

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

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## SUMMARY

Japan has been free from rabies since 1958. A strict import regimen has been adopted since 2004 consisting of identification of an 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 and simulations were run using @RISK. The probability of infection in a single dog or cat imported into Japan is estimated to be  $2.16 \times 10^{-9}$  [90% prediction interval (PI)  $6.65 \times 10^{-11}$ – $6.48 \times 10^{-9}$ ]. 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 regimen 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 a single vaccination, but serological testing should not be stopped.

**Key words:** Cat, dog, import, Japan, rabies, risk assessment.

## INTRODUCTION

Japan has been free from rabies since 1958, except for one introduced human case from Nepal in 1970 and two introduced human cases from the Philippines in

2006 [1]. The last local human case of rabies occurred in 1956, while the last domestic animal case occurred in a cat in 1957. Under the Rabies Prevention Law enforced since 1950, Japan has a strict regimen for the importation of dogs and cats from countries and territories throughout the world. An old regimen consisting of rabies vaccination, a waiting period of 30–180 or 30–365 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.

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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 regimen in November 2004 for dogs and cats and other designated animals at risk of rabies infection including raccoons, foxes and skunks. The new regimen consists of identification of the animal with a microchip, a two-time rabies vaccination (not necessary for dogs and cats from designated rabies-free regions including Australia, New Zealand, Fiji, Guam, Hawaii, Iceland), neutralizing antibody titration test and a waiting period of 180 days [1, 2]. In addition, this new regimen 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.* [2], this regimen reduced the risk of rabies introduction into Japan by 25- to 70-fold compared to the previous regimen.

Importation of pets into Japan is mainly through the Animal Quarantine Service (AQS) and there are over 8000 dogs and cats imported each year. Apart from this importation through AQS, there is also a considerable number of dogs and cats (over 1100) imported into Japan each year through the United States Force Japan (USFJ).

Quantitative risk assessment (QRA) has been widely used to provide scientific evidence for policy decisions relating to rabies at both national and international levels [3–5]. 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 regimen. The risk is quantified as (i) the probability of infection in a single dog or cat imported into Japan; (ii) the annual probability of importing at least one infected dog or cat into Japan; and (iii) 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 regimen in Japan be amended in the future.

## MATERIAL AND METHODS

### Risk pathways

A stochastic scenario tree model was developed based on Goddard *et al.* [4] with specific re-parameterization to accommodate the situation in Japan. In this model, a total of 14 risk pathways through which rabies may

enter Japan were identified (Fig. 1). Pathways 1–12 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.

*Pathway 1.* A rabies-infected animal is selected; it is vaccinated but not protected (i.e. antibody level does not rise); 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.* The 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 a 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 forged documents in an attempt to avoid the testing of antibody level 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.* The 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.* The 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).

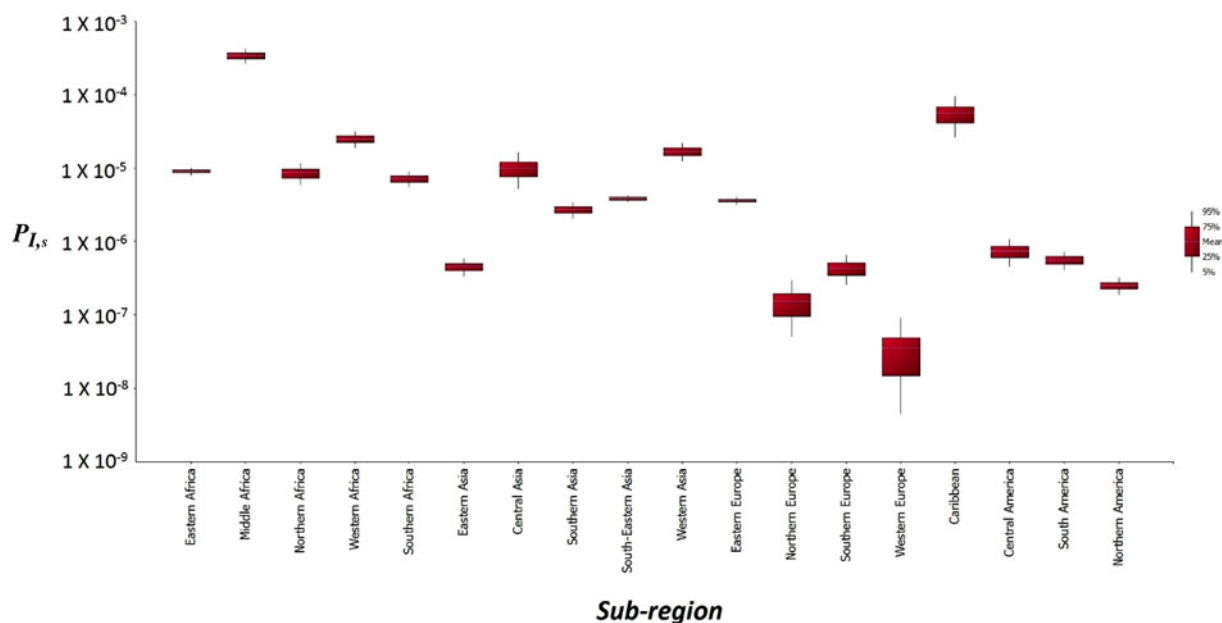
*Pathway 6.* The same as pathway 5 except that the animal is not inspected; this scenario is used to test the effect of non-compliance of the personnel.

*Pathways 7–12.* Serves as the counterpart of pathways 1–6, 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.* Besides importation through AQS, there are also a substantial number of dogs and cats imported



**Fig. 1.** Scenario trees showing the 14 risk pathways of rabies introduction into Japan. (a) Rabies introduction through importation via the 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. 2.** Probability that an animal from a subregion ( $s$ ) 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 subregions: Australia/New Zealand, Melanesia, Micronesia and Polynesia.

into Japan through USFJ (Fig. 2). 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 USFJ personnel by modelling the scenario where an animal without complete documentation is not subject to the mandatory 180-day quarantine.

### 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 six regions with 22 subregions (Table 1).

### Parameter estimation

An alphabetical list of parameters and quantities used in the current model is shown in Table 2.

### 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.* [4].

### Probability that an animal from a subregion ( $s$ ) is incubating rabies ( $P_{I,s}$ ) (Fig. 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 [6, 7]:

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

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

The maximum annual incidence was considered for two reasons: first, incidence provides a direct estimate of the probability or risk of a disease [8] and second, the effect of under-reporting would be taken in account by considering the maximum number of cases. The maximum number of unobserved rabies cases at a particular instant of time was calculated by multiplying  $I_s$  with the mean of the incubation period ( $\bar{IP}$ ) and dividing the product by 365. Assuming new rabies cases follow a Poisson process, a gamma

Table 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	Subregion	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, USA (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

distribution was used to describe the uncertainty of the Poisson mean [9]:

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

Finally,  $P_{I,s}$  is given by dividing  $\lambda_s$  with the companion dog and cat population in the corresponding subregion ( $N_{\text{companion},s}$ ) based on international databases [7, 10]. The  $P_{I,s}$  estimated for each subregion is assumed to be representative of all the countries within the subregion taking into account the effect of incomplete or unavailable data on rabies cases and/or companion animal population for individual country.

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

For each subregion, this probability was given by:

$$P_{I^*,s} = 1 - (1 - P_{I,s})^T,$$

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:

$$\frac{\text{Gamma}(I_s + 1, 1)}{365 \times N_{\text{companion},s}}.$$

The estimates for  $P_{I,s}$  are presented in Fig. 2. The number of rabies cases was assumed to be zero for the following rabies-free countries/regions recognized



Table 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 $j$
$I_j^{(\text{year})}$	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 subregion $s$
$j$	Exporting country
$N_{\text{aqs},s}$	Maximum annual number of dogs and cats imported from subregion $s$ through the Animal Quarantine Service (AQS) during 2010 to 2013
$N_{\text{companion},s}$	Companion dog and cat population in subregion $s$
$N_{\text{usfj},s}$	Maximum annual number of dogs and cats imported from subregion $s$ by United States Force Japan (USFJ) during 2010 to 2013
$P_{\text{aqs},r}$	Annual probability of importing at least one infected dog or cat through AQS from region $r$
$P_{\text{aqs},\text{worldwide}}$	Annual probability of importing at least one infected dog or cat through AQS from the world
$P_{I,s}$	Probability that an animal from a subregion ( $s$ ) is incubating rabies
$P_{r,s}$	Daily probability of an animal becoming infected with rabies in subregion $s$
$P_{r^*,s}$	Probability that an animal becomes infected during the waiting period in subregion $s$
$P_{\text{Md}+}$	Probability that a Madivak-vaccinated animal acquires an antibody titre $>0.5$ IU/ml
$P_{\text{Nb}+}$	Probability that a Nobivak-vaccinated animal acquires an antibody titre $>0.5$ IU/ml
$P_{\text{NP}}$	Probability that an animal is not protected against rabies after two-time vaccination
$P_{\text{Rb}+}$	Probability that a Rabisin-vaccinated animal acquires an antibody titre $>0.5$ IU/ml
$P_{\text{usfj},\text{worldwide}}$	Annual probability of importing at least one infected dog or cat by USFJ from the world
$P_V$	Probability that an animal is vaccinated (compliance parameter)
$P_{\text{worldwide}}$	Annual probability of importing at least one infected dog or cat from the world
$R_{\text{aqs},s}$	Probability of infection in a single dog or cat imported through AQS from subregion $s$
$R_{s,\text{pathway}}$	Probability of rabies introduction from subregion $s$ through a specific pathway (1, 2, 3, ..., 14)
$R_{\text{usfj},s}$	Probability of infection in a single dog or cat imported through USFJ from subregion $s$
$s$	Subregion
$Sp_{\text{FAVN}}$	Specificity of fluorescent antibody virus neutralization
$Sp_{\text{RFFIT}}$	Specificity of rapid fluorescent focus inhibition test
$T$	Exposure time in the exporting country
$Y_{\text{worldwide}}$	The number of years until the introduction of a rabies case into Japan
$\lambda_s$	Maximum number of unobserved rabies cases at a particular instant of time in subregion $s$

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.

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

This was calculated using data in Cliquet *et al.* [11] and the methodology in Goddard *et al.* [4]. Two serological tests, fluorescent antibody virus neutralization (FAVN) and the rapid fluorescent focus inhibition test (RFFIT) were included and their specificities ( $Sp_{\text{FAVN}}$  and  $Sp_{\text{RFFIT}}$ ) 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.  $P_{\text{ST}+}$  was given by:

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

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

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

The AQS follows the international standard of World Organization for Animal Health (OIE) and test results of antibody level must be  $>0.5$  IU/ml to be regarded satisfactory [1]. Therefore,  $P_{\text{NP}}$  was calculated based on this cut-off using the method described in Goddard *et al.* [4] which combines the data of four vaccination studies [12, 13, 14, 15]. Three rabies vaccines, Rabisin (Rb), Madivak (Md) and Nobivak (Nb), were considered and  $P_{\text{NP}}$  was given by:

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

The mean  $P_{\text{NP}}$  was estimated to be 0.056 (90% PI 0.017–0.11). For animals that are infected with rabies

before vaccination (pathways 1–4), the  $P_{NP}$  was assumed to be 1.

*Probability that an infected animal does not show clinical signs upon arrival in Japan ( $P_{NCS}$ )*

For pathways 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 pathways 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 (1 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.

*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 an 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 to 0 for pathways 5, 6, 11 and 12.

*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 forged documentation would be able to pass the inspection.

*Annual number of dogs and cats imported from each subregion through AQS and USFJ ( $N_{aq,s}$  and  $N_{usfj,s}$ )*

The maximum annual number of importations during 2010–2013 was chosen in order to calculate the risk for the worst-case scenario (Fig. 3).

**Risk estimation and model outputs**

The formulas for the probability of rabies introduction through each risk pathway [for each subregion ( $s$ )] 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:  $R_{s,5} = P_{I,s} \times (1 - P_V) \times (1 - P_{ST}) \times P_{NCS} \times P_C \times P_{C+}$
- Pathway 6:  $R_{s,6} = P_{I,s} \times (1 - P_V) \times (1 - P_{ST}) \times P_{NCS} \times (1 - P_C) \times P_{C+}$
- Pathway 7:  $R_{s,7} = (1 - P_{I,s}) \times P_V \times P_{NP} \times P_{ST} \times P_{ST+} \times P_{I^*,s} \times P_{NCS} \times P_C \times P_{C+}$
- 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:  $R_{s,14} = P_{I,s} \times (1 - P_C)$ .

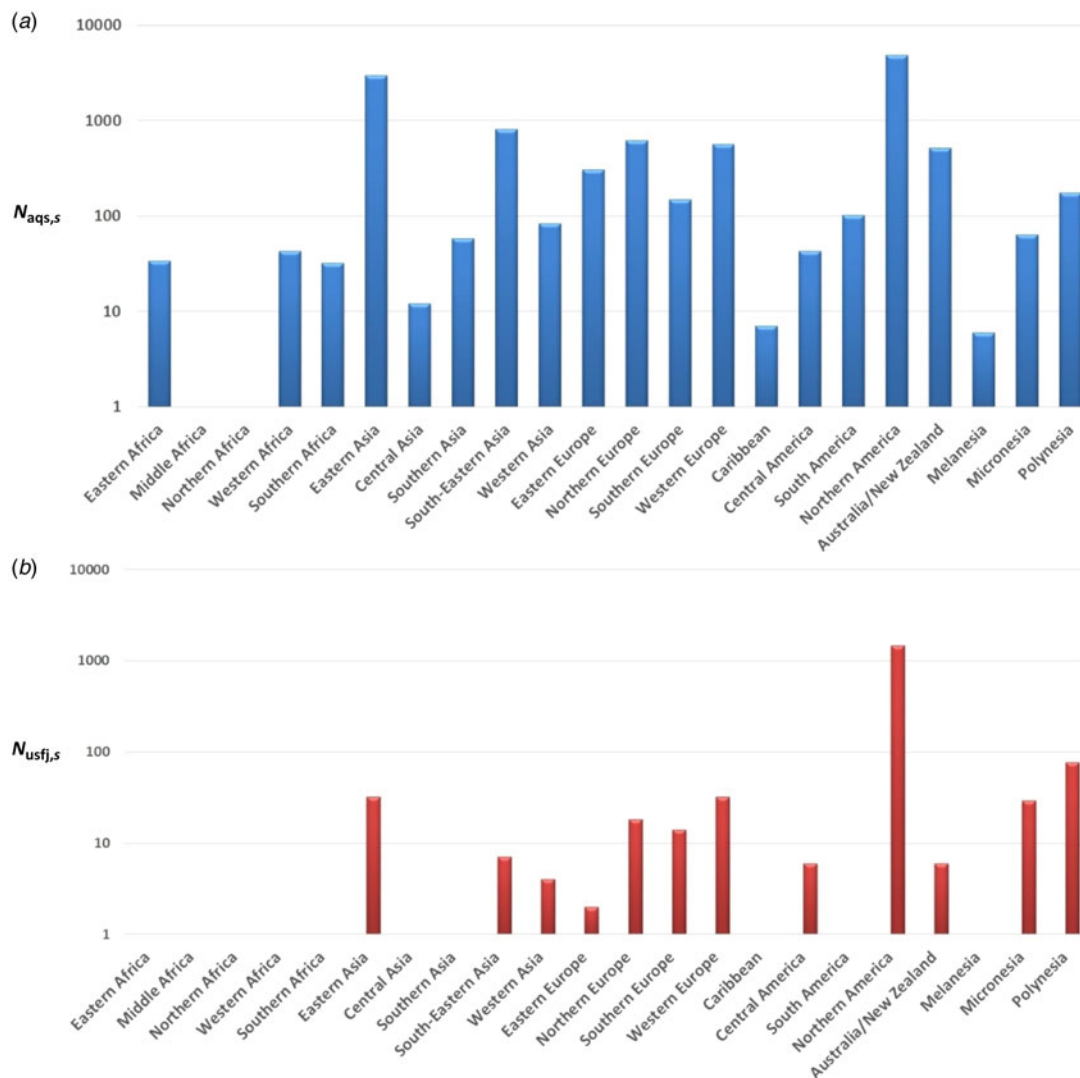
The probability of infection in a single dog or cat imported from each subregion was calculated by summing up the  $R_{s,i}$  of pathways from 1 to 12 (for AQS) and of pathways 13 and 14 (for USFJ):

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

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

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 subregion  $s$  was calculated by taking into account the  $N_{aq,s}$  and  $N_{usfj,s}$ , respectively:

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



**Fig. 3.** Maximum annual number of dogs and cats imported to Japan during 2010–2013 through (a) the Animal Quarantine Service and (b) United States Force Japan from each subregion, denoted as  $N_{aq,s}$  and  $N_{usfj,s}$ , respectively.

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

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

$$P_{aq,r} = 1 - \prod_s (1 - P_{aq,s})$$

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

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

$$P_{aq,worldwide} = 1 - \prod_r (1 - P_{aq,r})$$

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

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:

$$P_{worldwide} = 1 - (1 - P_{aq,worldwide}) \times (1 - P_{usfj,worldwide})$$

The number of years until the introduction of a rabies case into Japan was then estimated:

$$Y_{worldwide} = 1/P_{worldwide}$$



### Model implementation

The model was developed in @Risk version 6.3 (Palisade, USA) within Microsoft Excel 2013, and was run with 50 000 iterations using Latin Hypercube sampling for each simulation. Results of model outputs are presented as: mean (5th percentile, 95th percentile).

### 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  $Y_{\text{worldwide}}$ . Scenario analysis was performed to assess the effect of changes in selected input parameters summarized in Table 3.

## RESULTS

### Risk quantification

The lists of model outputs for each subregion and region are shown in Table 4, and Supplementary Tables S1 and S2. For the probability of infection in a single dog or cat imported into Japan, the  $R_{\text{aqs, worldwide}}$  is estimated to be  $1.62 \times 10^{-9}$  (90% PI  $5.76 \times 10^{-12}$ – $7.14 \times 10^{-9}$ ), while the  $R_{\text{usfj, worldwide}}$  is estimated to be  $4.04 \times 10^{-9}$  (90% PI  $1.74 \times 10^{-9}$ – $3.39 \times 10^{-9}$ ), giving a  $R_{\text{worldwide}}$  of  $2.16 \times 10^{-9}$  (90% PI  $6.65 \times 10^{-11}$ – $6.48 \times 10^{-9}$ ). For the annual probability that at least one infected dog or cat is imported into Japan, the  $P_{\text{aqs, worldwide}}$  is  $2.02 \times 10^{-5}$  (90% PI  $5.15 \times 10^{-6}$ – $4.65 \times 10^{-5}$ ), while the  $P_{\text{usfj, worldwide}}$  is  $5.45 \times 10^{-6}$  (90% PI  $4.51 \times 10^{-6}$ – $6.51 \times 10^{-6}$ ), giving a  $P_{\text{worldwide}}$  of  $2.57 \times 10^{-5}$  (90% PI  $1.06 \times 10^{-5}$ – $5.22 \times 10^{-5}$ ). In terms of the number of years until the introduction of a rabies case,  $Y_{\text{aqs, worldwide}}$  is 78 034 (90% PI 21 479–194 204), while  $Y_{\text{usfj, worldwide}}$  is 185 762 (90% PI 153 500–221 892), giving an overall  $Y_{\text{worldwide}}$  of 49 444 (90% PI 19 170–94 641).

### Sensitivity analysis

The results of the sensitivity analysis are shown in Figure 4. The top-five most correlated parameters include  $P_{V+, Nb}$ ,  $Sp_{\text{RFFIT}}$ ,  $P_{V+, Rb}$ ,  $P_{V+, Md}$  and  $Sp_{\text{FAVN}}$ .

### Scenario analysis

The effect of different scenarios on the number of years until the introduction of a rabies case

( $Y_{\text{worldwide}}$ ) was investigated and results are shown in Figure 5. From this analysis, it was concluded that non-compliance would significantly increase the risk of rabies introduction, with  $Y_{\text{worldwide}}$  decreasing to 249 (90% PI 231–268) years with a 80% compliance level (Fig. 5a). Increases in the number of imports and rabies cases would also increase the risk of rabies introduction respectively as  $Y_{\text{worldwide}}$  is reduced to 9878 (90% PI 3771–18 723) years with a fivefold increase in the import level (Fig. 5b) and to 5030 (90% PI 1845–10 051) years with a tenfold increase in the number of cases (Fig. 5c). The scenario where rabies vaccines with poor efficacy are used in the exporting country (which may represent less-developed countries) was tested and  $Y_{\text{worldwide}}$  was predicted to decrease to 7015 (90% PI 3590–12 457) years if the efficacy falls to 50% (Fig. 5d). In addition, if the required number of rabies vaccination is changed from two times to one time due to policy amendment,  $Y_{\text{worldwide}}$  would decrease to 18 453 (90% PI 7608–37 553) years (Fig. 5e). If the compulsory serological testing were to be ceased, there would be a large increase in risk of rabies introduction as  $Y_{\text{worldwide}}$  was estimated to be 1971 (90% PI 811–4004) years (Fig. 5f). The risk of rabies introduction would also increase as the waiting period is shortened as, with a 1-day waiting period,  $Y_{\text{worldwide}}$  was estimated to be 7996 (90% PI 3963–14 566) years (Fig. 5g). The impact of using different probability distributions for the incubation period was also assessed (Fig. 5h); the risk of rabies introduction would decrease with the use of a shorter incubation period, e.g.  $Y_{\text{worldwide}}$  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 [16]. This is because the probability that the infected animal does not show clinical signs upon arrival in Japan ( $P_{\text{NCS}}$ ) would decrease as the incubation period is shortened. For the final scenario analysis (Fig. 5i), under the policy amendment recommended by the authors, i.e. a 90-day waiting period and one-time vaccination, the risk of rabies introduction would only increase fourfold with  $Y_{\text{worldwide}}$  decreasing to 12 314 (90% PI 4971–24 350) years.

## 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

Table 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 $N_{ustj}$ )	1	Baseline	To assess the effect of an increased level of importation
	2	Twofold increase	
	3	Threefold increase	
	4	Fivefold 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	Twofold increase	
	3	Fivefold increase	
	4	Tenfold 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	
	2*	0.19 (one-time vaccination)	
Probability that an unprotected animal passes serological testing ( $P_{ST+}$ )	1	0.031 (current regimen)	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 authors
	2	Recommended policy amendment: 90-day waiting period and one-time vaccination	

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

introduction of a rabies case ( $Y_{worldwide}$ ) is especially large when compared to the results of similar QRA performed by others such as the UK which estimated 211 (90% PI 177–247) years [4] and Taiwan which estimated 1822 years (median, 5th percentile is 473 years) [17]. 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

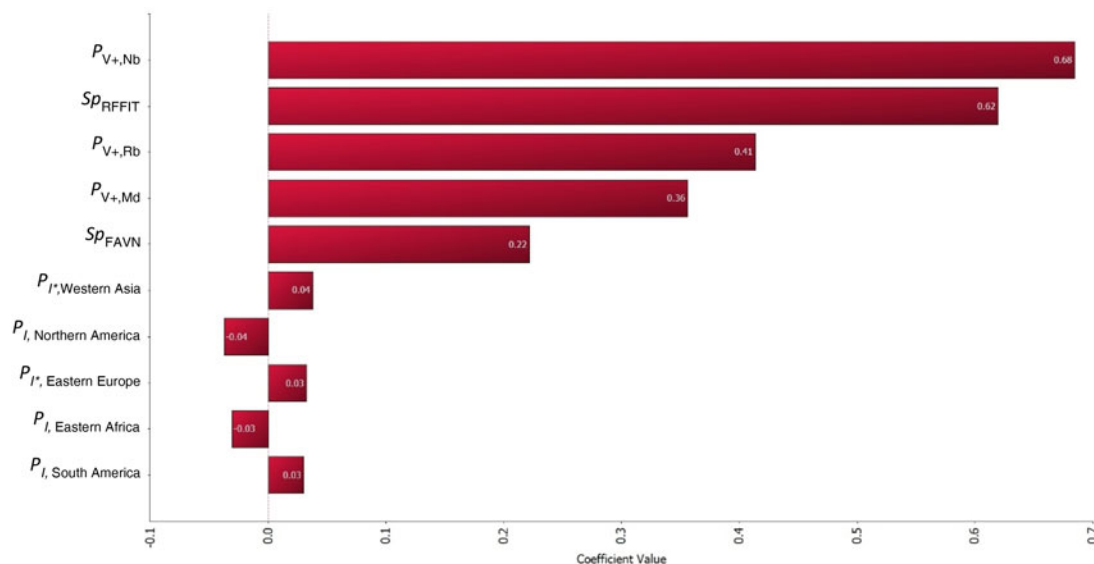
UK model). Both UK and Taiwan have a strict import regimen resembling that of Japan. Taiwan’s regimen additionally requires a 21-day quarantine upon arrival and a second serological testing. The results from Goddard et al. 2012 were estimated according to the European Union Pet Movement Policy (EUPMP), which was implemented in 2012. Compared to the previous UK Pet Travel Scheme (PETS), the EUPMP has a shorter waiting

Table 4. Number of years until the introduction of a rabies case into Japan (*Y*) from each subregion or region

Region	Subregion	$Y_S$	$Y_R$	$Y_{\text{aqS,worldwide}}/Y_{\text{usfj,worldwide}}$	$Y_{\text{worldwide}}$	
AQS	Africa	Eastern Africa	$2.72 \times 10^6$ ( $7.3 \times 10^5$ , $6.89 \times 10^6$ )	$5.26 \times 10^5$ ( $1.4 \times 10^5$ , $1.35 \times 10^6$ )	$7.8 \times 10^4$ ( $2.15 \times 10^4$ , $1.94 \times 10^5$ )	$4.94 \times 10^4$ ( $1.92 \times 10^4$ , $9.46 \times 10^4$ )
		Western Africa	$7.92 \times 10^5$ ( $2.12 \times 10^5$ , $2.02 \times 10^6$ )			
		Southern Africa	$3.69 \times 10^6$ ( $9.86 \times 10^5$ , $9.39 \times 10^6$ )			
	Asia	Eastern Asia	$6.32 \times 10^5$ ( $1.69 \times 10^5$ , $1.61 \times 10^6$ )			
		Central Asia	$7.61 \times 10^6$ ( $2.01 \times 10^6$ , $1.93 \times 10^7$ )			
		Southern Asia	$5.39 \times 10^6$ ( $1.45 \times 10^6$ , $1.37 \times 10^7$ )			
		South-Eastern Asia	$2.26 \times 10^5$ ( $7.14 \times 10^4$ , $6.77 \times 10^5$ )			
		Western Asia	$6.05 \times 10^5$ ( $1.62 \times 10^5$ , $1.54 \times 10^6$ )			
	Europe	Eastern Europe	$7.54 \times 10^5$ ( $2.08 \times 10^5$ , $1.88 \times 10^6$ )			
		Northern Europe	$1.12 \times 10^7$ ( $3.02 \times 10^6$ , $2.82 \times 10^7$ )			
		Southern Europe	$1.38 \times 10^7$ ( $3.73 \times 10^6$ , $3.44 \times 10^7$ )			
		Western Europe	$9.3 \times 10^7$ ( $2.25 \times 10^7$ , $2.45 \times 10^8$ )			
	Latin America and Caribbean	Caribbean	$2.39 \times 10^6$ ( $6.36 \times 10^5$ , $5.99 \times 10^6$ )			
		Central America	$2.78 \times 10^7$ ( $7.48 \times 10^6$ , $7.11 \times 10^7$ )			
South America		$1.52 \times 10^7$ ( $4.06 \times 10^6$ , $3.87 \times 10^7$ )				
North America	Northern America	$6.99 \times 10^5$ ( $1.87 \times 10^5$ , $1.79 \times 10^6$ )				
USFJ	Africa	Northern America	$6.99 \times 10^5$ ( $1.87 \times 10^5$ , $1.79 \times 10^6$ )	$1.86 \times 10^5$ ( $1.54 \times 10^5$ , $2.22 \times 10^5$ )		
		Southern Africa	$1.47 \times 10^7$ ( $1.15 \times 10^7$ , $1.86 \times 10^7$ )			
	Asia	Eastern Asia	$7.31 \times 10^6$ ( $5.56 \times 10^6$ , $9.5 \times 10^6$ )			
		South-Eastern Asia	$3.84 \times 10^6$ ( $3.44 \times 10^6$ , $4.28 \times 10^6$ )			
		Western Asia	$1.56 \times 10^6$ ( $1.18 \times 10^6$ , $2.04 \times 10^6$ )			
	Europe	Eastern Europe	$1.43 \times 10^7$ ( $1.29 \times 10^7$ , $1.59 \times 10^7$ )			
		Northern Europe	$5.09 \times 10^7$ ( $1.93 \times 10^7$ , $1.12 \times 10^8$ )			
		Southern Europe	$1.85 \times 10^7$ ( $1.13 \times 10^7$ , $2.9 \times 10^7$ )			
		Western Europe	$2.49 \times 10^8$ ( $3.56 \times 10^7$ , $7.18 \times 10^8$ )			
	Latin America and Caribbean	Caribbean	$2.12 \times 10^6$ ( $1.08 \times 10^6$ , $3.87 \times 10^6$ )			
		Central America	$2.49 \times 10^7$ ( $1.6 \times 10^7$ , $3.75 \times 10^7$ )			
	North America	Northern America	$2.88 \times 10^5$ ( $2.2 \times 10^5$ , $3.73 \times 10^5$ )			

AQS, Animal Quarantine Service; USFJ, United States Force Japan.

Values are presented as: mean (5th percentile, 95th percentile);  $\times 10^n$  refers to multiplying by  $10^n$ . There was no import of dogs or cats into Japan during 2010–2013 from the following subregions: 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 subregions: Australia/New Zealand, Melanesia, Micronesia and Polynesia. The  $Y_S$  for all these subregions were therefore assumed to be zero.



**Fig. 4.** Tornado graph illustrating the results of sensitivity analysis. All model input parameters are ranked by Spearman's correlation coefficient according to their contributions to the variance of model output  $Y_{\text{worldwide}}$ . 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  $Sp_{FAVN}$ .

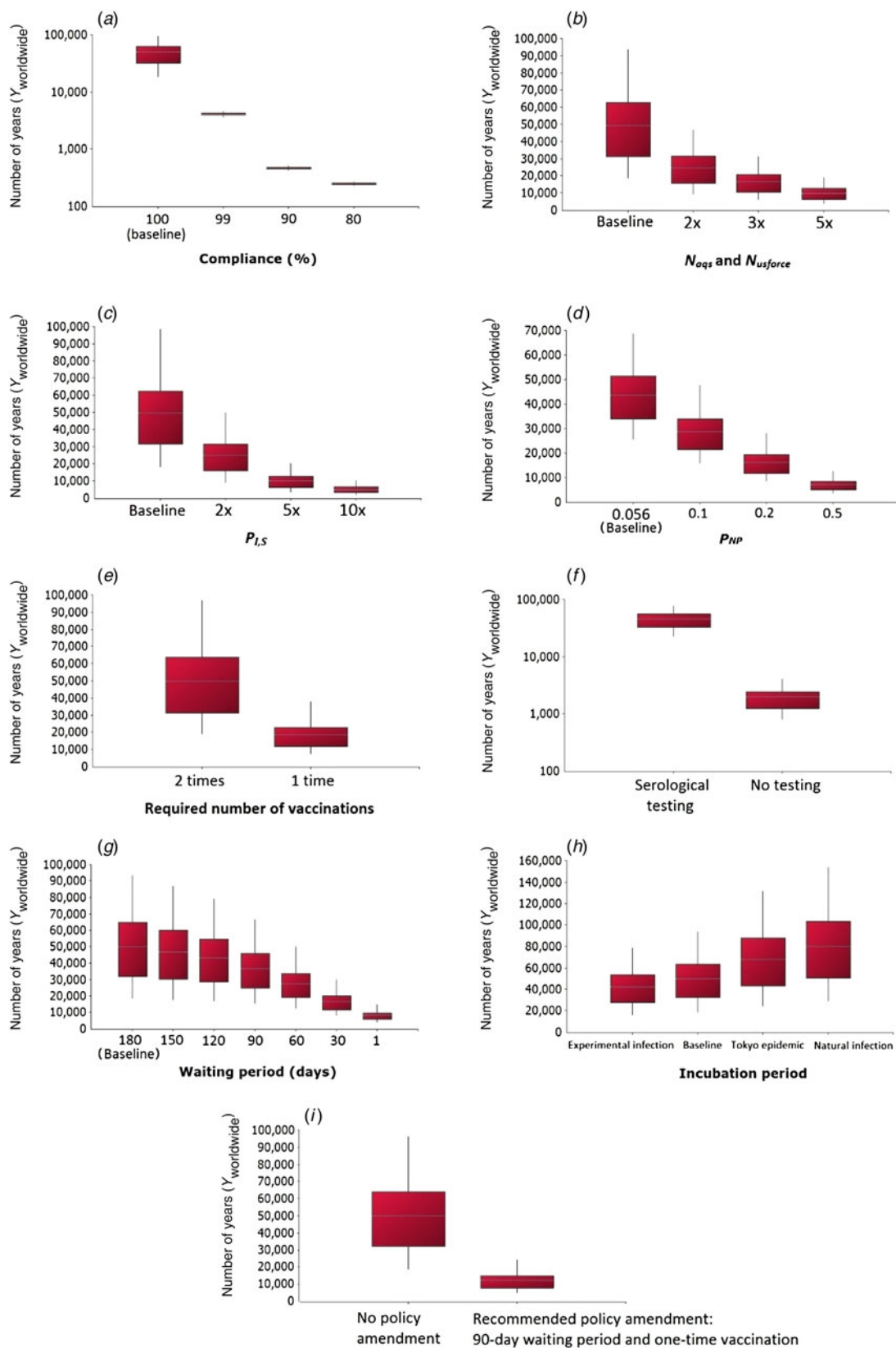
period (it was shortened from 180 days to 21 days for EU and listed countries or 3 months for unlisted countries) and the requirement of serological testing restricted only to unlisted countries.

In terms of the number of dogs and cats imported via AQS and USFJ (Fig. 3), the total  $N_{\text{aq},s}$  is 11 445, while the total  $N_{\text{usfj},s}$  is 1690 which is 6.8-fold lower. The USA (mainland) from the subregion North America is the highest exporter contributing to 41% of the total  $N_{\text{aq},s}$  and 86% of the total  $N_{\text{usfj},s}$  (the  $N_{\text{aq}}$  and  $N_{\text{usfj}}$  from USA is 4362 and 1458, respectively). Eastern Asia (mostly from China, Republic of Korea and Taiwan) is the second highest exporter ( $N_{\text{aq}}$  is 2979) contributing to 26% of the total  $N_{\text{aq},s}$ . In terms of the probability that an imported animal is incubating rabies (Fig. 2), the  $P_{I,s}$  is highest for Middle Africa with a mean of  $3.44 \times 10^{-4}$  (90% PI  $2.68 \times 10^{-4}$ – $4.88 \times 10^{-4}$ ). Nonetheless, there was no importation of dogs and cats from this subregion during 2010–2013. The  $P_{I,s}$  is lowest for Western Europe with a mean of  $3.51 \times 10^{-8}$  (90% PI  $4.44 \times 10^{-9}$ – $9.00 \times 10^{-8}$ ). In terms of the overall annual probability of rabies introduction, the  $P_{\text{aq},\text{worldwide}}$  is highest for Southeastern Asia with a mean of  $5.95 \times 10^{-6}$  ( $1.47 \times 10^{-6}$ – $1.4 \times 10^{-5}$ ), while the  $P_{\text{aq},\text{usfj}}$  is highest for North America with a mean  $3.56 \times 10^{-6}$  (90% PI  $2.68 \times 10^{-6}$ – $4.55 \times 10^{-6}$ ).

Illegal importation or smuggling of animals is a serious issue which could greatly compromise a country's

import regimen in preventing the introduction of diseases and its effect on the risk of rabies entry has been evaluated in various QRA [4, 5, 17, 18]. 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. 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 1–20%, the result of our scenario analysis could be overestimating 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 regimen since 2004 is effective in reducing the risk of rabies introduction into Japan by 22-fold (Fig. 5f), agreeing with the results in Kamakawa *et al.* [2]. 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. 5g). Indeed, if the waiting period is 90 days, the risk of rabies introduction is only increased 1.3-fold. The reduction in waiting period has been a topic in import policy because of animal welfare issues



**Fig. 5.** Scenario analysis depicting the effects of tested scenarios on the number of years until the introduction of a rabies case  $Y_{\text{worldwide}}$ . For each box-whisker plot, the white dotted line indicates the mean; the length of the box indicates the interquartile range; the whiskers indicate the 5th and 95th percentiles, respectively. For panels (a) and (f) a base-10 log scale was used for the y axis. For panel (d), a fixed value of 0.056 was used as the baseline.



and also the potential encouragement of smuggling activities [4, 5, 17]. Although it is difficult to measure the relationship between the strictness of the import regimen and the level of smuggling activities, there is the potential for policy amendment to promote compliance. Indeed, under the recommended policy amendment with a 90-day waiting period and single vaccination (Fig. 5i), the risk of rabies introduction is still very low and would only increase fourfold with  $Y_{\text{worldwide}}$  decreasing to 12 314 (90% PI 4971–24 350) years. Since even a 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. However in reality, perhaps counterintuitively, there is a possibility that this risk could actually be reduced due to the policy amendment leading to increased compliance.

The incubation period ( $IP$ ) distribution of rabies is a fundamental input variable commonly used in QRA. Tojinbara *et al.* [16] 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 [19–22] and naturally infected animals or naturally acquired cases [23–26]. 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. 5h).

In terms of the risk associated with importation of rabies from the United States of America (mainland), our study estimated a  $Y_{\text{aqs}}$  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 ( $Sp_{\text{FAVN}}$  and  $Sp_{\text{RFFIT}}$ ), 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 [8, 27]. 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.  $P_{V+,Nb}$ ,  $Sp_{\text{RFFIT}}$ ,  $P_{V+,Rb}$ ,  $P_{V+,Md}$  and  $Sp_{\text{FAVN}}$  (Fig. 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  $P_{\text{usfj, worldwide}}$  is  $5.45 \times 10^{-6}$ ) is only 3.7-fold lower than the risk through the importation via AQS (mean  $P_{\text{aqs, worldwide}}$  is  $2.02 \times 10^{-5}$ ). 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 regimen in USFJ and the level of compliance are warranted for a more accurate risk assessment.

## CONCLUSION

The risk of rabies introduction into Japan through the importation of dogs and cats is very low. The current import regimen 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 vaccination 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.

## SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit <https://doi.org/10.1017/S0950268816002995>.

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## DECLARATION OF INTEREST

None.

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