



***Risk Analysis to Evaluate Entry of Rabies Virus
into the State of Hawaii***

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- Hawaii is currently the only US state that is rabies free.
 - The US territory of Guam is also rabies free
 - Countries that are rabies free include UK, Iceland, Japan
 - In 1991, a bat in a shipping container from California to Hawaii was captured and tested positive for rabies
- Current procedures are costly and burdensome
 - 120 days at \$10-20/day
 - 5 day or less requires additional costly testing and more rigid vaccination history
- How would shorter quarantines affect the likelihood of rabies introduction?
 - 30, 60, 90 days?

Hawaii seeks a balance between the time and expense of quarantine and the risk of a mainland pet introducing rabies to Hawaii.

Rabies: among the Oldest and Deadliest of Diseases



- Neurotropic virus of the family *Rhabdoviridae*, genus of interest is *Lyssavirus*
 - Replicates in muscle and nervous tissues
 - Travels along nervous pathways to the central nervous system and brain
- Virus transmitted through saliva of infected animal; Most mammals are susceptible
- Can incubate for a few days to a few months to years (cases of 8-22 years are known!) in the infected mammal
- The disease presents three distinct phases (each lasting a few days)
 - Promordial: Fever, headache, sore throat, anxiety, and sensitivity to light
 - Excitation: Increased anxiety, ocular palsies, hydrophobia
 - Paralytic: Hydrophobia recedes, paralysis sets in, death
- Once clinical signs appear, rabies is almost always fatal.
 - Fewer than 10 documented cases of human survival without post exposure vaccination

US spends approximately \$300 million/year on prevention and control.

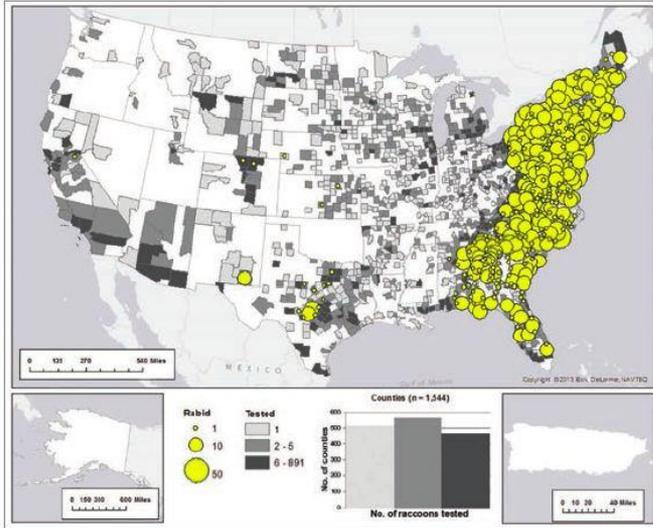


- Rabies is endemic in North America
- Reservoir species maintain the virus and infect other species, each with its own variant(s) of the virus
 - Bats
 - Raccoons
 - Skunks
 - Foxes
 - Mongooses (Puerto Rico)
- Rabies in rodents and other mammals is rare
- Contact between wild animals and domestic animals leads to pet infection
- Skunks, Raccoons and Mongoose (PR)
 - Raccoons: 67% of infected pets
 - Skunks: 30% of infected pets

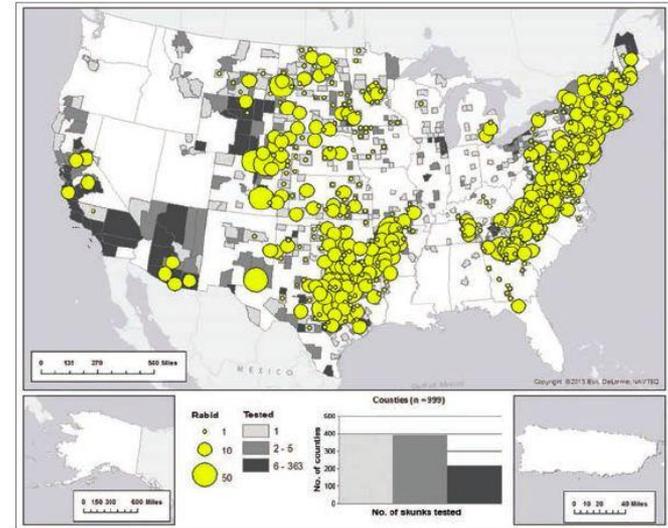


Source: Blanton *et al*, (2012) JAVMA 241(6)

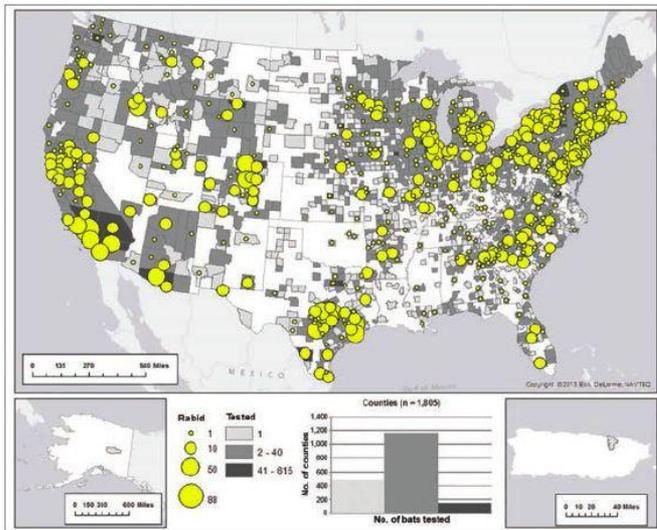
Rabid Animal Distributions, US (2012)



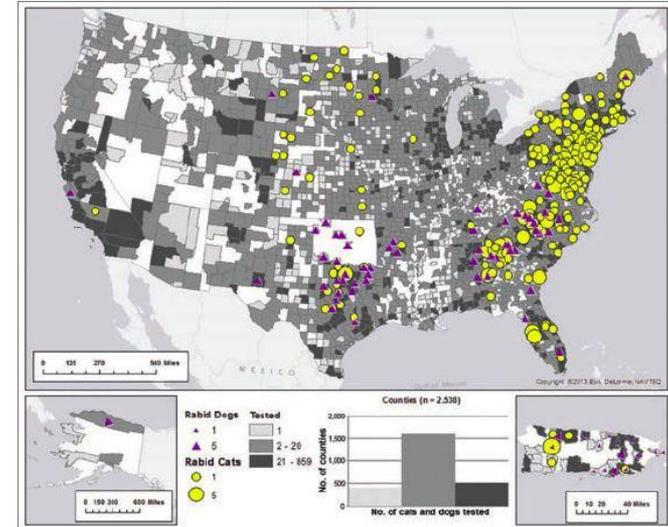
Raccoons: 1953 cases



Skunks: 1539 cases



Bats: 1680 cases



Dogs: 84; Cats: 257

Human Rabies Cases



- Approximately 55,000 deaths worldwide each year
 - About 95% from Africa and Asia
 - About 97% from dog bites
- 34 Cases in the US from Jan 2003 – May 2013

Agent	Bat	Dog	Raccoon	Fox	Unknown
Cases	18	9	3	1	3

Exposure	Bat	Contact	Transplant	Unknown
Cases	13	9	5	7

Data from Dyer *et al.* (2013), *JAVMA* 243(6)

- Agent and exposure determined by witness accounts, virus variant
 - Roughly 10% of submitted samples from humans test positive
- Mortality is nearly 100% once the patient exhibits symptoms



- Of the traditional reservoir populations, only bats and mongooses exist on Hawaii
- The bat population comprises an endangered species
 - Unlikely to provide an endemic disease reservoir
 - Bats, however, generally pose the greatest direct threat to humans
- Mongooses, on the other hand, are a growing nuisance population
 - Imported in the 1880's to control rats on sugar plantations
 - Prey on birds and bird eggs
 - Mongooses provide the primary reservoir in Puerto Rico
- Hawaii maintains stringent vaccination requirements on pets
 - And tracking chip/RFID implants!
- Importation of animals is difficult
 - Rigorous quarantine procedures are designed to prevent infected animals from entering



- The standard 120-day quarantine requirements:
 - A Health Certificate prepared by an accredited veterinarian within 14 days of arrival
 - Electronic microchip implanted for positive ID and tracking.
 - Up-to-date vaccinations including rabies
- The 5-day-or-less quarantine requirements:
 - At least two vaccinations
 - One no earlier than the vaccine maker's interval.
 - A second no later than 90 days prior to entry
 - Microchip implantation for positive ID and tracking
 - OIE-FAVN blood test
 - Checks for sufficient level of antibodies
 - Two approved labs: DoD and Kansas State University
 - Sample must have been provided to the lab between 120 days and 36 months prior to arrival
- Certain exemptions exist
 - UK, Guam, Australia, and New Zealand are also rabies-free
 - Service animals must meet the requirements of the 5-day-or-less to be exempt from quarantine



- Quarantines of 30, 60, 90, 120 days and the 5-day-or-less program
 - Focus on cats and dogs from mainland US
- The narrow focus is due to the nature of the problem
 - Changes in the quarantine will not affect other risks
 - Animals from other destinations will require traditional quarantine.
 - Smuggled animals, accidental transport risks remain the same.
 - A relative risk assessment is appropriate
- Even in this simplified risk scenario, many problems must be solved
 - Identifying risk pathways
 - Quantifying risk probabilities

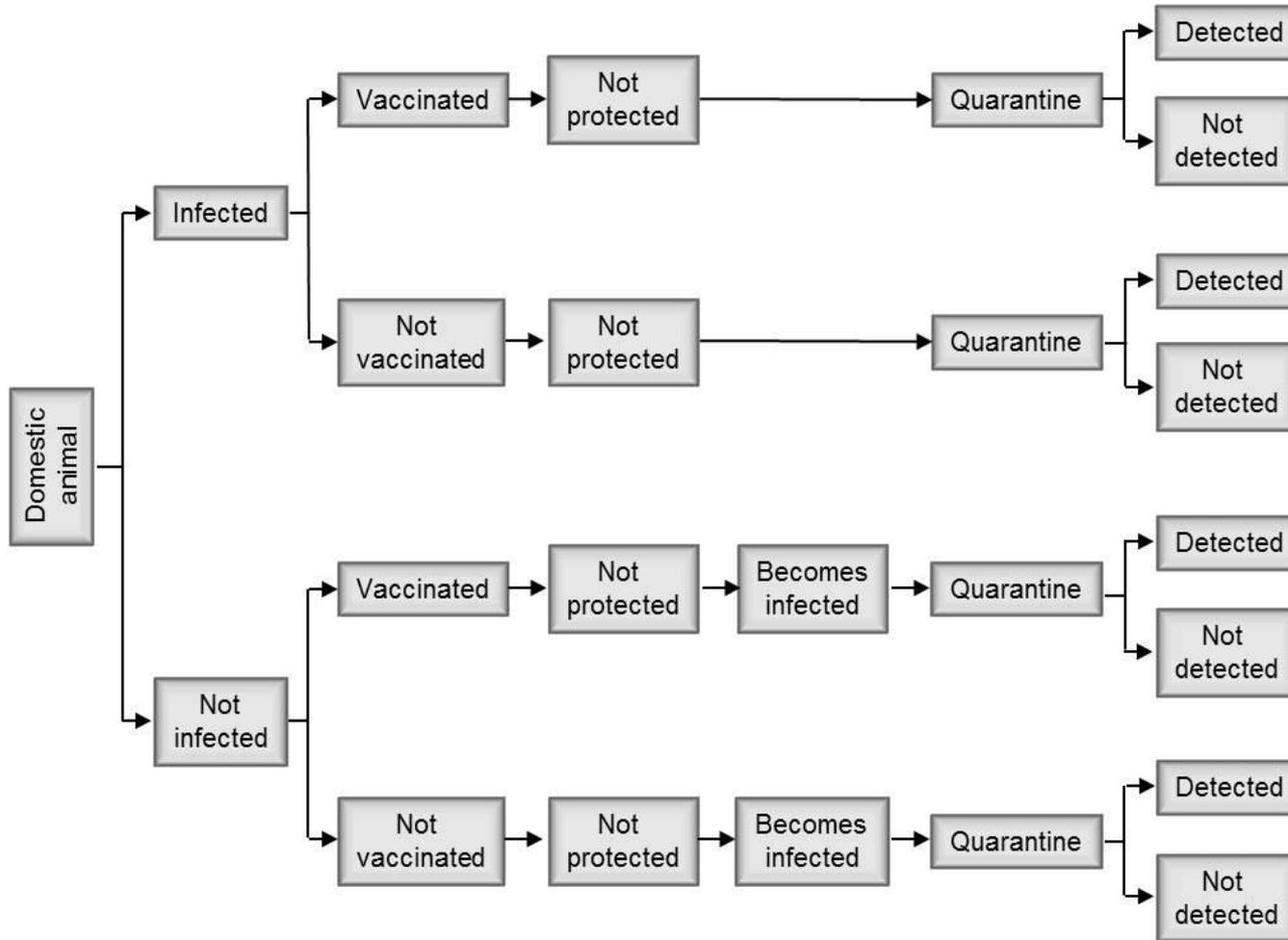


- Release assessment
 - Dog or cat from mainland US imported into Hawaii and infected with rabies
 - Hawaii's primary concern for this study
- Exposure assessment
 - Indigenous pets infected
 - Reservoir populations
 - Human exposure
- Consequence assessment
 - Adverse effects on humans
 - Adverse effects on pets
 - Environmental concerns
- Risk estimation
 - Quantitative analysis of release, exposure, consequence
 - Hawaii's primary concern is on release estimation



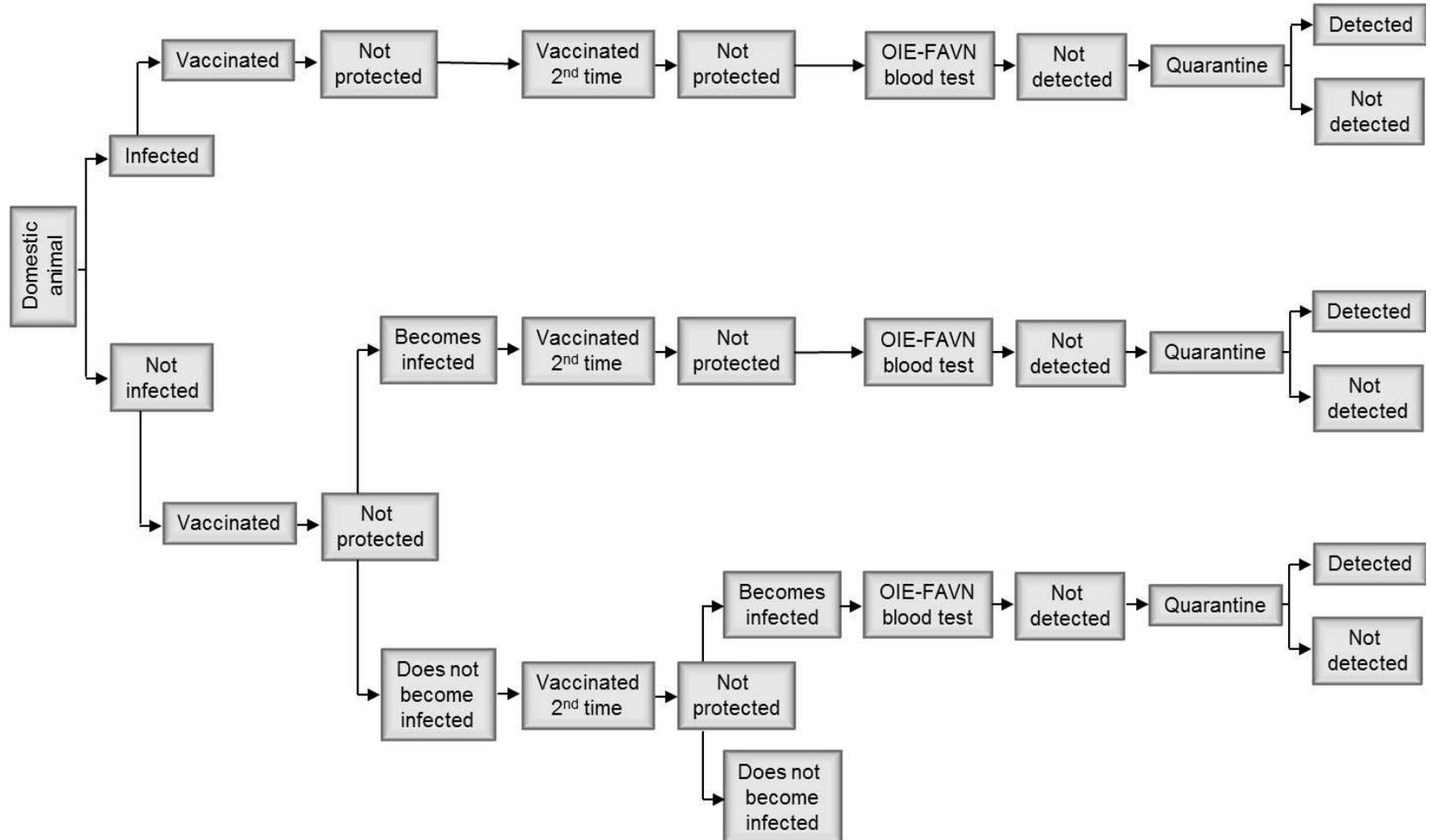
- Introduction of an infected cat or dog from the US mainland
 - Scope creates a highly simplified tree
- Events relevant to the risk estimation
 - Pet is infected (or not)
 - Pet is vaccinated (or not)
 - Order of the preceding events affects estimation
 - Pet exhibits symptoms in quarantine (or not)
 - Pet is released to owner
- Five-day-or-less is more involved
 - Two distinct vaccinations with specified timing
 - OIE-FAVN test for vaccination effectiveness

Scenario Tree for the Standard Quarantine



Note that many paths lead to an irrelevant (and/or non-risky) consequence!

Scenario Tree for the 5-Day-Or-Less Quarantine



A number of irrelevant paths have been left off this tree.



- Over the past 6 years, 78.67 +/- 9.63 rabid dogs and 288.50 +/- 19.83 rabid cats have been submitted for testing (data from *JAVMA* rabies surveillance reports) in the US
 - These numbers represent cases detected in samples submitted to approximately 120 state health, agriculture, university agencies, and the USDA
 - As such, these numbers are likely to be underestimates of actual cases
- There are approximately 69.9 million pet dogs and 74.0 million pet cats in the US (AVMA data from 2012)
 - These numbers are down 5%, 10% respectively, from 2007 AVMA estimates
- Feral dogs and cats create additional issues
 - Dog estimates range from 50 million to over 100 million (but may overlap with pets)
 - Cat estimates are similar, around 50 million
 - Ferals are more likely to over-represent in the infected category
 - Ferals are less likely to be brought to Hawaii



- Likelihood of vaccination is not well-quantified
 - Every US state requires vaccinations
 - Compliance rates, however, are not known
 - One survey, from Texas, considered the impact of 3-year vs. 1-year vaccination frequency (Murray *et al* 2009 *JAVMA* 235(6))
 - Dog vaccination rates: 46% in 1999-2002, 56% in 2004-2007
 - Cat vaccination rates: 18% in 1999-2002, 30% in 2004-2007
 - Required vaccination by Hawaii may follow infection?
- Vaccine effectiveness is not well-quantified
 - In the past 6 years of *JAVMA* US rabies surveillance reports, no dog or cat known to be up-to-date on vaccination has tested positive for rabies
 - A study of dogs and cats from 1997-2001 provides some data
 - 264 rabid dogs and 840 rabid cats
 - 13 dogs and 22 cats had history of vaccination
 - 2 dogs and 3 cats were considered current on vaccination
 - 0.00453 probability of an exposed vaccinated animal contracting rabies
 - Required vaccination by Hawaii may precede infection?



- Incubation period of the infection varies widely
 - Ranges from days to years
 - Goddard *et al* (2012) *Risk Analysis* **32** (10) uses
 - Lognormal distribution
 - Mean of 35 days
 - Standard deviation of 36.8 days
- The FAVN test is required in 5-day-or-less quarantine
 - This test assesses the level of rabies antibodies, not the presence of the disease
 - Generally tests classify as “protected” or “not protected” based on antibody levels (OIE/WHO standard is at least 0.5 IU/ml)
 - Servat *et al* (2007) *J Imm Meth* **318** derive error rates as follows:
 - Sensitivity = 0.793 (true positive), Specificity = 0.993 (true negative)
 - Moore *et al* compared VLA (UK) and Kansas St FAVN testing
 - Sensitivity = 0.987 (VLA+ | KS+), Specificity = 0.51 (VLA- | KS-)
 - Goddard *et al* (2012) data indicate vaccinations pass the FAVN at a rate of 0.935



- Approximately 3700 pets per year are moved through Hawaii's quarantine
 - We model the number of pets as $U[3500,3900]$
- To import rabies, the pet must be exposed
 - Exposure rates are small but highly uncertain
 - Yearly exposure rate modeled as Beta, $\mu=2.2388e-6$, $s=8.3476e-08$
 - Additional modeling multiplies this rate by a factor > 1
- Pets are required to have vaccination record
 - Could it be falsified?
 - Cheaper by far to vaccinate
 - Probability of vaccination is 0.99



- If exposed, time till symptoms appear is lognormally distributed
 - Mean 35 and standard deviation 36.8 days
- Pets may be exposed prior to vaccination
 - Triangle distribution of difference in vaccination and exposure date within one year: exposure day-vaccination day in $[-365,365]$
 - Exposure prior to vaccination = full exposure
 - Exposure post vaccination = exposure if vaccine fails to protect
- Failure probability mean 0.004529, standard deviation 0.002021
 - Modeled as Beta
 - Additional modeling increases this rate by a factor > 1

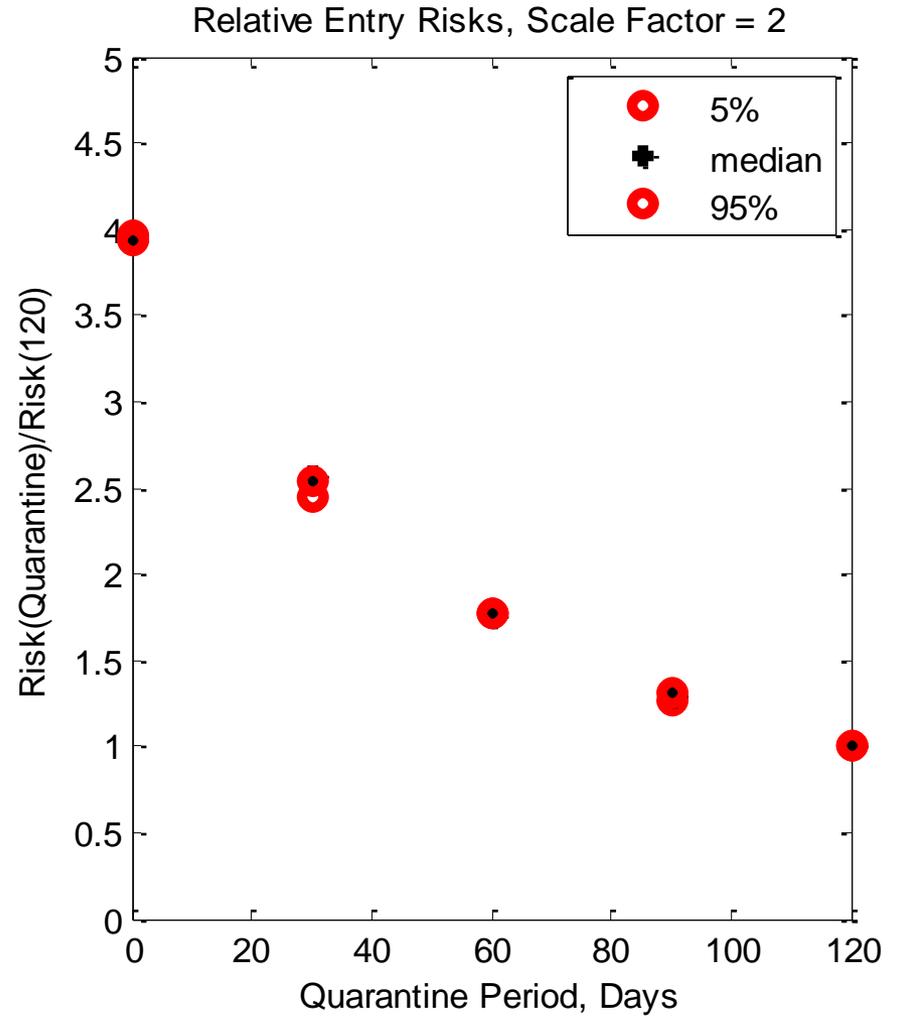
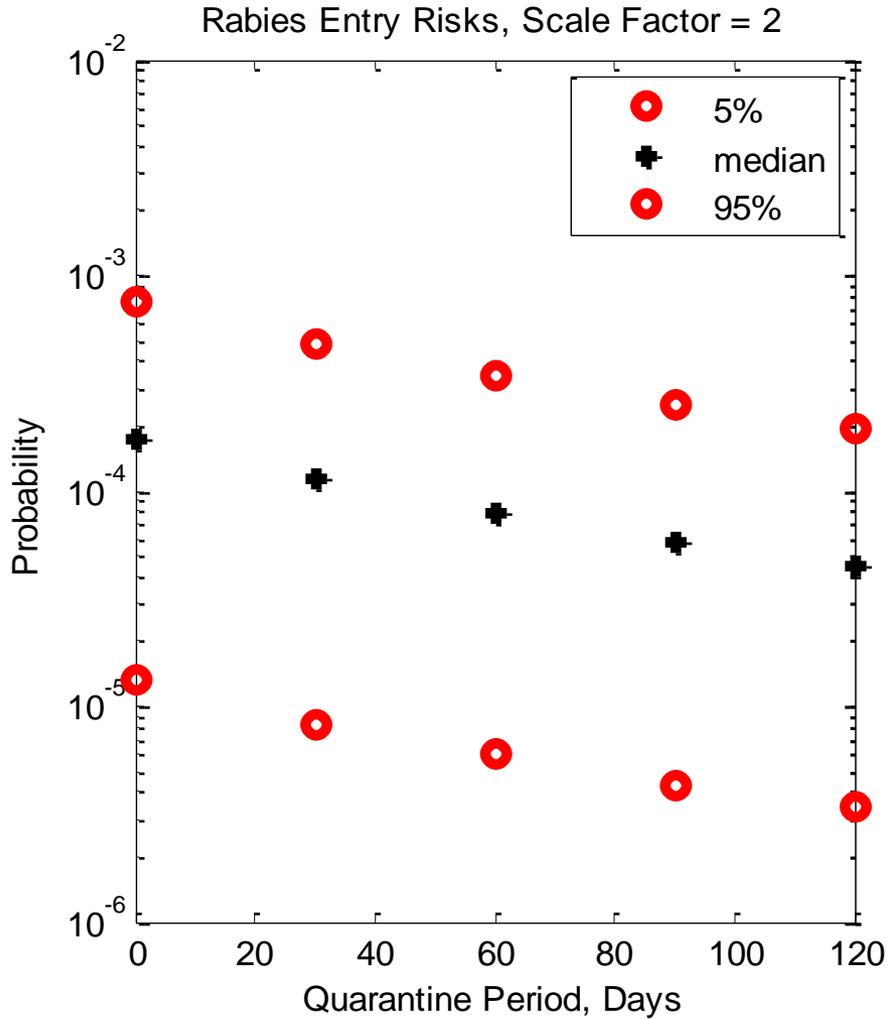


- We simulate 50000 years
- Within each year, we generate a number of pets to be processed
- Within each year, we generate a baseline exposure rate
- For each pet, we generate
 - An exposure time
 - A vaccination time
 - A probability of vaccine failure
 - A probability of remaining asymptomatic through quarantine

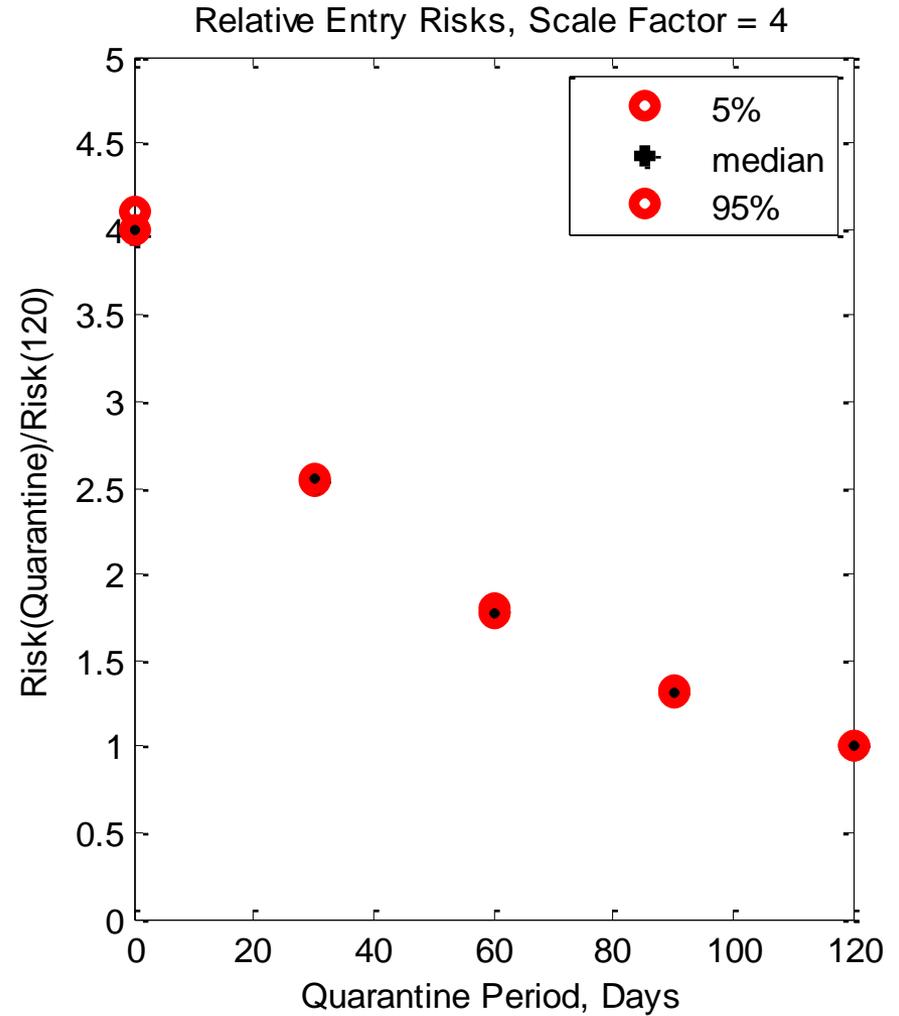
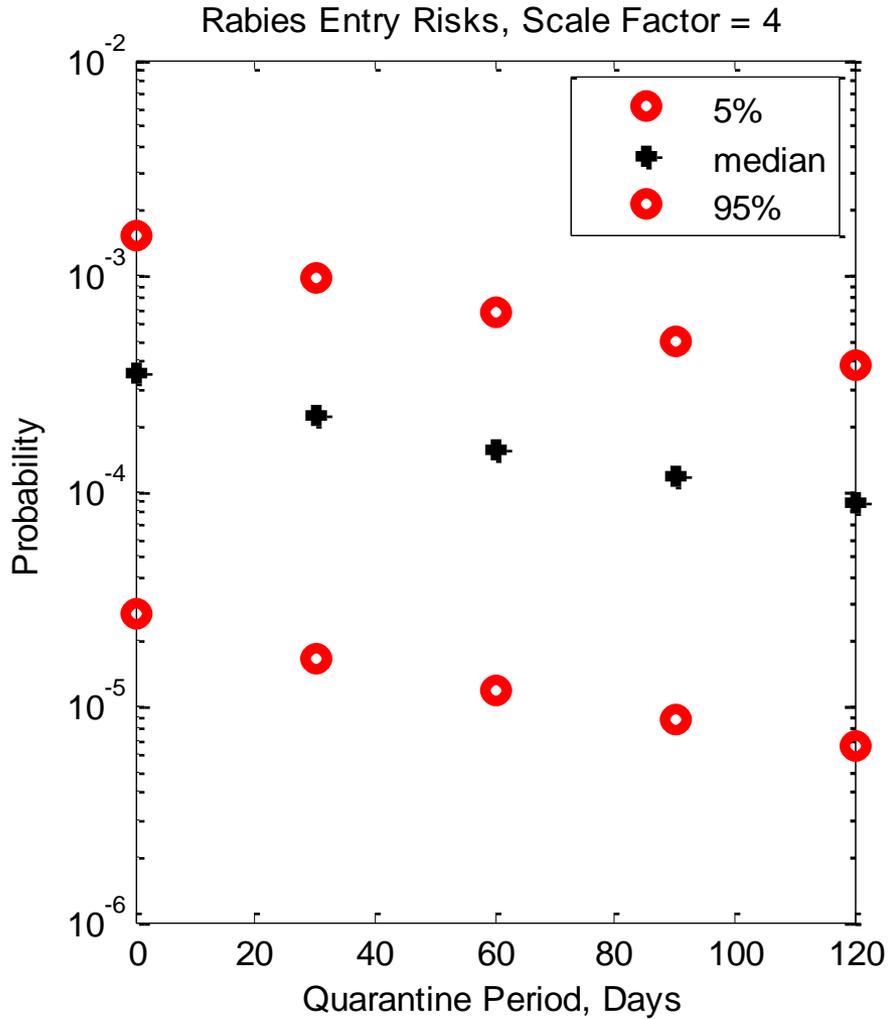
$$P_{\text{rabies imported}} = 1 - \prod_{i=1}^{N_{\text{pets}}} \left\{ 1 - P_{\text{infection}} \left(\frac{1}{2} P_{\text{vaccinated}} P_{\text{asymptomatic}} + \frac{1}{2} P_{\text{vaccine fail}} P_{\text{asymptomatic}} \right) \right\}$$

- Monte Carlo statistics are simulated for the 50000 years

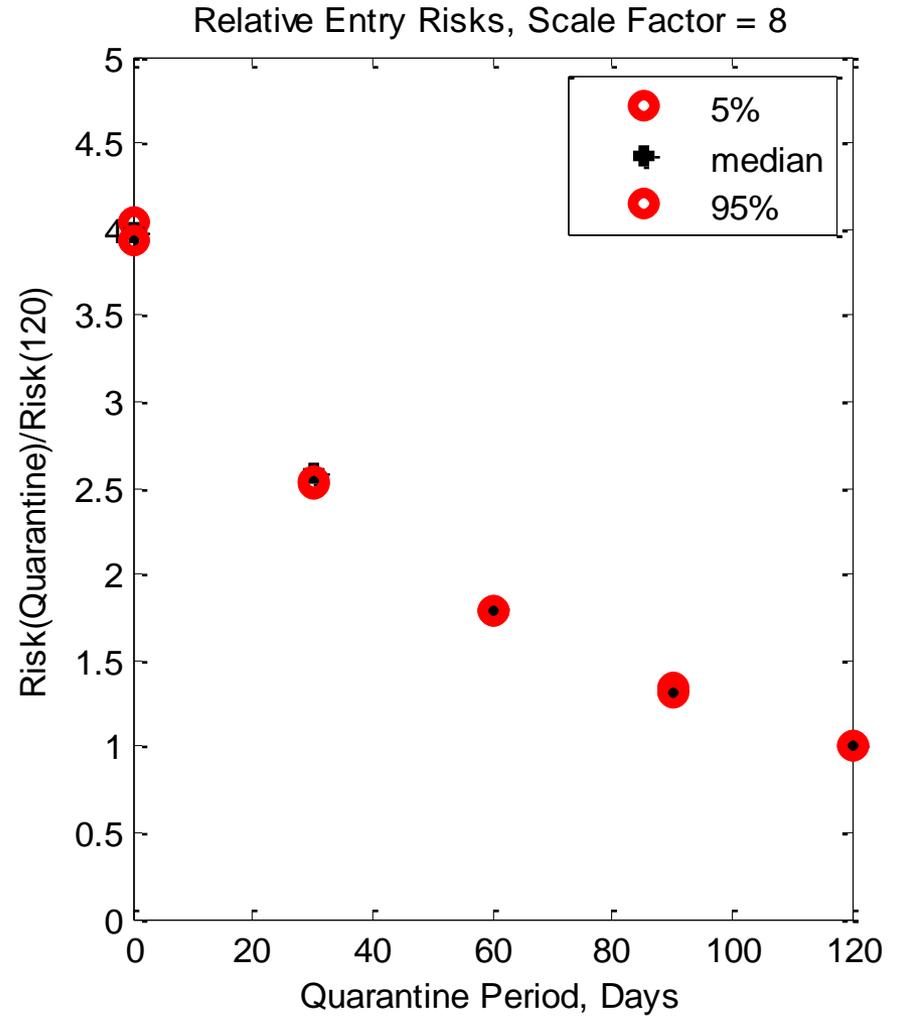
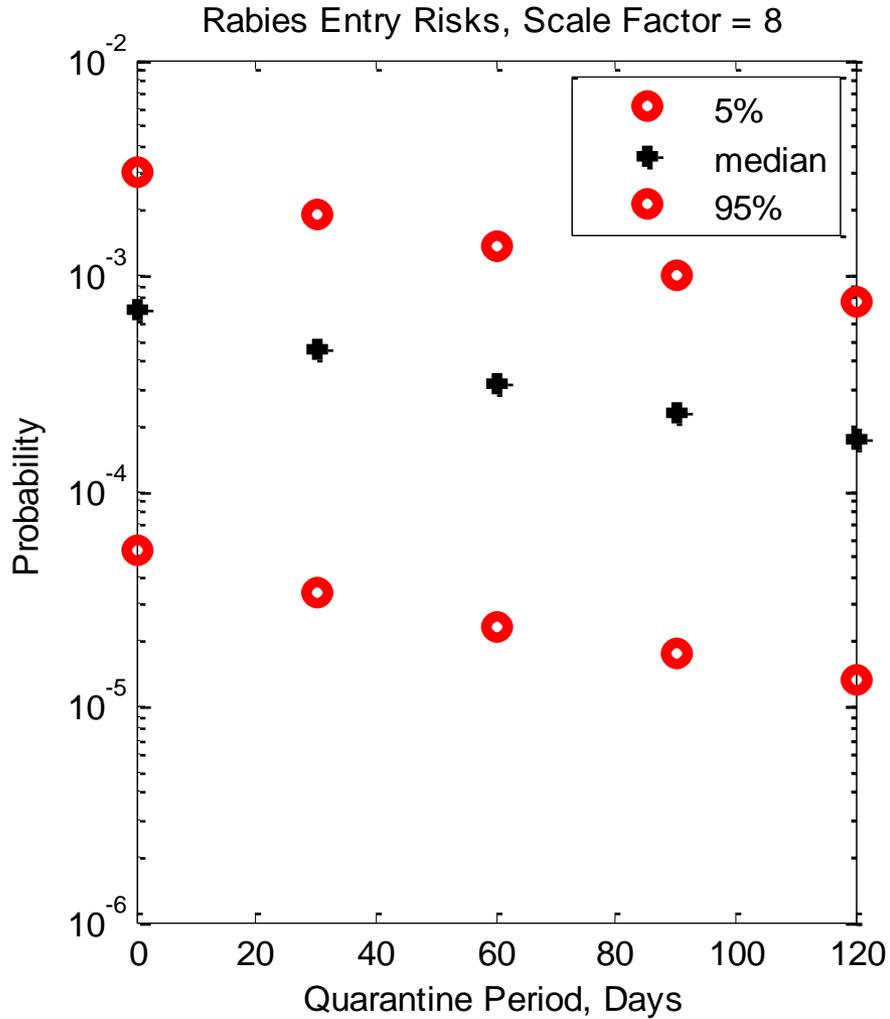
Risks with Probability Scale Factor = 2



Risks with Probability Scale Factor = 4



Risks with Probability Scale Factor = 8





- Relative risk analyses suggest
 - 1.30 increase in risk for a 90 day quarantine
 - 1.75 increase in risk for a 60 day quarantine
 - 2.55 increase in risk for a 30 day quarantine
 - 4.00 increase in risk for a 0 day quarantine
- Absolute risk estimates cover a significant range
 - Worst case among the simulations yielded a median risk of 0.0007 and a 95% percentile risk of 0.003 for 0 days of quarantine
 - 0.034 risk of Rabies in a 50 year period
 - “Baseline case” yielded a median risk of 0.00004 and a 95% percentile risk of 0.0002 for 120 days of quarantine
 - 0.002 risk of Rabies entry in 50 year period
- Concerns
 - Insuring vaccination compliance (FAVN test?) for reduced quarantine plans?
 - A number of uncertain parameters
 - With difficult to quantify uncertainty
- Future work
 - Hierarchical models to improve treatment of uncertainty in rates
 - Direct collaboration with Veterinarians to collect
 - Consider the epidemiology: mongoose reservoir?



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