Tempest Technologies

Conducting Quantitative Pathogen Risk Analyses via Monte Carlo Simulation

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1. Introduction

Critical to reducing the impact of disease-causing organisms, a risk analysis is a qualitative and quantitative process that involves the identification and characterization of potential hazards and analyses of outcomes and action steps should the hazard occur. This type of analytic process provides governments, state officials and policy makers with a clear method of assessing the disease risks associated with the entry/importation of animals and animal-related products[1].

Tempest Technologies (Tempest) recently had the opportunity to consider a risk analysis of rabies entry into Hawaii, a state that has never reported a single case of the virus. Such an undertaking required an understanding of the viral pathogen, a strong background of applied mathematics, mathematical and statistical modeling, and data analysis.

The purpose of this white paper is to summarize the approach and methodology that may be applied to conduct a Risk Analysis associated with the migration of domestic animals. Using the case in Hawaii as an example, the following components of a Risk Analysis will be discussed:

- ***Hazard Identification.*** Provides the essential foundation for the risk assessment and involves the qualitative evaluation of the rabies threat including, the etiology of the rabies virus, epidemiological trends and the current status of rabies in Hawaii including current entry policies.
- ***Risk Assessment*.** This process allows the quantification of the risk of rabies entry into Hawaii and includes:
    a. Release Assessment: Exploration of the likelihood of rabies entry into Hawaii via the importation of domestic animals; and
    b. Risk Estimation: Quantitative assessment that involves the development of a mathematical model that can estimate the yearly risk of rabies introduction under various entry and quarantine scenarios.

Conducting a Risk Analysis requires both a strong background in data gathering and analyses as well as a keen understanding of applied mathematics and the power unleashed through its correct application. Executed correctly, a Risk Analysis can assist with the reduction of the impact of pathogens, provide an action plan and ultimately lead to improved health outcomes.

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[1] World Organisation for Animal Health. http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_1.2.1.htm

2. The Rabies Epidemic

Considered one of the oldest documented infectious diseases, rabies remains a dangerous zoonotic disease threat today exhibiting a global geographic spread, a broad spectrum of mammalian reservoirs and vectors, and possesses the highest case fatality rate of any disease-causing agent[2]. The rabies virus is considered a neurotropic virus in the genus *Lyssavirus*, family *Rhabdoviridae* that affects both wild as well as domestic animals. Transmitted via the saliva of an infected mammal, the rabies virus aggressively attacks the central nervous system and if left untreated is almost always fatal[3,4]. Despite significant advancements and insights into its pathology and immunology, rabies continues to represent a serious public health burden. Recent data indicates that nearly 3.3 billion people are at risk of acquiring rabies across 85 countries and is currently responsible for roughly 55,000 deaths annually[5].

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In the U.S., rabies has not only compromised the safety and well-being of communities and wildlife alike, but also negatively impacted the national economy. Indeed, it has been reported that the health care costs associated with the detection, prevention and control of rabies in the U.S. exceeds $300 million annually[6]. While programs targeted at animal control via vaccinations as well as advances in human vaccines and immunoglobulin therapies have dramatically improved the rabies epidemic in the U.S. over the past century, the number of annual reported rabies cases – while gradually decreasing – continues to present a concern. According to the most recent data collected by the Centers for Disease Control (CDC), a total of 6,031 rabid animal and 6 human rabies cases were reported in the U.S. in 2011[7].

Distinguishing itself from all other U.S. states, Hawaii maintains a rabies-free status and has never reported an indigenous rabies case (animal or human)[8]. The state has upheld this status due to a quarantine law enacted in 1912 that requires a post-arrival confinement period of 120 days for imported dogs and cats.

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2 Centers for Disease Control. www.cdc.gov
3 Rabies and Rabies-Related Lyssaviruses. The Center for Food Security and Public Health. Iowa State University. http://www.cfsph.iastate.edu/Factsheets/pdfs/rabies.pdf
4 National Network for Immunization Information. http://www.immunizationinfo.org/vaccines/rabies
5 Initiative for Vaccine Research (IVR). http://www.who.int/vaccine_research/diseases/zoonotic/en/index4.html
6 Centers for Disease Control. www.cdc.gov
7 Blanton JD, et al. Rabies surveillance in the United States during 2011. JAVMA, Vol 241, No. 6, September 15, 2012
8 State of Hawaii – Department of Health. http://hawaii.gov/health/DIB/Rabies.html

3. Tempest's Approach and Proposed Methodology

The outputs of a Risk Analysis enable risk assessors to analyze and understand data regarding a potential threat and allows for policy development and the prioritization of research efforts[9].

As an initial step to the Risk Analysis, a ***Hazard Identification*** must be performed in order to provide sufficient data and information regarding the rabies virus, reservoirs of infection, transmission in cats and dogs and the status of rabies in Hawaii. These analyses act as the platform from which a ***Risk Assessment*** can be conducted.

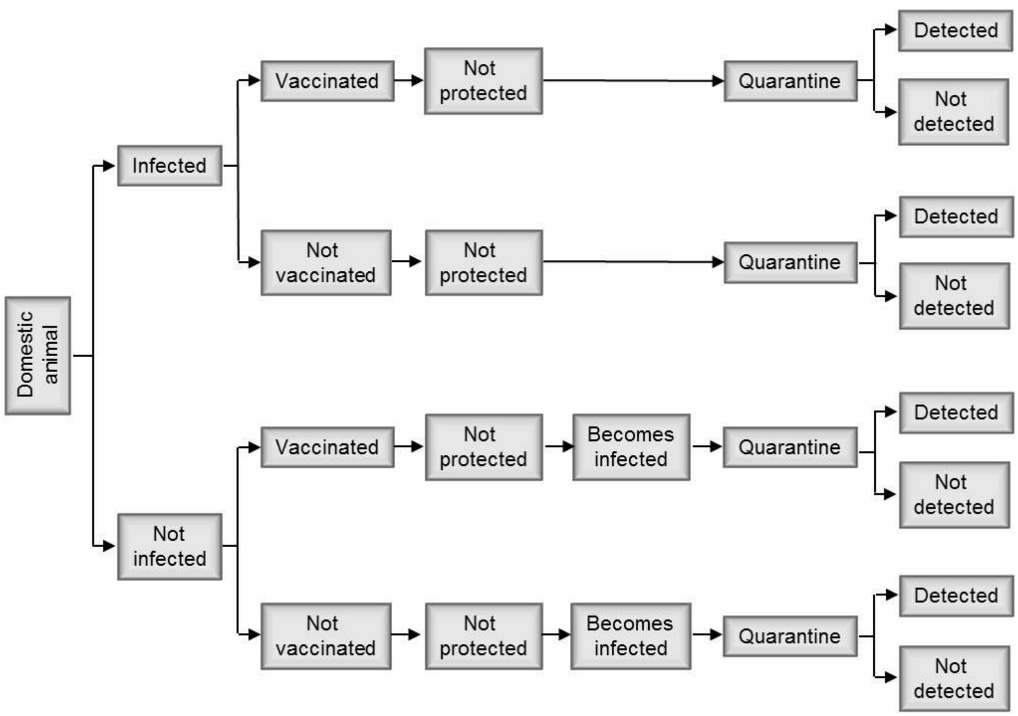

Figure 1. Scenario Tree for 120-Day Quarantine.

Based on this secondary research, mathematical and statistical models can be created to assess the likelihood of rabies entry into an area. The current quarantine regime in Hawaii involves two paths: (1)120-Day Quarantine; and (2) 5-Day-or-Less expedited quarantine procedure.

This Risk Analysis was to be conducted in order to consider new potential quarantine regimes of 90, 60, 30, and 0 days via the development of a mathematical model. A two-step approach was designed to tackle the Risk Assessment.

[9] Microbial Risk Assessment Guideline. U.S. Environmental Protection Agency (EPA) and U.S. Department of Agriculture/Food Safety and Inspection Service (USDA/FSIS). 2012.

Release Assessment

As defined by Covello and Merkhofer[10], the release assessment will evaluate the potential for rabies to be introduced into Hawaii under various quarantine conditions. In this example, a number of possibilities surrounding the introduction of an infected dog or cat into the state were considered. The modes of entry of interest include the following: an infected animal passes through quarantine, or an infected animal enters illegally.

Bringing an animal into Hawaii requires evidence of vaccination(s) and a clear result from the Office International des Epizooties - Flourescent Antibody Virus Neutralization (OIE-FAVN) serum test in addition to a quarantine period. Within the six proposed quarantine regimes, two risk scenario trees (Figures 1 and 2) model the release assessment.

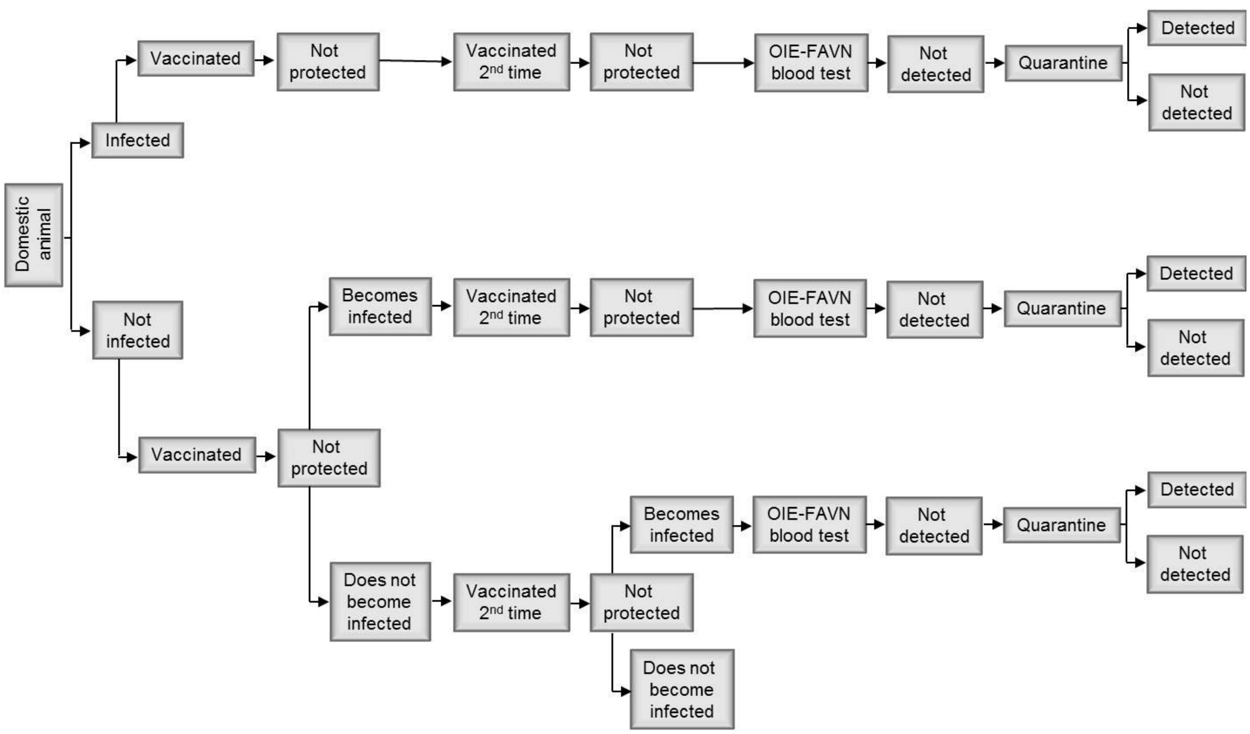

Figure 2. Scenario Tree for 5-Day-or-Less Protocol.

Within these scenario trees, the risk pathways of importing infected animals involve infection that persists through vaccination, produces a negative test result (in the case of the 5-Day-or-Less protocol), and goes undetected through the quarantine period. It should be noted that the preliminary scenario trees omit a number of pathways that do not lead to the risk outcome of

10 Covello VT and Merkhofer MW. Risk Assessment Methods: Approaches for Assessing Health and Environmental Risks. New York: Plenum Press 1993. Print.

interest; the probabilities of interest can be modeled by following the paths leading to the passing through quarantine of an undetected case.

Risk Estimation

The basic approach to Risk Estimation involves propagating uncertainties through the scenario trees described in the release assessment step using the mathematical techniques of probability theory.

Probabilities that must be specified include: (a) the likelihood that a pet is infected, (b) the likelihood that a vaccination does not protect the pet, (c) the likelihood that a second vaccination does not protect the pet, (d) the likelihood that the OIE-FAVN test produces a false negative, and (e) the likelihood that the infected pet does not exhibit detectable symptoms during quarantine periods of varied length.

The computation of probabilities associated with risk estimation is most frequently conducted with Monte Carlo simulation, in which individual scenarios are simulated by sampling from the probability models specified. Simulation software such as @Risk and Crystal Ball are typically used for risk analysis. These packages work well in problems with simple structures to events and with well-behaved tails, and in many engineering and business decision problems, such assumptions are perfectly reasonable. In ecological and epidemiological risk assessments, however, event flow and timing, as well as low probability events and extended distribution tails, can be major issues.

Tempest has developed special purpose Monte Carlo simulations for decision problems and risk analyses specifically for situations involving complex sequencing of extremely unlikely events. We conducted simulations requiring hundreds of thousands of Monte Carlo realizations in order to resolve probabilities representing one in a million to one in a billion odds. One key aspect of such simulations is importance sampling in which one oversamples from the distribution tails and corrects for the oversampling probabilities by weighting the Monte Carlo averaging. This approach can be much more accurate when the primary interest of the analysis is in the extreme events (severe storms, strong turbulence, or unlikely exposures and rare failures).

Generally speaking, these likelihoods are modeled with parametric probability distributions, and the parameters themselves contain uncertainty, a situation that requires a sensitivity analysis. Sensitivity analysis involves perturbing model inputs to examine uncertainty in outputs. The computational efficiencies gained with our special purpose simulation will be leveraged to great effect in perturbing parameters for sensitivity studies.

4. Results

Developing a Model for the Standard Quarantine

Based on previous research and available data, we make the following assumptions and state the following conditions:

1. Approximately 3700 pets per year are moved through Hawaii's quarantine
   - We model the number of pets as U[3500,3900]
2. To import rabies, the pet must be exposed
   - Exposure rates are small but highly uncertain
   - From epidemiological studies, we assume a mean probability of exposure of 2.2388e-06
   - Exposure probabilities are modeled as Beta distributed with standard deviation of 8.3476e-08
   - Assuming exposures are underreported, additional modeling multiplies this rate by a factor > 1
3. From previous rabies studies, time till symptoms appear is assumed lognormally distributed, with a mean 35 and standard deviation 36.8 days
4. Pets may be exposed before or after 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
5. Vaccination failure probability is based on clinical data with a mean of 0.004529, standard deviation of 0.002021, and a Beta distribution model

We simulate 50000 realizations of a year of pet entries

1. Within each year, we generate a number of pets to be processed
2. Within each year, we generate a baseline exposure rate
3. For each pet, we generate
   - Exposure time and vaccination time
   - A probability of vaccine failure
   - A probability of remaining asymptomatic through quarantine
4. Probability of rabies importation is given by

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

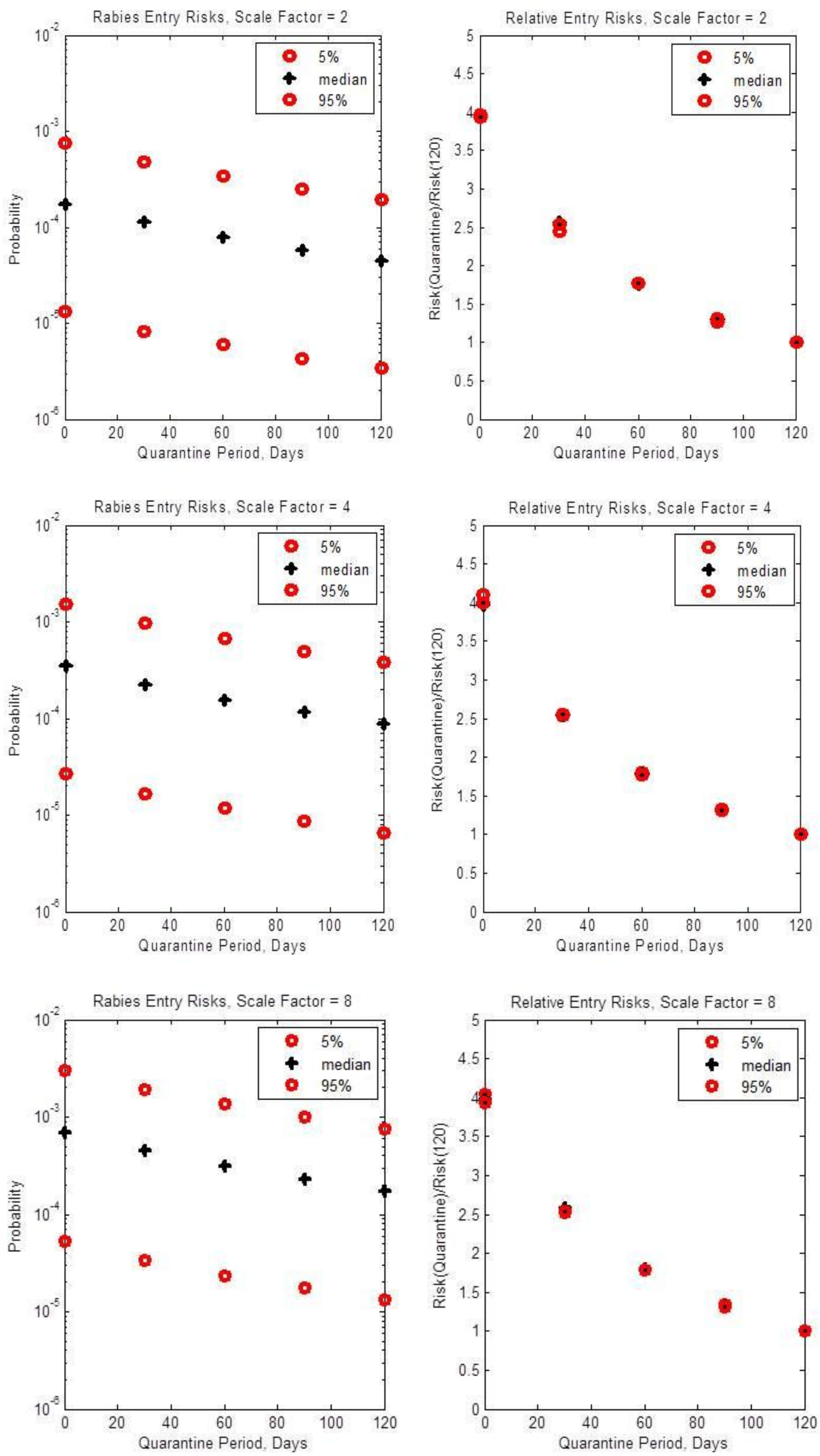

Figure 3. Risk of Rabies Entry with Probability Scale Factors 2, 4 and 8.

The 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

Based on these simulations, the relative risk of reducing quarantine periods is small. Reduction to a 60 day quarantine, for example, poses very little additional risk and should be considered as a reasonable policy modification.

5. Conclusions

We have assessed the impact of predetermined parameters to understand the risk of rabies entry into a population. Understanding the correct mathematical tools and having the knowledge to apply them to different risk analysis scenarios enables the production of data that can inform decision-making. While several unknowns will always be a concern to policy-makers, such as vaccination effectiveness and compliance, utilizing Monte Carlo methodologies allows one to conduct powerful quantitative risk analyses that will lead to policy decisions related to the entry of companion animals into a population.