[2]	n/a
Murakawa et al. 1992	Experimental	Kumamoto	VNT	60% (*n*=10)[2]	n/a
Ezoe et al. 2007b	Experimental	Not mentioned	VNT	75% (*n*=12)[2]	92.3% (*n*=13)[2]
Watanbe et al. 2013	Observational	Oita and Tokyo	Rapid fluorescent focus inhibition test (RFFIT)	76.9% (*n*=13)[4]	97.9% (*n*=145)[5]
Shiraishi et al. 2014	Experimental	Chiba	Fluorescent antibody virus neutralization test (FAVN)	n/a	100% (*n*=10)[2]
Tokyo Veterinary Journal 2012–15[6]	Observational	Tokyo	VNT	73.3% (*n*=15)[7]	97.2% (*n*=42)[7]

[1] An antibody titre of ≥1:25 using VNT or ≥0.5 IU/ml using RFFIT or FAVN was considered satisfactory

[2] Serological test was performed 12 months since last vaccination

[3] Observational study refers to the collection of serum samples from dogs with known vaccination history at veterinary clinics

[4] Serological test was performed a least 13 months since last vaccination

[5] Serological test was performed 13–18 months since last vaccination

[6] Data selected by the author for meta-analysis

[7] Serological test was performed 12–18 months since last vaccinat

Table 4.4 Association between the probability of having a satisfactory rabies antibody level and number of vaccinations and duration since last vaccination predicted by multiple logistic regression

Variable	Coefficient (β)	Standard error of β	Odds ratio	95% CI of odds ratio	*p*-value
Constant	1.98	0.54	-	-	<0.0001
Number of vaccinations					
1 time (reference)	0.00	-	1.00	-	-
2 to 4 times	2.25	0.63	9.48	2.76 – 32.53	<0.0001
5 times or more	3.27	0.82	25.44	5.14 – 125.99	<0.0001
Duration since last vaccination (months)	-0.07	0.01	0.93	0.90 – 0.96	<0.0001
Model statistics	χ^2 (3) = 71.814, p = <0.0001; Nagelkerke R^2 = 0.574; Hosmer and Lemeshow test: p = 0.691				

Table 4.5 Proportion of dogs vaccinated with the Japanese rabies vaccine and having a satisfactory antibody level lasting for 12 months ($P\_protected_{12}$), 24 months ($P\_protected_{24}$) and ($P\_protected_{36}$)[1]

Number of vaccinations	$P\_protected_{12}$	$P\_protected_{24}$	$P\_protected_{36}$
1 time	74.7% (51.4% – 90.5%)[2]	54.8% (27.2% – 82.4%)	33.4% (11.4% – 71.6%)
2 to 4 times	96.6% (83.1% – 99.3%)	92.1% (64.2% – 98.5%)	83.0% (39.4% – 97.1%)
5 times or more	98.7% (96.9% – 99.6%)	96.9% (76.2% – 99.6%)	93.0% (59.7% – 99.2%)

[1] $P\_protected_{12}$, $P\_protected_{24}$ and $P\_protected_{36}$ were calculated by setting the duration since last vaccination ($X_{\text{months eplased}}$) in the logistic regression equation as 12, 24 and 36, respectively

[2] Median (95% prediction interval) of the simulated values are presented

Study 5

Benefit-cost analysis of the policy of mandatory annual rabies vaccination of domestic dogs in rabies-free Japan

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Summary

Japan is one of the few rabies-free countries/territories which implement the policy of mandatory vaccination of domestic dogs. In order to assess the economic efficiency of such policy in reducing the economic burden of a future canine rabies outbreak in Japan, a benefit-cost analysis (BCA) was performed using probabilistic decision tree modelling. Input data derived from simulation results of published mathematical model, field investigation conducted by the author at prefectural governments, literature review, international or Japanese database and empirical data of rabies outbreaks in other countries/territories. The current study revealed that the annual costs of implementing the current vaccination policy would be US$160,472,075 (90% prediction interval [PI]: $149,268,935 – 171,669,974). The economic burden of a potential single canine rabies outbreak in Japan were estimated to be US$1,682,707 (90% PI: $1,180,289 – 2,249,283) under the current vaccination policy, while it would be US$5,019,093 (90% PI: $3,986,882 – 6,133,687) under hypothetical abolition of vaccination policy, which is 3-fold higher. Under a damage-avoided approach, the annual benefits of implementing the current vaccination policy in expected value were estimated to be US$85.75 (90% PI: $55.73 – 116.89). The benefit-cost ratio (*BCR*) was estimated to be 5.35 X 10^{-7} (90% PI: 3.46 X 10^{-7} – 7.37 X 10^{-7}), indicating that the implementation of the current policy is very economically inefficient for the purpose

of reducing the economic burden of a potential canine rabies outbreak. In worse-case scenario analysis, the *BCR* would become above 1 (indicating economic efficiency) if the risk of rabies introduction increased to 0.04 corresponding to a level of risk where rabies would enter Japan in 26 years while the economic burden of a rabies outbreak under the abolition of vaccination policy increased to $7.53 billion. Best-case analysis further revealed that under relatively extreme circumstances the economic efficiency of the current policy could be improved by decreasing the vaccination price charged to dog owners, relaxing the frequency of vaccination to every two to three years and implementing the policy on a smaller scale, e.g. only in targeted prefectures instead of the whole Japan.

1. Introduction

Japan is one of the few rabies-free countries/territories which still implement the policy of mandatory vaccination of domestic dogs (Takahashi-Omoe et al. 2008). In accordance with the Rabies Prevention Law enacted since 1950, the policy of registration and vaccination of domestic dogs against rabies is enforced by the prefectural governments under the order of Ministry of Health, Labour and Welfare (MHLW) (Takahashi-Omoe et al. 2008). Pet owners in Japan are obliged to vaccinate their dogs against rabies every year either by attending a private veterinary clinic anytime during the year or a vaccination campaign organised by prefectural governments and Japan Veterinary Medical Association (JVMA) during April to June. Each year the respective prefectural government would assign the duty and provide a fund to the local Veterinary Medical Association to organise the rabies vaccination campaign mentioned above in multiple cities within the prefecture. During the decade 2007–2016, the official national vaccination rate reported by MHLW averages 73.1%; the actual vaccination coverage is however estimated to be only 43.2% when adjusted for the estimated registration rate (which averages 59.2% during the same period) (MHLW 2017; JPFA 2018).

The current risks of rabies re-introduction into Japan have recently been assessed as very low in Study 1 and 2 and it would take on average 49,444 years until the introduction of one rabies case through the importation of dogs and cats worldwide due to a strict import regime managed by the Ministry of Agriculture, Forestry and Fisheries of Japan (MAFF). Further, mathematical simulation model predicted a very low risk of local spread, if rabies were to be introduced into Japan, as the mean outbreak size was estimated to be 3.1 and 4.7 dogs in Hokkaido and Ibaraki Prefectures, respectively (Kadowaki et al. 2018). Together with the low owner compliance mentioned above, massive debate has been raised in the country over whether the current annual rabies vaccination policy in domestic dogs should be maintained.

The main advantage of implementing a pre-emptive vaccination policy in a rabies-free setting is that it facilitates a pre-existing herd immunity which could lessen the magnitude or impact of an introduced outbreak. For canine rabies-endemic countries/territories, the World Health Organization (WHO) recommends a minimum 70% vaccination coverage in domestic dog population as the most cost-effective control measure (Laven et al. 2017). In contrast, there is no international standard on the prevailing conditions that should prompt a rabies-free country/territory to implement a pre-emptive vaccination policy (WHO 2018b). Major rabies-free countries including United Kingdom, France and Australia generally perceive that early detection of suspected cases and an immediate response to contain the outbreak are the key in controlling a rabies incursion. Alternatively, Hong Kong has been a rabies-free territory since 1988, enforcing a compulsory triennial dog vaccination policy to manage the significant risk of rabies introduction from the neighbouring China. Likewise, Malaysia (rabies-free until 2015) and Taiwan (rabies-free until 2013) have been adopting their specific pre-emptive rabies vaccination strategy, i.e. for Malaysia, an immune belt of dog vaccination along the border with Thailand; for Taiwan, compulsory vaccination in both domestic dogs and cats (Bamaiyi 2015; Chang et al. 2016).

Benefit-cost analysis (BCA) is an important tool at both a global and national level that illustrates the benefits of disease management projects per dollar spent and determines the economic efficiency of alternative management actions (FAO 2016). BCA on the control interventions against various animal diseases have been conducted, particularly on the oral vaccination against wildlife rabies (Sterner et al. 2009; Shwiff et al. 2016). The current study aimed to perform a BCA using decision tree modelling to assess the economic efficiency of the current annual rabies vaccination policy in domestic dogs in Japan and serve as a pilot study providing scientific insight into the rationale behind the maintenance of such policy.

2. Materials and Methods

2.1 Decision tree model and cost estimation framework

A stochastic decision tree model was constructed comparing two strategies: 1) under the current annual vaccination policy a rabid dog is introduced into Japan resulting in an outbreak and 2) under hypothetical abolition of vaccination policy a rabid dog is introduced into Japan resulting in an outbreak with greater impact (Fig. 5.1). The annual probability of rabies introduction into Japan through the international importation of dogs and cats identified in Study 1 (*P_annual*), i.e. 2.57×10^{-5}, was input into the relevant chance nodes of the decision tree, while the effect of any increase in the risk of rabies introduction, e.g. illegal importation, was tested in scenario analysis described below. There are potentially other rabies entry pathways, e.g. via fishing boat, passenger ferry and shipping containers. However, it was assumed that the risk of introduction would not increase significantly even if the base model took into account the risk of introduction through these pathways, which is a reasonable assumption considering the very small number of dogs and cats imported through these pathways and the results of Study 2. Finally, it should be noted that rabies introduction via the land route was not considered given that Japan is geographically isolated by the sea. The time horizon of the model was one year and so no discount rate was applied to the calculations of benefits and costs. The monetary values reported in the current study were based on the exchange rate of 1 US dollar = 112.17 Japanese yen (2017 World Bank data).

The present BCA adopted a societal perspective where the benefits and costs of maintaining the current annual rabies vaccination policy were considered for every relevant stakeholder in the community. In essence, such policy was considered to benefit everyone in the community since it could reduce the impact of a potential rabies outbreak (in terms of both the number of cases and the duration), hence decreasing the economic burden of the outbreak in terms of lower costs in implementing rabies control measures for the government and lower risk of contracting rabies for the local people (which would lead to fewer people receiving medical treatment as well as a lower probability of human death). Hence, the benefits of maintaining the current rabies vaccination policy were calculated as incremental benefits using a damage-avoided approach described below. On the contrary, the costs of maintaining the current policy were considered to be borne by dog owners who vaccinate their dogs against rabies (note that they also bear the gross profits made by JVMA or private veterinary clinics) and the government in providing funds to JVMA to organize the vaccination campaign.

The annual costs of implementing the rabies vaccination policy and the economic burden of a canine rabies outbreak in Japan were estimated based on published frameworks with specific modifications to accommodate the rabies-free setting of Japan (Knobel et al. 2005; Hampson et al. 2015). The author conducted three investigation trips to Ibaraki, Tokushima and Miyazaki Prefectures during 20 July 2016 to 29 September 2016 and interviewed the prefectural government officials to obtain necessary information regarding local rabies prevention system. Other data derived from extensive literature review, international or Japanese database and empirical data of rabies outbreaks in Asian countries/territories including Taiwan and Malaysia and European countries such as France and the Netherlands.

2.2 Estimation of the annual costs of implementing the dog rabies vaccination policy in Japan ($Costs_{\text{annual}}$)

2.2.1 Direct vaccination costs

The key characteristics of companion dog ownership in Japan are summarized in Table 5.1. In 2015, 4,688,240 companion dogs were vaccinated against rabies based on the official figures published by MHLW (2017) and the number of owners involved was estimated to be 3,780,839 assuming one representative from each household with dog ownership. Approximately 47.2% to 48.6% of dog owners would attend the vaccination campaign based on information from the investigated prefectural governments. The standard price of single vaccination charged in vaccination campaign in the 47 prefectures of Japan ranges from $20.50 to $27.64. The average single vaccination price was estimated to be $24.61 based on a weighted mean of all the vaccination prices accounting for the number of registered dogs vaccinated in each prefecture. In addition, owners would need to pay $4.90 for a tag certifying the dog's vaccination. Overall, the direct cost of a single dog rabies vaccination for dog owners ($Cost_{vac}$) was set as $29.52 assuming this proxy includes vaccine cost, material costs such as needle, syringe and alcohol swab, overhead costs (including staff salaries and administrative cost), logistic costs and gross profits. It should be noted that the value of $Cost_{vac}$ excluding gross profits would correspond to the unit value of the funds provided by the government to JVMA for organisation of annual vaccination campaign, i.e. the total amount of funds divided by the number of dogs vaccinated in campaign each year. The direct cost of single dog rabies vaccination for owners attending a veterinary clinic was also set as $Cost_{vac}$ based on the observation that the dog rabies vaccination price charged in annual campaign would be very similar to the median price charged in veterinary clinics in each respective prefecture, e.g. at Tokyo Metropolis the vaccination price (excluding the price of certification tag) was $26.25 in campaign, while the median price was $27.64 in veterinary clinics (n=1,365) based on 2015 Tokyo Veterinary Medication Association survey data.

2.2.2 Indirect costs

Indirect costs included opportunity costs of time and transport costs for dog owners and advertisement costs for the government. The opportunity costs of time were estimated using the human capital approach based on productivity or income loss. Such loss was calculated by weighing the number of working days lost by the daily gross domestic product (GDP) per capita. No transport cost was considered for owners attending vaccination campaign assuming that the majority of them would either walk or cycle based on information from the investigated prefectural governments. For owners who attend a veterinary clinic for vaccination, it was assumed half of them would drive and the other half would walk. Advertisement costs were considered for the production of publicity materials such as posters and leaflets by MHLW.

2.3 Estimation of the economic burden of a canine rabies outbreak in Japan

The current model predicted the economic burden of a hypothetical canine rabies outbreak in Ibaraki Prefecture under the current vaccination policy with a coverage of 51.8% ($Burden_{vac}$) and under the abolition of such policy, i.e. vaccination coverage of

0% ($Burden_{abolish}$), respectively, according to the simulation results in Kadowaki et al. (2018). Ibaraki Prefecture was selected for investigation because it is representative of the current situation of dog ownership in Japan in terms of proportion of households with dog ownership, dog registration and rabies vaccination rates, companion dog density and dog-to-human ratio (Table 5.1). The main epidemiological characteristics of the simulated outbreak were considered in terms of the number of rabid dogs, i.e. mean outbreak size, and the duration of the outbreak, i.e. mean epidemic period – an outbreak would last for 68.2 days involving 4.7 rabid dogs under the current vaccination policy, while it would last for 152.5 days involving 21.7 dogs under the abolition of vaccination policy. It was assumed that the introduced rabies disease would not become endemic in the country and would come to an end under control interventions as predicted by the simulation model and according to the experiences in Western Europe (Ribadeau-Dumas et al. 2016). Thus, the economic burden was considered on the basis of incurred expenses of a single rabies outbreak.

2.3.1 Dog rabies control costs

Based on the national rabies contingency plan, it was assumed that the prefectural government rabies control team would respond to the outbreak by taking actions including epidemiological investigation (this involves contact tracing of all the dogs and other susceptible animals in close contact with the index case and identification of potential rabid dog-bite victims), emergency vaccination of dogs and depopulation of stray dogs around the outbreak area (MHLW 2013). The cost of stray dog population management was calculated as an incremental cost since the capture and humane removal of unwanted stray dogs and dogs without a tag certifying registration or vaccination are already being conducted as part of the daily rabies prevention system.

2.3.2 Human rabies prevention costs, i.e. post-exposure and pre-exposure prophylaxis (PEP and PrEP) costs

2.3.2.1 PEP due to rabid dog exposure

The number of human victims bitten or injured by a rabid dog was based on Kadowaki et al. (2018). It was assumed that all victims suffer either a Category II or III exposure requiring PEP under WHO recommendations and all of them can receive timely complete PEP given the fact that Japan is a developed country with a very high human development index of 0.903 (WHO 2014; Hampson et al. 2015; UNDP 2015). Currently there are two types of human rabies vaccine available in Japan, i.e. Japanese PCEC-K vaccine and imported vaccine such as Verorab and Rabipur (Morimoto & Saijo 2009). A 5-dose Essen regimen (which is commonly used in local hospitals and clinics) with a fixed cost of $129 was considered for the direct medical cost of PEP, while the indirect costs were considered in a similar manner mentioned above (Suganuma et al. 2013; WHO 2014).

In terms of rabies immunoglobulin (RIG), it was assumed that human RIG and/or equine RIG would be imported for emergency use in case of a rabies outbreak (no such product is currently available in Japan) (Morimoto & Saijo 2009). The number of patients with Category III exposure requiring RIG on Day 0 was estimated based on the data of outbreaks in the Netherlands and Greece: 50% (*n*=42) to 72% (*n*=96) of the patients receiving PEP would have a Category III exposure when bitten by a rabid dog (Tsiodras et al. 2014; Van Rijckevorsel et al. 2014). The efficacy of timely complete PEP was assumed to be 100% and so no human death, i.e. Years of Life Lost (YLL), was considered.

2.3.2.2 PEP due to public panic

In the early stage of the 2013 Taiwan epizootic, 5,335 persons injured with animal bites or scratches (78% due to a dog or cat) applied for free government-funded PEP during a 72-day period when 157 rabies cases were confirmed (Huang et al. 2013). However, 35.5% of these applicants came from areas where no rabies case was reported, and only seven applications were ultimately proved to be caused by a rabid animal, i.e.

Chinese ferret-badger. Since Japan has been rabies-free for over half a century, it can be foreseen that a rabies outbreak would cause massive public panic in the country leading to unnecessary use of PEP same as the situation in the Taiwan epizootic. Nonetheless, it would be unreasonable to use the data of the Taiwan epizootic to infer the potential number of PEP due to public panic in Japan considering the differences in the magnitude of the outbreak (in terms of types of animal species involved, speed of onset, number of cases and duration) and also in the incidence rate of victims with injuries of animal bites or scratches. Instead, the author assumed that a proportion of the daily victims with injuries of animal bites or scratches in Japan (who may not receive PEP under normal circumstances) would receive PEP due to public panic in face of the canine rabies outbreak considered in the current model. According to the Ministry of the Environment (2017), the average daily number of dog-bite victims was reported to be 12 persons in 2016 (note that the number of victims exposed to animals other than dogs was not included in the calculation due to a lack of official data). Thus, it was assumed that each day six persons (50% of the daily reported number) and ten persons (80% of the daily reported number) would receive PEP due to public panic under the current vaccination policy and the abolition of such policy, respectively. The direct and indirect costs involved were then estimated in a similar manner as described above, while the use of RIG was not considered for Category III exposure in this case.

2.3.2.3 Occupation PrEP

The original members of the prefectural government rabies control team and the diagnostic laboratories were assumed to have all received PrEP. Therefore, the direct costs of PrEP, using a 3-dose WHO-recommended regimen, were considered for the additional government officers who join the rabies control team in face of an outbreak (Yanagisawa et al. 2010). The indirect costs were assumed to be reflected in the labour costs of the officers and therefore were not considered.

2.3.3 Surveillance costs

Surveillance costs involve: 1). diagnostic testing of all rabid dogs, i.e. the positive cases and 2) ongoing testing of all suspected animals during the outbreak and after the outbreak for two years to declare and verify rabies-free status according to OIE standards. In terms of the testing of suspected animals, the surveillance data of France was used as a proxy since the country has an intensified surveillance system due to regular rabies introductions, i.e. a daily average number of five suspected animals had been tested for rabies during 2008–2017 (Rabies - Bulletin - Europe). It was assumed that the level of active surveillance in Japan in face of a rabies outbreak under the abolition of vaccination policy would be the same as that in France, i.e. five suspected animals are tested each day, while it would not be as intensified during an outbreak under the current vaccination policy, i.e. three suspected animals are tested each day. The above data was considered in terms of the actual number of animals tested rather than an estimated incidence rate due to the following two reasons: 1) it was assumed that the level of active surveillance on rabies would be mainly influenced by the diagnostic capacity of reference laboratories in the country and to a lesser extent by other factors such as the size of the susceptible animal population and 2) currently in Japan the level of active surveillance on rabies, particularly on wild animals, is rather limited but is expected to be continuously strengthened given the national guideline for animal rabies survey was published in 2015.

2.4 Model implementation and outputs

The decision tree model (Fig. 5.1) was developed in PrecisionTree and @Risk Version 7.5.1 (Palisade Corporation) within Microsoft Excel 2016, and was run with 5,000 iterations using Latin Hybercube sampling for each simulation. Information on cost data and input variables into the model is summarised in Table 5.2.

Outputs of the model included the economic burden of a rabies outbreak in Japan under mandatory vaccination policy ($Burden_{vac}$) and under abolition of vaccination policy ($Burden_{abolish}$), respectively, and annual costs of implementing the current vaccination policy ($Costs_{annual}$) were estimated. Utilising a damage-avoided approach, the annual benefits of implementing the current vaccination policy in expected value ($Benefits_{annual}$) was calculated:

$$Benefits_{annual} = P\_annual \text{ X } (Burden_{abolish} - Burden_{vac})$$

The benefit-cost ratio (*BCR*) was then given by:

$$BCR = \frac{Benefits_{annual}}{Costs_{annual}}$$

If the *BCR* is greater than 1, the implementation of the current annual vaccination policy is an economically-efficient strategy and vice versa (Shwiff et al. 2016).

2.5 Sensitivity and scenario analyses

To assess the uncertainty in the current model, sensitivity analysis was conducted using Spearman's correlation coefficient to rank all the input parameters according to their contributions to the variance in *BCR*.

The following three scenario analyses were performed to assess their effects on *BCR*:

1. Reduction in the direct cost of single dog rabies vaccination, i.e. $Cost_{vac}$ (the price

of single vaccination charged to owners) – owners bear most of the costs of implementing the current rabies vaccination policy including direct and indirect costs involved in bringing their dogs to annual vaccination. The potential to reduce $Cost_{vac}$, through decreasing the profit margin made by JVMA or private veterinary clinics, has been highlighted in a few clinics in certain prefectures where a vaccination price as low as $8.92 is charged;

2. Worst-case scenario – this aimed to analyse the following two possible events: 1) the economic burden of a rabies outbreak under the abolition of vaccination policy, i.e. $Burden_{abolish}$, was underestimated (relative to that under the current vaccination policy, i.e. $Burden_{vac}$), 2) and the risk of rabies introduction into Japan increases in unforeseen circumstances, e.g. smuggling of animals. The parameters $Burden_{abolish}$ and *P_annual* were increased in a stepwise fashion to model such situation. It should be noted that, by increasing the value of $Burden_{abolish}$ (relative to $Burden_{vac}$), this worse-case analysis would also indirectly address the effect of additional economic burden due to outbreak situations not considered in the current model, e.g. the rabies outbreak spreads to other prefectures surrounding Ibaraki Prefecture resulting in an increased final outbreak size;

3. Best-case scenario – this aimed to explore under what specific circumstances the economic efficiency of maintaining the current dog rabies vaccination policy could be maximized. $Costs_{annual}$, by considering the number of companion dogs vaccinated with rabies, the frequency of vaccination and $Cost_{vac}$, were decreased, while $Burden_{abolish}$ and *P_annual* were increased to model the best-case situation. In particular, it has been highlighted in Study 4 that the current annual vaccination policy could be amended to one requiring less frequent boosters with the domestic RC-HL strain vaccine currently in use, i.e. a booster is required within one year after primary vaccination and then every two to three years.

3. Results

3.1 Model outputs

Information on the simulated model outputs is summarised in Table 5.3 and Fig. 5.2. The annual costs of implementing the current dog rabies vaccination policy were estimated to be $160,472,075 (90% prediction interval [PI]: $149,268,935 – 171,669,974). The economic burden of a single canine rabies outbreak in Japan was estimated to be $1,682,707 (90% PI: $1,180,289 – 2,249,283) under the current vaccination policy (i.e. an outbreak involving 78.2 days of rabies control action followed by two years of active surveillance), while it would be $5,019,093 (90% PI:

$3,986,882 – 6,133,687) under the abolition of vaccination policy (i.e. an outbreak involving 162.5 days of rabies control action followed by two years of active surveillance), which is 3-fold higher. The annual benefits of maintaining the current vaccination policy in expected value (i.e. based on an annual probability of 2.57×10^{-5} which represents that rabies is introduced into Japan every 49,444 years) were estimated to be $85.75 (90% PI: $55.73 – 116.89). The benefit-cost ratio was estimated to be 5.35×10^{-7} (90% PI: 3.46×10^{-7} – 7.37×10^{-7}).

3.2 Sensitivity and scenario analyses

Result of sensitivity analysis is illustrated in Fig. 5.3. The top five most uncertain parameters are the number of patients receiving PEP due to public panic under the abolition of vaccination policy ($N_{panic,abolish}$), the daily number of suspected rabid animals tested under active surveillance under the abolition of vaccination policy ($N_{\text{d-survey,abolish}}$) and under the current vaccination policy ($N_{\text{d-survey,vac}}$), respectively, the number of patients receiving PEP due to public panic under the current vaccination policy ($N_{panic,vac}$) and the number of working days lost per owner per dog vaccination ($T_{\text{lost,vac}}$).

Results of scenario analysis are shown in Table 5.4 and 5.5 and Fig. 5.4 and 5.5. The analysis of reduced direct medical cost of single dog rabies vaccination revealed that the *BCR* was 3.59 X 10^{-6} when $Cost_{vac}$ was reduced to zero, highlighting that the implementation of the current annual vaccination policy would still be economically inefficient if one only considered the indirect costs of vaccination for the dog owners (Fig 5.4). The worst-case scenario analysis demonstrated that the *BCR* (including the 90% PI) would become above 1 when the annual risk of rabies introduction into Japan (*P_annual*) and the economic burden of a rabies outbreak under the abolition of vaccination policy ($Burden_{abolish}$) simultaneously increased 1500-fold (Table 5.4). The best-case scenario analysis further revealed that, although under relatively extreme circumstances, the implementation of a pre-emptive dog vaccination policy in rabies-free Japan could be maintained with improved economic efficiency, i.e. mean *BCR* = 2.61, if there were a 100-fold increase in both *P_annual* and $Burden_{abolish}$ and if the policy were implemented on a smaller scale, i.e. in only one of the 47 prefectures in Japan using Ibaraki Prefecture as an example, with a 3-fold decrease in $Cost_{vac}$ to $8.92 at a frequency of every two to three years (Table 5.5).

4. Discussion

The current study assessed the merit of implementing mandatory annual rabies vaccination in domestic dogs in Japan using benefit-cost analysis. The estimated values of benefit-cost ratio (*BCR*) were very low, i.e. well below 1, indicating that the implementation of the current vaccination policy in rabies-free Japan is very economically inefficient for the purpose of reducing the economic burden of a potential canine rabies outbreak. The annual costs of implementing such vaccination policy ($Costs_{\text{annual}}$) were estimated according to the data on registered dogs reported by MHLW and might have been under-estimated since the average national registration rate during 2007–2016 is estimated to be only 59.2%. Nonetheless, it is anticipated that companion dogs which are not registered by their owners are less likely to be vaccinated regularly against rabies. The study by Hidano et al. (2012) highlighted that companion dogs taken infrequently for walks are significantly less likely to be vaccinated against rabies in Japan. In addition, adverse drug reaction and vaccine wastage were expected to contribute to only a minor component of $Costs_{\text{annual}}$ and hence were not considered (Gamoh et al. 2008).

The economic burden of a single canine rabies outbreak in Japan was estimated to be $1.69 million and $5.02 million, under the current vaccination policy and the abolition of such policy, respectively. Such level of burdens, although not directly comparable due to the differences in model framework, appears similar to the annual costs of rabies control in Flores Island, Indonesia which were estimated to be $1.12 million

(Wera et al. 2013). Further, the government of Taiwan have initially spent over $4.5 million for the support of contingency actions and procurement of human and animal rabies vaccines for the epizootic started in 2013 (Chang et al. 2016).

It should also be noted that the results of the current study could be generalized to other potential rabies situations in Japan, e.g. a canine rabies outbreak with domestic cat being the spillover species, particularly stray cats which are twice as common as stray dogs (Ministry of the Environment 2017), or an outbreak primarily involving wildlife species such as common racoon and red fox which are common in the country, with other animals, e.g. domestic dog, being the spillover species. If the above outbreak situations occurred in Japan, dog rabies control measures considered in the current model including emergency dog vaccination, stray dog depopulation and epidemiological investigation would still take place as part of the contingency plan, while the costs of PEP due to public panic would still be expected to constitute a considerable part of the economic burden as demonstrated in the Taiwan epizootic of Chinese ferret-badger (Huang et al. 2013). On top of these basic components of the economic burden, there would be additional costs incurred in containing a rabies outbreak involving multiple animal species, e.g. extra manpower might be needed to reinforce stray cat population control in face of an outbreak involving domestic cat as the spillover species, while oral rabies vaccination (ORV) might be implemented in the long term if a wildlife rabies outbreak became endemic in the country (Maki et al. 2017). Overall, the current study provided a generic framework for future research to estimate the potential economic burden of different rabies outbreak situations in Japan.

To accommodate the unique situation in Japan, the current study did not consider certain components of the economic burden of canine rabies as suggested in Hampson et al. (2015) and Knobel at al. (2005). Livestock losses were not included as significant losses were considered unlikely due to a single dog rabies incursion as indicated in historical incidence (Jibat et al. 2016; Kurosawa et al. 2017). In addition, the costs of potential human death, i.e. Years of Life Lost (YLL), were not considered as explained above, but it is possible that some patients with Category III exposure from a rabid dog could not receive timely rabies immunoglobulin (RIG) since it is currently not available in Japan. The reported probability of contracting rabies after Category III exposure to a rabid dog ranges between 0.03 and 0.25 when an incomplete post-exposure prophylaxis (PEP) without RIG is used (Manning et al. 2008). Zhang et al. (2016) have emphasized the importance of RIG in a PEP regimen and the inefficacy of receiving vaccination alone, while Morimoto et al. (2016) demonstrated the potential of infiltrating a Category III wound site with rabies vaccine as an alternative to the administration of RIG. Moreover, although a five-dose Essen regimen was considered for simplicity in the calculation of the direct costs of PEP, it has been indicated that the Japanese PCEC-K vaccine is less potent than those produced overseas (Benjavongkulchai et al. 1997). The PEP regimen using the Japanese vaccine requires five to six intramuscular doses, i.e. a potential extra sixth dose on Day 90, with clinical data suggesting that up to 85.4% of the patients (*n*=813) acquired satisfactory antibody titres after five vaccinations (Arai et al. 2002; Suganuma et al. 2013). Finally, anxiety associated with a dog bite that may develop into rabies has been suggested as an additional component in Years of Life lived with Disability (YLD) contributing to the economic burden of the disease, but it was not considered in the current model due to a lack of scientific validation of this assumption (Hampson et al. 2015).

Results of scenario analysis demonstrated that the implementation of the current annual dog rabies vaccination policy could be maintained with improved economic efficiency if several conditions were met. In worse-case analysis, the *BCR* would become above 1 if the risk of rabies introduction increased to 0.04 corresponding to a level of risk where rabies would enter Japan every 26 years while the economic burden of a rabies outbreak under the abolition of vaccination policy increased to $7.53 billion, a level close to the annual global burden of endemic canine rabies which was estimated to be $8.6 billion previously (Hampson et al. 2015) (Table 5.4). The best-case analysis further illustrated that, although under relatively extreme circumstances, the economic efficiency of the current policy could be improved by decreasing the price of single rabies vaccination charged to dog owners, relaxing the frequency of vaccination to every two to three years and implementing the policy on a smaller scale, e.g. only in targeted prefectures with the highest risk of rabies incursion (similar to the concept of immune belt, an example would be the one built by Malaysia along the border with Thailand) (Table 5.5). Overall, future research is highly warranted to provide further evidence-based information to determine whether the continuation of the current vaccination policy, as part of national rabies prevention system, is scientifically justified in the long run or not. Before decision makers reaching a final conclusion, it is also worthwhile to investigate the intangible benefits of maintaining the current policy or the potential unintended consequences of abolishing the current policy, e.g. mandatory rabies vaccination may be the primary reason for some owners to seek veterinary care for their dogs and so abolition of the current policy might lead to a reduction in the use of veterinary service which could impact the overall dog health in Japan.

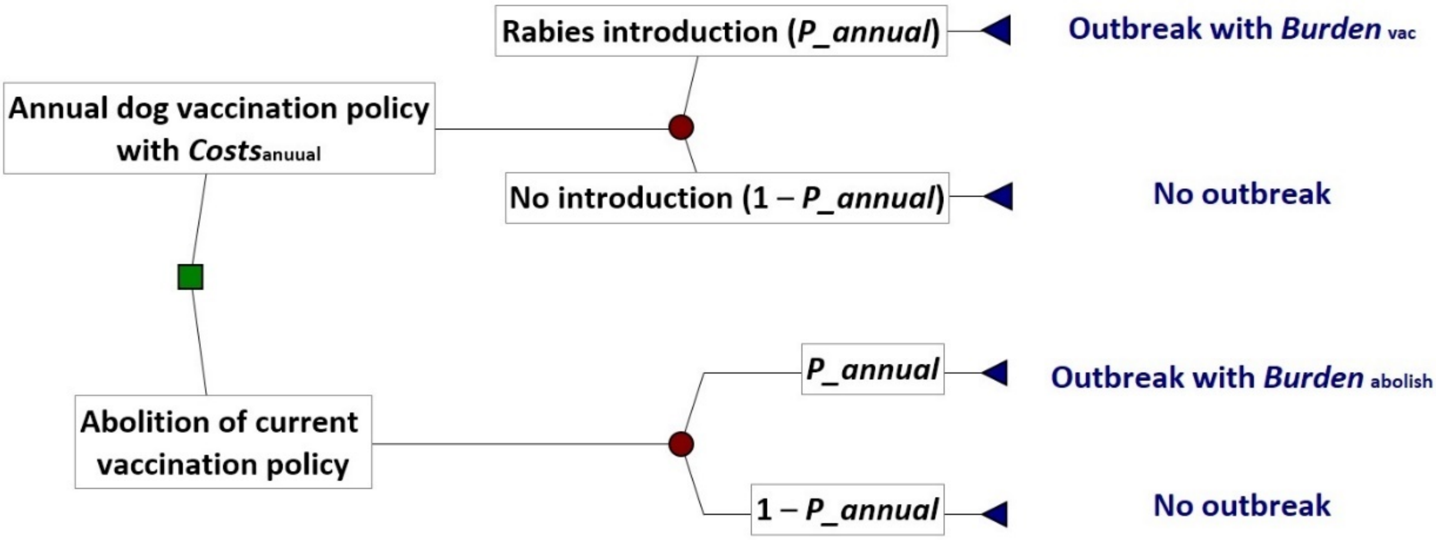
If the current policy were to be abolished, resources, specifically the recurrent funds provided by the government to JVMA for organization of annual vaccination campaign in all the 47 prefectures of Japan, could be allocated to more efficient uses to strengthen the national rabies prevention system. Based on the information from the investigated prefectural governments, a vaccination campaign in a particular prefecture with a capacity to vaccinate 12,000 to 14,000 dogs would receive financial support of about $173,665 and this suggests that with the abolition of the current policy a fund of around $12 to $14 could potentially be saved from each dog that would otherwise be vaccinated in the campaign. It should be noted that dog owners would still have the option to voluntarily vaccinate their dogs against rabies in private clinic even when vaccination campaign became unavailable under the abolition of the current policy. In terms of recommended reinforcement of the current rabies prevention system, simulation exercises of the contingency plan should be conducted regularly and continuous training of private veterinary clinicians and government officers in the rabies control team are very important (Bourhy et al. 2015). Moreover, the current PEP delivery system must be strengthened in terms of the stockpile of human rabies vaccine and the emergency supply of RIG. Currently, there are approximately 114 local hospitals or clinics which offer rabies PrEP or PEP and about 40,000 to 50,000 Japanese human rabies vaccines are produced locally with a similar amount being imported each year (Morimoto & Saijo 2009). Nevertheless, the local stockpile of human rabies vaccines appeared temporarily exhausted when there were two reports of introduced human rabies cases from the Philippines in November 2006 and the number of tourists seeking PEP after returning from overseas increased three-fold (Morimoto & Saijo 2009; Suganuma et al. 2013). Training of doctors and medical professionals is also essential to facilitate correct and efficient delivery of PEP to patients with real need. The potential use of PEP due to public panic would incur a substantial and unnecessary economic burden, emphasising that the importance of continuous public education to raise awareness and knowledge of rabies (Fig. 5.2). Furthermore, the cost-effectiveness of PEP has been an international research topic and regimens consisting of fewer doses to reduce costs and fewer consultations to promote patient's compliance have been examined (Ren et al. 2015; WHO 2018a). The use of Japanese PCEC-K vaccine in a three-dose intradermal PrEP regimen has been proved safe and efficacious (Shiota et al. 2008; Yanagisawa et al. 2012). Thus, further research on the suitability of the Japanese vaccine to time-and dose-sparing PEP regimens such as 4-dose Essen regimen, Zagreb regimen and one-week, 2-site ID regimen is highly warranted (WHO 2018a).

5. Conclusions

The implementation of the policy of mandatory annual vaccination of domestic dogs in rabies-free Japan is very economically inefficient for the purpose of reducing the economic burden of a potential canine rabies outbreak. Scenario analysis revealed that the economic efficiency of the current policy could be improved by decreasing the vaccination price charged to dog owners, relaxing the frequency of vaccination to every two to three years and implementing the policy on a smaller scale such as targeted prefectures instead of the whole Japan.

6. Figures and tables

Fig. 5.1 Conceptual framework of the current benefit-cost analysis through decision tree modelling



$$Benefits_{annual} = P\_annual \text{ X } (Burden_{abolish} - Burden_{vac})$$

$$BCR = \frac{Benefits_{annual}}{Costs_{annual}}$$

The economic efficiency of implementing the current dog vaccination policy for the purpose of reducing the economic burden of a potential canine rabies outbreak in rabies-free Japan is indicated by the benefit-cost ratio (*BCR*).

Fig. 5.2 Pie charts comparing the components of the economic burden of a potential canine rabies outbreak in Japan under the current annual vaccination policy (A) and under the abolition of vaccination policy (b), respectively

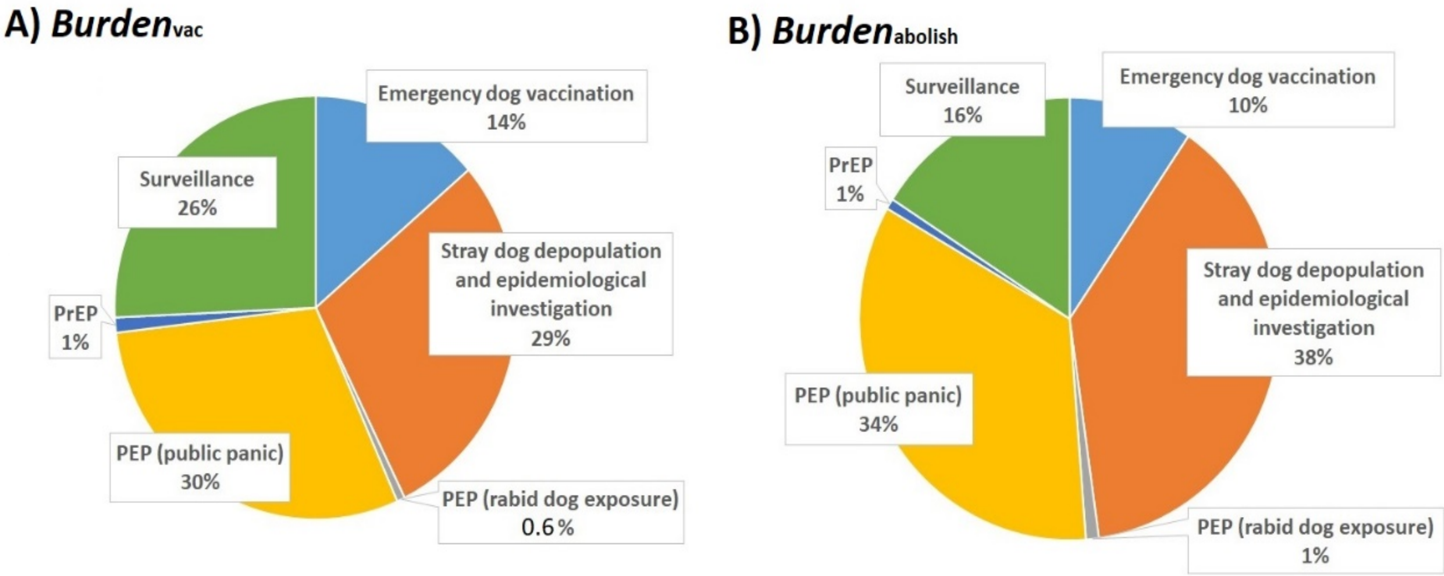
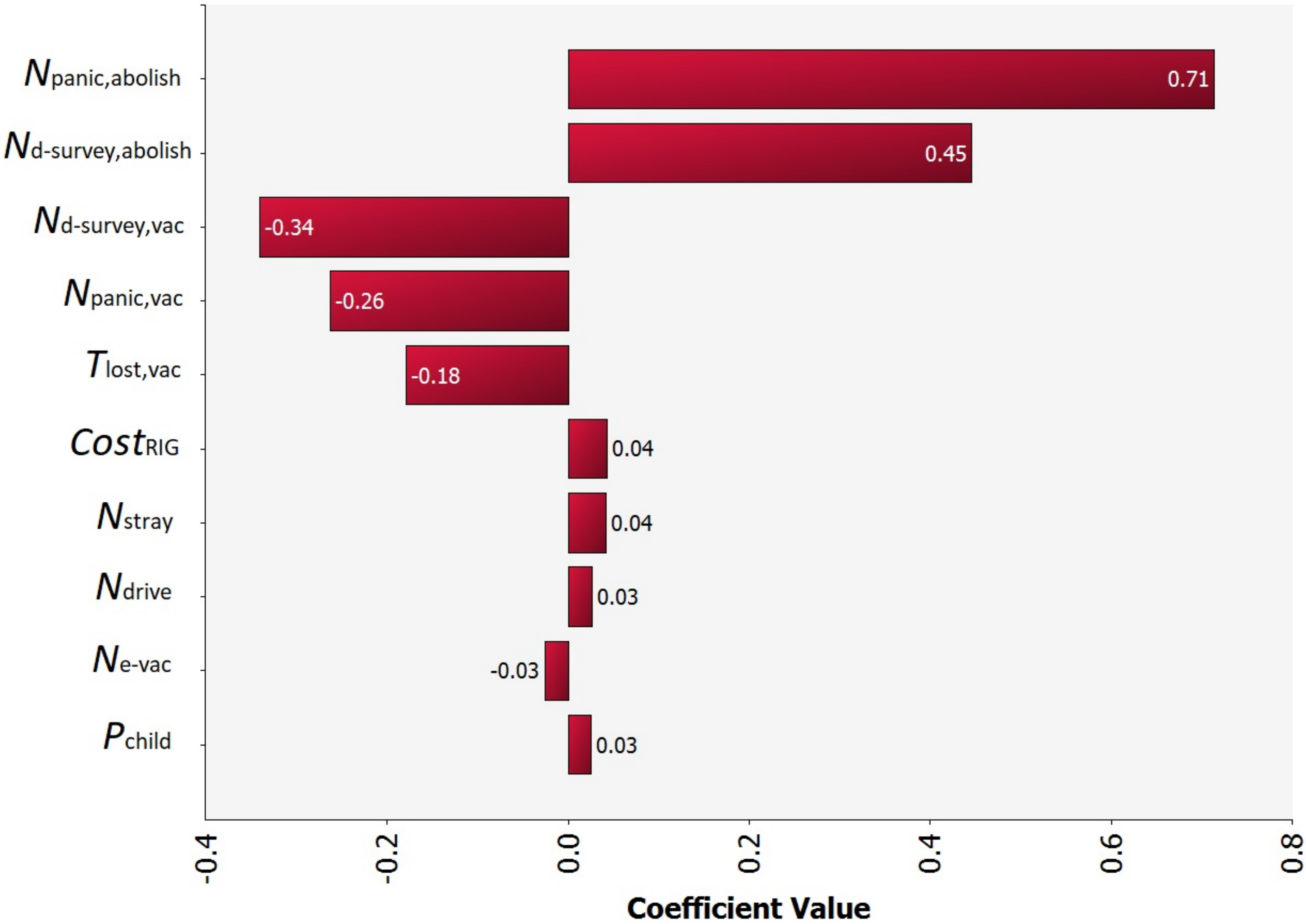
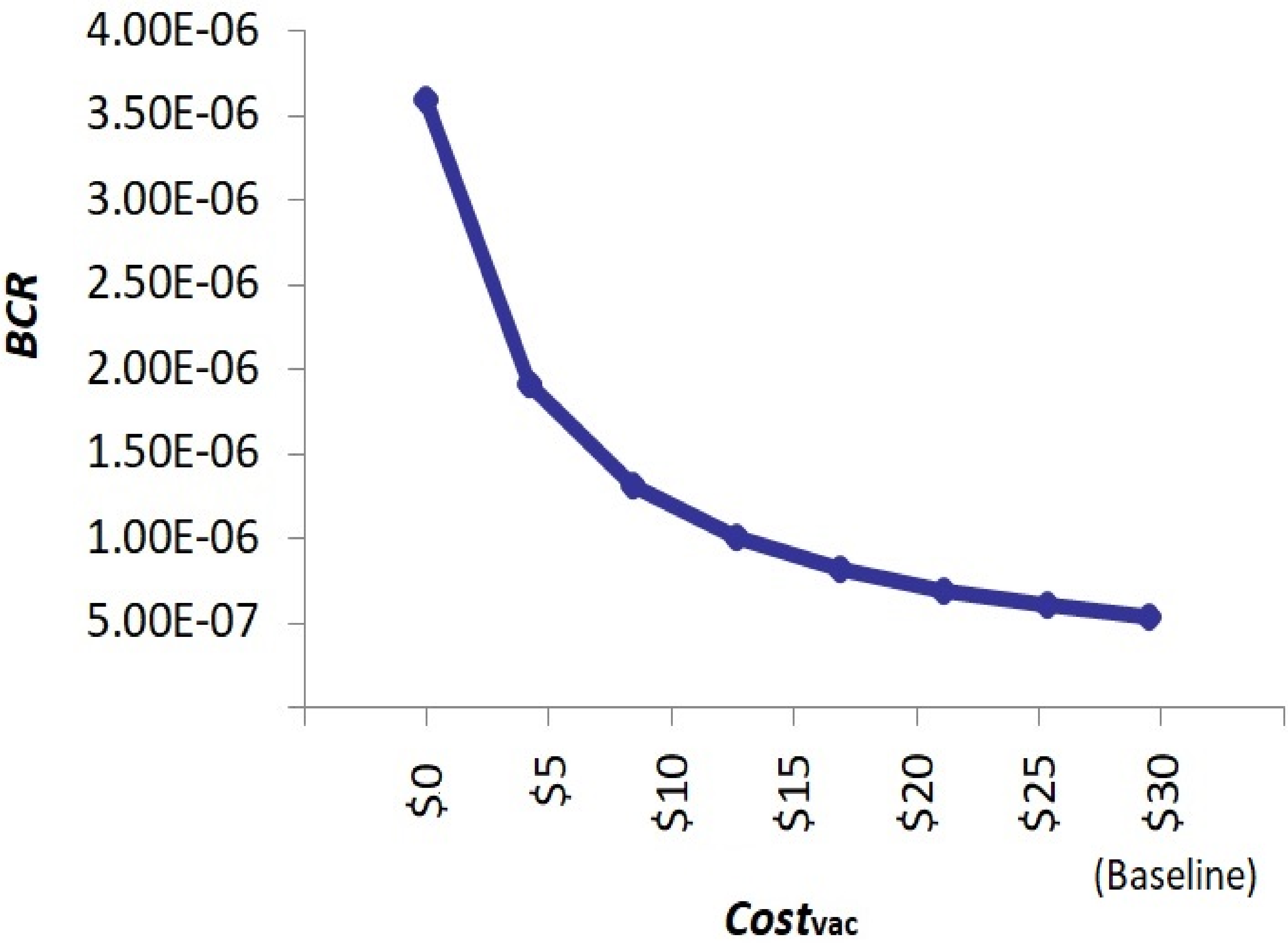


Fig. 5.3 Tornado graph depicting the result of sensitivity analysis



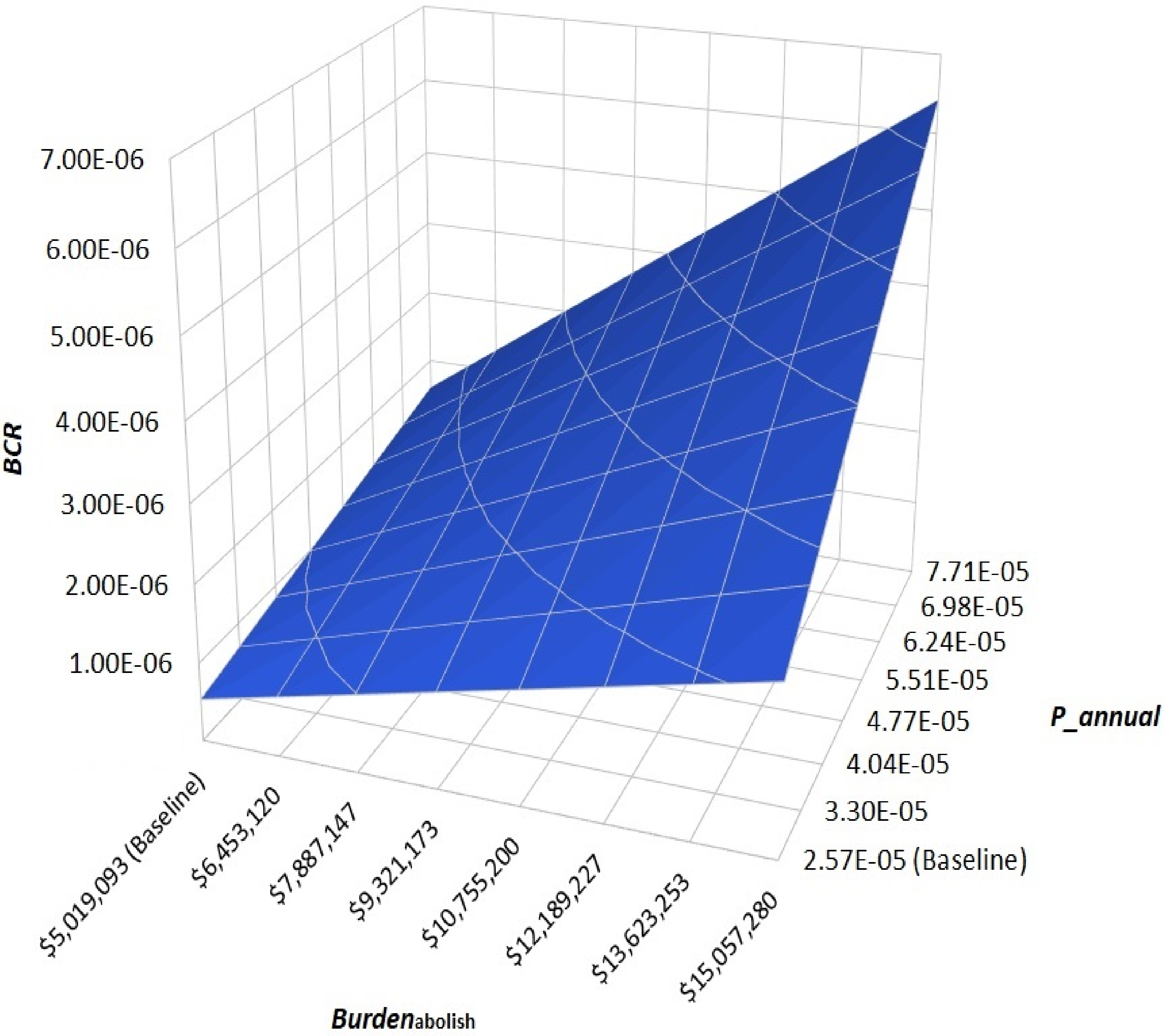
All model input parameters were ranked by Spearman's correlation coefficient according to their contributions to the variance of model output *BCR*. The 10 most correlated input parameters are shown in this figure.

Fig. 5.4 Scenario analysis of the effect of reduced direct medical cost of single dog rabies vaccination ($Cost_{vac}$) on the benefit-cost ratio (*BCR*)



Note that when $Cost_{vac}$ was reduced to zero, the *BCR* was still well below 1, i.e. 3.59 X 10^{-6}, illustrating that the implementation of the current rabies vaccination policy would still be economically inefficient even if one only considered the indirect costs of vaccination for the dog owners in Japan.

Fig. 5.5 Two-way sensitivity graph illustrating the result of worse-case scenario analysis



Simultaneous 3-fold increases in the economic burden of a dog rabies outbreak in Japan under the abolition of current vaccination policy (*Burden*$_{abolish}$), i.e. from $5.02 million to $15.06 million, and in the annual probability of rabies introduction into Japan (*P_annual*), i.e. from 2.57 X 10^{-5} to 7.71 X 10^{-5}, resulted in a 12-fold increase in the benefit-cost ratio (*BCR*) from 5.34 X 10^{-7} to 6.43 X 10^{-6}.

Table 5.1 List of cost data and input variables included in the current benefit-cost analysis

Parameter	Probability distribution / fixed value	Unit	Estimated mean (90% prediction interval) / estimated fixed value	Source / Explanation
Annual costs of implementing current rabies vaccination policy in Japan ($Costs_{annual}$)				
Direct costs **=** N_{vac} **X** $Cost_{vac}$				
Number of registered companion dogs vaccinated with rabies in 2015 (N_{vac})	4,688,240	dog	Not applicable (n/a)	2015 Ministry of Health, Labour and Welfare data (MHLW 2017)
Single rabies vaccination cost ($Cost_{vac}$)	\$29.52	US dollar	n/a	Proxy inferred from the weighted mean of the prices charged at vaccination campaign in the 47 prefectures of Japan
Indirect costs **=** N_{owner} **X** $T_{lost,vac}$ **X** GDP_{lost} **+** N_{drive} **X** D_{clinic} **X** $Cost_{fuel}$ **+** $Cost_{ad}$				
Time (income) loss				
Annual number of owners vaccinating their dogs (N_{owner})	N_{vac} ÷ 1.24	person	3,780,839	Calculated from 2015 national survey information that a single household owns on average 1.24 companion dogs (JPFA 2018)
Number of working days lost per owner per dog vaccination ($T_{lost,vac}$)	*Uniform* (0.5 , 2) ÷ 24	day	0.05 (0.02 – 0.08)	Author's assumption
Daily gross domestic product per capita (GDP_{lost})	\$105.31	US dollar	n/a	2017 International Monetary Fund data
Transport costs				
Number of owners vaccinating their dogs at clinic and travelling by car (N_{drive})	N_{owner} X *Uniform* (0.514 , 0.528) X 0.5	person	984,908 (972,998 – 996,817)	Assuming 51.4% to 52.8% of owners would vaccinate their dogs at clinic and 50% of them would drive; no transport costs were considered for owners attending vaccination

				campaign and for owners who walk to clinic
Driving distance of a return trip to an animal clinic (D_{clinic})	$2 \times \sqrt{377,962 \div 11,83}$	km	6.38	Estimation based on the area of Japan, i.e. 377,962 km^2, and the reported number of companion animal clinics in Japan, i.e. 11,839 (MAFF 2018)
Fuel cost per km ($Cost_{fuel}$)	$0.21	US dollar	n/a	Author's assumption
Advertisement costs ($Cost_{ad}$)	$4,333	US dollar	n/a	2015 MHLW data
Economic burden of a dog rabies outbreak in Japan under current annual vaccination policy ($Burden_{vac}$) and under the abolition of such policy ($Burden_{abolish}$)*				
Dog rabies control costs = Emergency dog vaccination costs + Stray dog depopulation and epidemiological investigation costs				
Mean number of rabies cases (N_{case})	4.7 21.7	dog	n/a	Simulated outbreak in Ibaraki Prefecture (Kadowaki et al. 2018)
Mean epidemic period (D_{rabies})	68.2 152.5	day	n/a	
Days of action (D_{action})	$D_{rabies} - 30 + 40$	day	78.2 162.5	Assuming a 30-day delay in action and that rabies control actions would continue for another 40 days after the last case was observed based on the field experience of Malaysia outbreak (Bamaiyi 2015; Kadowaki et al. 2018)
Emergency dog vaccination costs = $N_{e\text{-}vac} \times Cost_{vac}$				
Daily number of dogs receiving emergency vaccination ($N_{e\text{-}vac}$)	*Poisson* (100)	dog	100 (84 – 117)	Assumption based on Kadowaki et al. 2018
Stray dog depopulation and epidemiological investigation costs = $D_{action} \times (N_{officer} \times Cost_{labour} + N_{car} \times Cost_{drive} + N_{stray} \times Cost_{stray})$				
Additional government officers in the rabies control team ($N_{officer}$)	50 100	person	n/a	Assumption based on the information from the

				investigated prefectural governments
Daily labour cost of an officer of the rabies control team ($Cost_{labour}$)	\$108.01	US dollar	n/a	Proxy based on the average monthly salary of prefectural public servants (2017 Ministry of Internal Affairs and Communications data)
Daily increase in the number of car vehicles used for capturing stray dogs and epidemiological investigation (N_{car})	15 30	car	n/a	Assumption based on the information from the investigated prefectural governments
Driving cost per car ($Cost_{drive}$)	50 X 0.21	US dollar	\$10.7	Assuming a mean travel distance of 50 km and \$0.21 for fuel cost per km
Daily increase in the number of stray dogs captured (N_{stray})	*Poisson* (5)	dog	5 (2 – 9)	Assumption based on the information from the investigated prefectural governments
Costs of basic care and euthanasia for each captured stray dog ($Cost_{stray}$)	*Uniform* (118 , 155)	US dollar	\$136 (\$120 – 153)	
Surveillance costs = N_{survey} X $Cost_{test}$				
Duration of active surveillance during and after the outbreak (D_{survey})	D_{action} + 730	day	808 893	Testing of suspected rabid animals for another two years to declare rabies-free status according to OIE standards
Daily number of suspected rabid animals tested under active surveillance ($N_{d\text{-}survey}$)	*Poisson* (3) *Poisson* (5)	animal	3 (1 – 6) 5 (2 – 9)	Assumption based on the surveillance data of France (2017 Rabies Bulletin Europe data)
Total number of animals tested including rabid dogs and suspected animals (N_{survey})	N_{case} + D_{survey} X $N_{d\text{-}survey}$	animal	2429 (813 – 4854) 4,484 (1,807 – 8,054)	n/a

Costs of single diagnostic testing including direct fluorescent antibody test and RT-PCR (*Cost*$_{test}$)	\$178	US dollar	n/a	Assumption based on the information from the investigated prefectural governments
Human rabies prevention costs, i.e. post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) costs				
Direct costs				
PEP costs due to rabid dog exposure = N_{PEP} **X (*****Cost*****$_{h\text{-}vac}$ X 5 +** P_{III} **X** ***Cost*****$_{RIG}$)**				
Number of patients receiving PEP due to rabid dog-bite injury (N_{PEP})	6.7 6.7 X 4.62	person	6.7 30.9	Assumption based on Kadowaki et al. 2018 and estimation based on the ratio of $N_{case,abolish}$: $N_{case,vac}$ which is 4.62 : 1
Cost of single rabies vaccination (*Cost*$_{h\text{-}vac}$)	\$129	US dollar	n/a	Proxy based on the price of Japanese PCEC-K vaccine charged at human hospital (2018 Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital data)
Probability of patients having a Category III exposure and requiring rabies immunoglobulin (RIG), i.e. proportion of Category III exposure among Category II and III exposures caused by rabid dogs (P_{III})	*Uniform* (0.5 , 0.72)	n/a	0.61 (0.51 – 0.71)	Van Rijckevorsel et al. 2012; Tsiodras et al. 2013
Cost of single RIG (*Cost*$_{RIG}$)	Uniform (600 , 1200)	US dollar	\$900 (\$630 – 1,170)	De Benedictis et al. 2016
PEP costs due to public panic = N_{panic} **X** D_{panic} **X** ***Cost*****$_{h\text{-}vac}$ X 5**				
Daily number of people receiving PEP for animal bites or scratches due to panic (N_{panic})	*Poisson* (6) *Poisson* (10)	person	6 (2 – 10) 10 (5 – 15)	Assumption based on the reported average daily incidence of dog-bite victims in Japan which is 12 persons

				(Ministry of the Environment 2017)
Duration of panic behavior (D_{panic})	D_{action}	day	78 163	Assumption based on the field experience of the Taiwan outbreak (Huang et al. 2013)
***Occupational PrEP costs* = $N_{officer}$ X $Cost_{h\text{-}vac}$ X 3**				
Indirect costs				
***Time (income) loss* (for PEP due to rabid dog exposure) = N_{PEP} X (1 + P_{child}) X 5 X T_{lost} X GDP_{lost}** ***Time (income) loss* (for PEP due to public panic) = N_{panic} X (1 + P_{child}) X 5 X T_{lost} X GDP_{lost}**				
Proportion of child patients receiving PEP accompanied by another adult (P_{child})	*Beta* (83 + 1 , 235 – 83 + 1)	person	0.35 (0.3 – 0.41)	Sudarshan et al. 2007
Time lost per visit (T_{lost})	0.5	day	n/a	Knobel et al. 2005
***Transport costs* (assuming half of the people receiving PEP would drive and the other half would take public transport)** ***Driving costs* (for PEP due to rabid dog exposure) = 0.5 X N_{PEP} X 5 X D_{drive} X $Cost_{fuel}$** ***Driving costs* (for PEP due to public panic) = 0.5 X N_{panic} X 5 X D_{drive} X $Cost_{fuel}$** ***Public transport costs* (for PEP due to rabid dog exposure) = 0.5 X N_{PEP} X (1 + P_{child}) X 5 X $Cost_{transport}$** ***Public transport costs* (for PEP due to public panic) = 0.5 X N_{panic} X (1 + P_{child}) X 5 X $Cost_{transport}$**				
Driving distance per return trip (D_{drive})	$2\ X\ \sqrt{377,962 \div 114}$	km	65	Estimation based on the area of Japan, i.e. 377,962 km^2, and the reported number of hospitals and clinics providing PEP and PrEP, i.e. 114 (2018 MHLW [FORTH] data)
Public transport fare per return trip ($Cost_{transport}$)	$8.92	US dollar	n/a	Author's assumption
Probability input into the chance nodes of the decision tree model				
Annual probability of rabies introduction into Japan (*P_annual*)	2.57×10^{-5}	n/a	n/a	Study 1

*When a table cell is split by a dashed line, the upper row presents information on a dog rabies outbreak under the current vaccination policy, while the bottom row presents information on an outbreak under the abolition of vaccination policy

Table 5.2 Characteristics of companion dog ownership in Japan and Ibaraki Prefecture based on official figures in 2015

Characteristics	Japan	Ibaraki Prefecture
Proportion of households with dog ownership	14.42%	17.52%
Number of households with dog ownership[1]	7,985,000	196,986
Estimated number of companion dogs	9,917,000	244,263
Habitable area (km^2)	122,631	3975
Companion dog density (dogs / km^2)	81	61
Human population	127,094,745	2,917,000
Dog-to-human (thousands) ratio	78	84
Number of registered dogs reported by MHLW	6,526,897	176,628
Estimated dog registration rate	65.82%	72.31%
Number of dogs vaccinated against rabies reported by MHLW	4,688,240	118,387
Estimated rabies vaccination rate	47.27%	48.47%

[1] Average number of dogs owned by each household with dog ownership was 1.24 (*n*=50,000) (JPFA 2018)

Table 5.3 Summary of the model outputs and breakdown of the annual costs of implementing the current dog rabies vaccination policy ($Costs_{annual}$) and economic burden of a rabies outbreak in Japan ($Burden_{vac}$ and $Burden_{abolish}$)

Model outputs		Mean value (90% prediction interval)	
Benefit-cost ratio (*BCR*)		5.35×10^{-7} (3.46×10^{-7} – 7.37×10^{-7})	
Avoided economic burden in expected value ($Benefits_{annual}$)		$85.75 ($55.73 – 116.89)	
Annual costs of implementing the current dog rabies vaccination policy in Japan ($Costs_{annual}$)			
Total		$160,472,075 ($149,268,935 – 171,669,974)	
Direct vaccination costs		$138,385,592	
Indirect costs	**Time (income) loss**	$20,738,625 ($9,538,214 – 31,933,764)	
	Transport costs	$1,343,885 ($1,327,628 – 1,360,131)	
	Advertisement costs	$4,333	
Economic burden of a rabies outbreak in Japan			
		Under current vaccination policy ($Burden_{vac}$)	Under abolition of vaccination policy ($Burden_{abolish}$)
Total		$1,682,707 ($1,180,289 – 2,249,283)	$5,019,093 ($3,986,882 – 6,133,687)
Dog rabies control costs	**Emergency dog vaccination**	$230,828 ($193,895 – 270,068)	$479,661 ($402,915 – 561,203)
	Stray dog depopulation and epidemiological investigation	$488,177 ($454,033 – 530,988)	$1,918,071 ($1,847,107 – 2,007,019)
Direct PEP/PrEP costs	**PEP due to rabid dog exposure**	$7,999 ($6,772 – 9,397)	$36,930 ($31,268 – 43,387)
	PEP due to public panic	$302,625 ($100,878 – 504,392)	$1,048,214 ($524,065 – 1,572,195)
	Occupational PrEP	$19,350	$38,700
Indirect PEP costs	**Time (income) loss for PEP due to rabid dog exposure**	$2,389 ($2,300 – 2,480)	$11,031 ($10,621 – 11,452)

	Time (income) loss for PEP due to public panic	$167,310 ($56,569 – 285,318)	$579,553 ($290,476 – 897,239)
	Transport costs for PEP due to rabid dog exposure	$435 ($428 – 443)	$2,009 ($1,974 – 2,045)
	Transport costs for PEP due to pubic panic	$30,473 ($10,226 – 51,337)	$105,555 ($52,834 – 161,383)
Surveillance costs		$433,117 ($144,941 – 865,454)	$799,377 ($322,136 – 1,436,070)

Table 5.4 Worse-case scenario analysis demonstrating the effect of simultaneous stepwise increases in *P_annual* and *Burden*$_{abolish}$ (relative to *Burden*$_{vac}$) on *BCR*

	Scenario 1 (Baseline)	Scenario 2 (500-fold)	Scenario 3 (1000-fold)	Scenario 4 (1500-fold)
Annual probability of rabies introduction into Japan (*P_annual*)	2.57×10^{-5}	0.01	0.03	0.04
Economic burden of a dog rabies outbreak in Japan under the abolition of current vaccination policy (*Burden*$_{abolish}$)[a]	\$5.02 million	\$2.51 billion	\$5.02 billion	\$7.53 billion
Ratio of *Burden*$_{abolish}$ to *Burden*$_{vac}$	3 : 1	1500 : 1	3000 : 1	4500 : 1
Benefit-cost ratio (*BCR*)[b]	5.35×10^{-7} (3.46×10^{-7} – 7.37×10^{-7})	0.20 (0.16 – 0.25)	0.81 (0.63 – 1.00)	1.81 (1.42 – 2.25)

[a] Mean value is presented

[b] Mean value (90% prediction interval) is presented

Table 5.5 Best case scenario analysis of the situation under which the economic efficiency of maintaining a pre-emptive dog vaccination policy in rabies-free Japan could be maximised

	Current situation (Baseline)	Best-case situation
Direct cost of a single dog rabies vaccination ($Cost_{vac}$)	\$29.52	\$8.92
Annual number of companion dogs vaccinated	4,688,240 (whole Japan)	118,387 (using the number of dogs vaccinated in Ibaraki Prefecture as an example)
Frequency of vaccination	Every year	Every two to three years
Annual costs of implementing the rabies vaccination policy ($Costs_{annual}$)[a]	\$160 million	\$492 thousand[b]
Annual probability of rabies introduction into Japan (*P_annual*)	2.57×10^{-5}	2.57×10^{-3}
Economic burden of a dog rabies outbreak in Japan under the abolition of current vaccination policy ($Burden_{abolish}$)[a]	\$5.02 million	\$502 million
Ratio of $Burden_{abolish}$ to $Burden_{vac}$	3 : 1	300 : 1
Benefit-cost ratio (*BCR*)[c]	5.35×10^{-7} (3.46×10^{-7} – 7.37×10^{-7})	2.61 (2.07 – 3.20)

[a] Mean value is presented

[b] Calculated by dividing the adjusted $Costs_{annual}$ by 2.5

[c] Mean value (90% prediction interval) is presented

General discussion and conclusion

The present doctoral thesis quantitatively assessed the effectiveness and appropriateness of the current rabies prevention system in Japan through a variety of mathematical tools including import risk analysis, regression analysis, meta-analysis and benefit-cost analysis. The risks of re-introduction of rabies into Japan, as illustrated in Studies 1 and 2, are very low given the effectiveness of the current national rabies prevention system. Although the current system is highly effective, it is unfortunately and conflictingly not the most appropriate one for today's Japan (in other words it is old-fashioned), particularly in relation to promoting everyone's compliance to such a strict system and addressing the behaviour of modern Japanese dog owners, as demonstrated in Studies 3, 4 and 5. In this regard, the present thesis proposed several evidence-based recommendations (Table 6.1) which aim to amend and update the current system to a more appropriate, relevant and user-friendly one. Implementing the recommendations proposed under Studies 1 to 4 should instantly and practically facilitate positive impacts to the current system. Importantly, amending the import regime for dogs and cats manged by MAFF is very feasible given the import regime was already amended once in 2004 and also the example of policy amendment in United Kingdom in 2012; relaxing the booster requirement of the Japanese rabies vaccine for dogs from every year to every 2 – 3 years should also be considered feasible given the example of policy implementation in Hong Kong. On the contrary, addressing the issue of economic inefficiency of the annual rabies vaccination of domestic dogs (also in terms of its appropriateness for the dog owners) is not as straightforward, where it is highly warranted for policy makers to consider the available options proposed under Study 5.

Table 6.1 List of evidence-based recommendations proposed in each of the five epidemiological studies of the current doctoral thesis

	Aspects of current Japanese rabies prevention system	Recommendations	Pros	Cons
Study 1	Import regime for dogs and cats managed by MAFF	● Shortening the waiting period from 180 days to 90 days ● Reducing the vaccination requirement from 2-times to 1-time	✓ Promote travellers' compliance with the import regime ✓ Actual risk of rabies introduction could be greatly reduced by promoting compliance	Absolute risk of rabies introduction would be increased due to relaxation of the import regime, which appears paradoxically a disadvantage if one does not consider the effect of non-compliance
Study 2	Control measures against the illegal landing of dogs from Russian fishing boats	● Maintain current control measures, e.g. education of Russian fishermen and daily patrol at the ports ● Implement further control measures, e.g. wildlife management around the port areas	Maintaining current control measures does not require additional resources	Implementing further control measures requires additional resources
Study 3	1. Contact rate between	● Conduct further infectious disease	✓ Better understand how rabies might spread in the	n/a

	companion dogs during dog walking, which is subject to the behaviour of dog owners 2. Practices towards potential cases of rabies among dog owners	modelling using contact rate data from Study 3 ● Conduct a survey of general dog owners in Japan to validate key findings from Study 3, e.g. early notification of suspected rabies can be expected from insured dog owners ● Review the current Japan-specific rules of dog identification (which involves using a dog registration tag and a rabies vaccination tag)	companion dog population to refine the contingency plan ✓ Better understand the knowledge, awareness and practices (KAP) of rabies among general dog owners in Japan ✓ Consider adopting compulsory dog microchipping which would facilitate storage of the dog's data such as rabies vaccination history	
Study 4	Efficacy of the Japanese rabies RC-HL strain vaccine in dogs	Relax the booster requirement from every year to every 2 – 3 years	✓ Increase actual herd immunity by promoting owner compliance with regularly dog rabies vaccination ✓ Reduce vaccine-associated adverse events (VAAE)	Herd immunity appears lower due to individuals receiving less frequent vaccinations, if one does not consider the effect of vaccination coverage
Study 5	Annual rabies vaccination of domestic dogs	Improve the economic efficiency of the current policy by decreasing the vaccination price charged to dog owners, relaxing the frequency of vaccination as recommended in Study 4 and implementing the policy on a smaller scale	✓ Promote owner compliance with regularly dog rabies vaccination ✓ Resources saved could be allocated to more efficient uses to strengthen the current rabies prevention system	➢ Economic efficiency is improved but overall is still very inefficient ➢ Implementing the policy in targeted prefectures rather than the whole Japan is practically difficult to achieve
		Abolish the current policy, i.e. no mandatory dog rabies vaccination	✓ Completely eliminate the issues of economic inefficiency	➢ Potential unintended consequences of abolishing the current

			✓ Resources saved could be allocated to more efficient uses to strengthen the current rabies prevention system	policy ➢ Further research is warranted to provide more scientific evidence supporting this policy change

The work of this thesis was initially conducted as part of the rabies research project “社会情勢の変化を踏まえた我が国における狂犬病対策のあり方に関する研究” under the collaboration between the University of Tokyo, Rakuno Gakuen University and Gifu University and funded by MHLW (grant number H25-Shinko-Shitei-004) [Available in Japanese from https://mhlw-grants.niph.go.jp/niph/search/NIDD00.do?resrchNum=201517006B]. The results of this research project are also published in English as “A comparative review of prevention of rabies incursion between Japan and other rabies-free countries or regions” in *Japanese Journal of Infectious Diseases* (Yamada et al. 2018). Readers are invited to refer to these publications for more information.

Just to mention again, the arguments raised in this thesis are also acknowledged at an international level by World Organisation for Animal Health and its Performance of Veterinary Services (PVS) Evaluation Report of the Veterinary Services of Japan (OIE 2016) gave the following recommendations related to rabies prevention programmes in Japan:

1) Review and revise the Rabies Prevention Act considering the current risks of rabies incursion and its management;
2) Some standards in Japan are overly rigorous by international norms and these would benefit from review considering acceptable risk and cost-effectiveness – consider particularly … rabies prevention;
3) Undertake a cost-benefit analysis of the mandatory rabies vaccination of dogs using a risk assessment approach and considering international 'best practices';
4) In the longer term, consider absorbing the Acts relating to rabies … into related generic animal health and public health acts, given declining risks.

Finally, the author truly hopes that this thesis can contribute to the prevention of rabies in Japan through promoting veterinary public health (VPH) and evidence-based veterinary medicine (EBVM). The readers are challenged to adopt critical thinking and become not afraid of bringing appropriate changes to break the status quo as it is often said that "one small step [of change today], one giant leap for mankind [tomorrow]".

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Author achievements

Publications

Rabies-related

1. **Kwan N.C.L.**, Inoue M., Yamada A. & Sugiura K., 2019. Evaluating the contact rate between companion dogs during dog walking and the practices towards potential cases of rabies among dog owners in Japan. *Zoonoses and Public Health*, vol. 66, no. 4, pp. 393–400
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の方法と EU の方法による評価結果の比較―]. *The Japanese Journal of Animal Hygiene*, vol. 42, no. 4, pp. 191–197 [in Japanese]
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<u>Oral presentations</u>

1. 49th Japan Society for Veterinary Epidemiology Conference, 25 March 2017 – "Benefit-cost analysis of the policy of mandatory annual rabies vaccination of domestic dogs in rabies-free Japan"
2. 85th The Japanese Society of Animal Hygiene Academic Meeting, 2 December 2016 – "*Fasciola hepatica* infection in water buffalo *Bubalus bubalis* in three provinces of the Nile Delta, Egypt: a cross-sectional study"
3. 84th The Japanese Society of Animal Hygiene Academic Meeting, 9 July 2016 – "Quantitative risk assessment of the introduction of rabies into Japan through the importation of dogs and cats worldwide"
4. 47th Japan Society for Veterinary Epidemiology Conference, 20 March 2016 – "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"

<u>Poster presentations</u>

1. JPN-ROK Joint Symposium in Veterinary Epidemiology, 11 June 2016 – "The sales amount of veterinary antimicrobial agents in food-producing animals in Japan from

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“An idea is like a virus, resilient, highly contagious. The smallest seed of an idea can grow … one simple little idea, that changed everything”

– *Inception* (2010)