

# **DETERMINISTIC AND STOCHASTIC MODELS OF AN EMERGING WILDLIFE DISEASE: HANTAVIRUS**

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# HANTAVIRUS IS A RODENT-BORNE ZONOTIC DISEASE

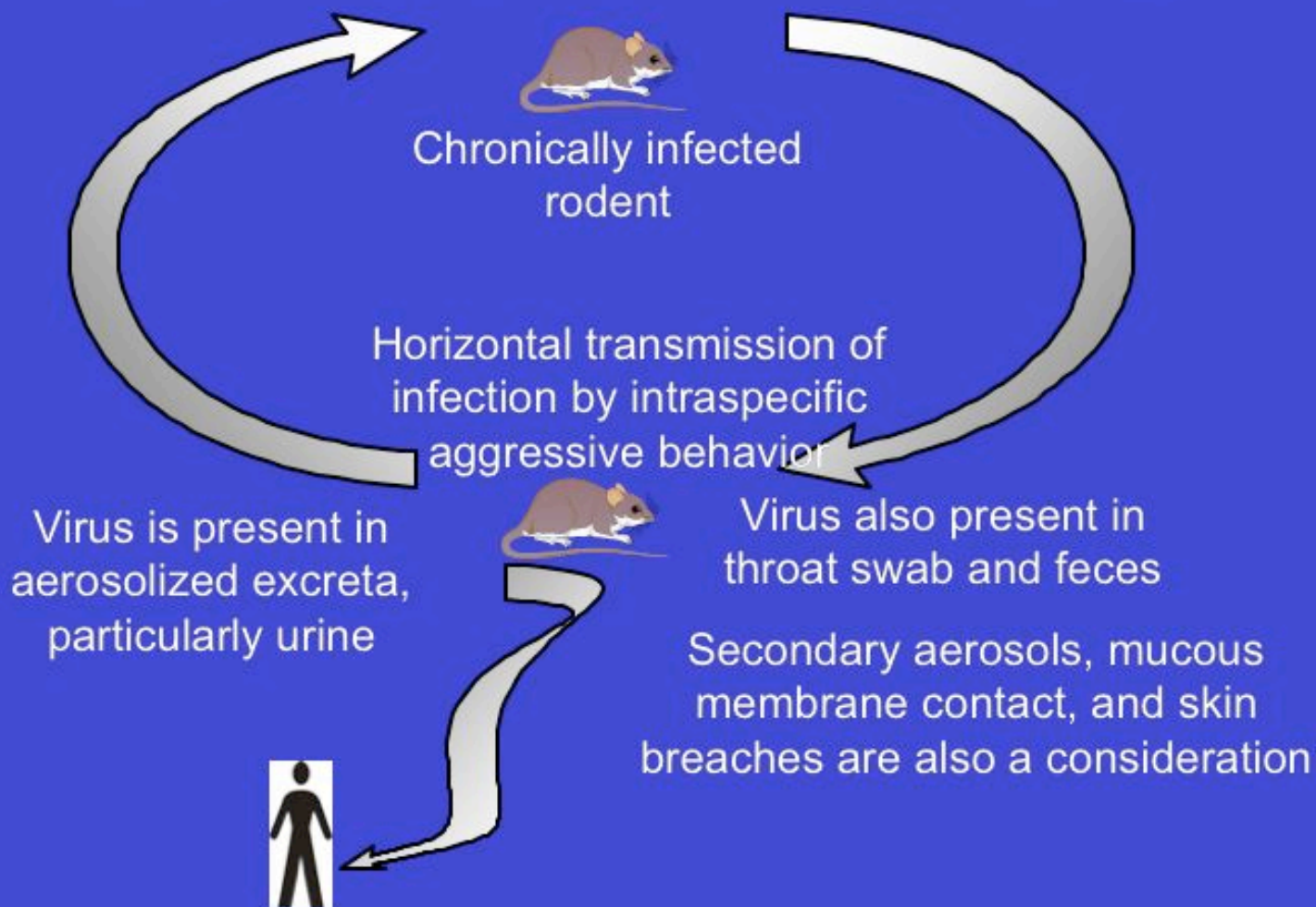
- Background Information on Hantavirus
  - Our Objective is to Model the Rodent Population to Help Understand Why Outbreaks Occur in the Rodent Population in Order to Prevent Spread to Humans.
  - We will Describe Some SEIR Male/Female Models
    1. Basic Model
    2. Model with Variable Carrying Capacity
    3. Model with Multiple Hosts
    4. Model with Multiple Patches

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## Background: Hantaviruses are Rodent-Borne Zoonotic Agents.

- In Humans the disease is manifested as either Hemorrhagic Fever with Renal Syndrome – **HFRS** (Europe, Asia) or Hantavirus Pulmonary Syndrome – **HPS** (Americas).
  - **HFRS** was first recognized in 1951 when an outbreak occurred in military personnel during the Korean War.
  - **HPS** was identified in 1993 from an outbreak in New Mexico. It is recognized as an emerging disease and more recently, a biodefense agent.
  - **HPS** case fatality rate in the US is 37%.
  - Hantaviruses pathogenic to Humans in the US include Sin Nombre virus, New York virus, Black Creek Canal virus, and Bayou virus.

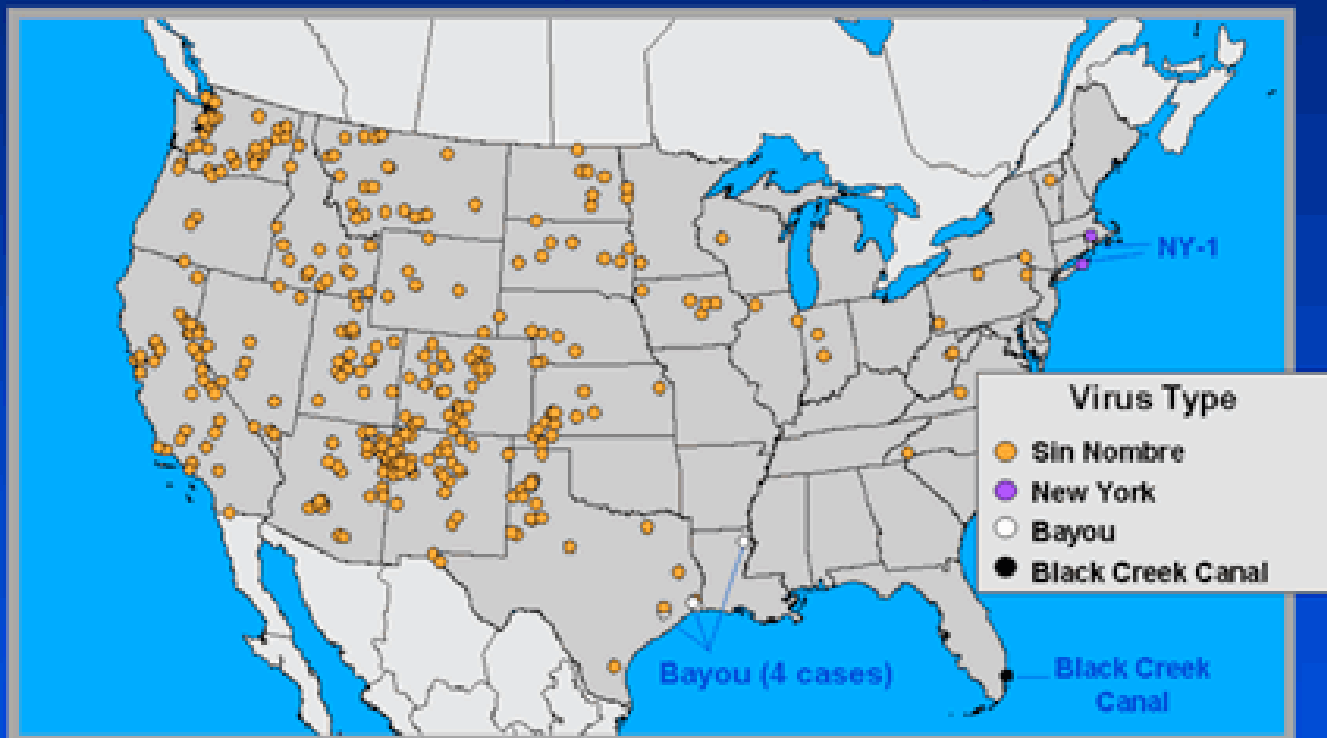
# Transmission of Hantaviruses



# New World Hantaviruses



**Location of HPS Cases by Virus Type  
as of July 6, 2005  
Total Cases (N=396 in 30 States)**



Although serologically confirmed as HPS, sequence data are not available for all cases. For non-sequenced cases, the specific infecting hantavirus is assumed to be that corresponding with the known rodent reservoir in the area of probable exposure.



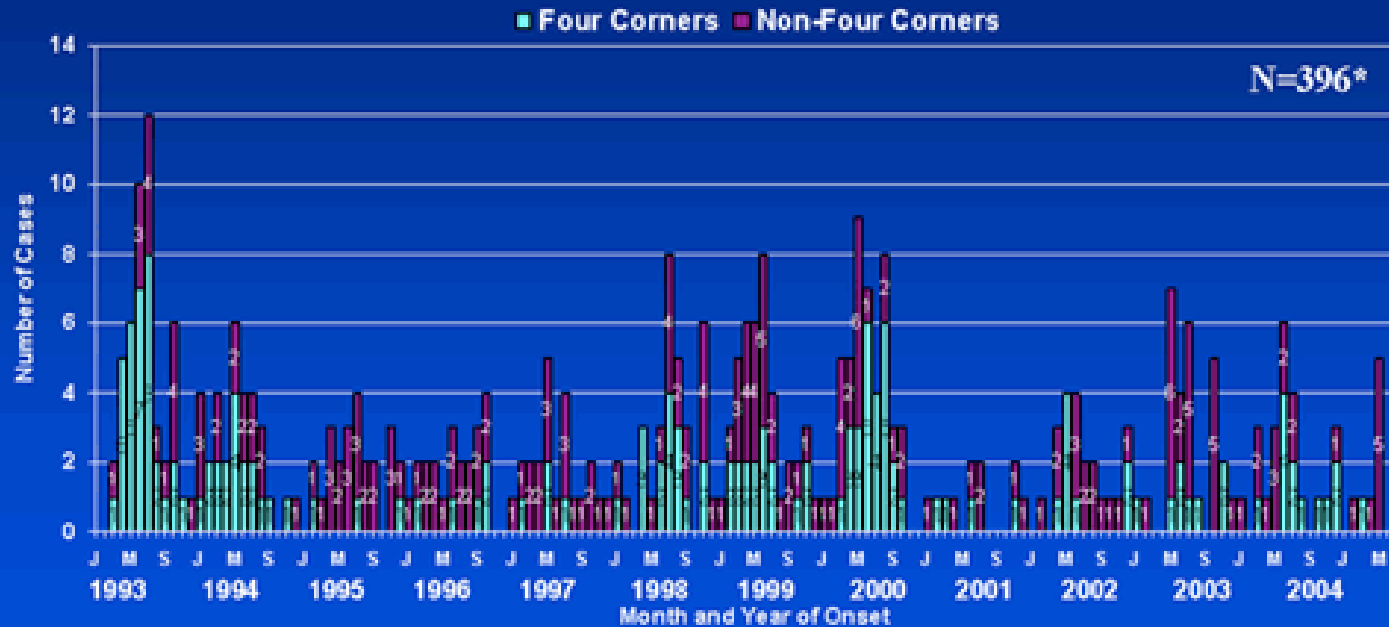
**Distribution\* of *Peromyscus maniculatus* and  
Location of HPS Cases as of July 6, 2005  
Total Cases (N=396 in 30 States)**



\*Rodent distributions from: Burt WH, Grossenheider RP. A Field Guide to the Mammals. 3rd ed. New York, New York: Houghton Mifflin Company; 1960

CDC

## Hantavirus Pulmonary Syndrome Cases by Region United States, as of July 6, 2005



\* Eleven Four Corners and twenty-one Non-Four Corners cases with onset before 1993 not shown.



**CDC:** Monthly HPS cases, Four Corners versus non-Four Corners (the Four Corners include the states Arizona, Colorado, New Mexico, and Utah).

## Our Model Assumptions Rely on the Biology of the Rodents and the Epizology of the Rodent-Hantavirus Interaction.

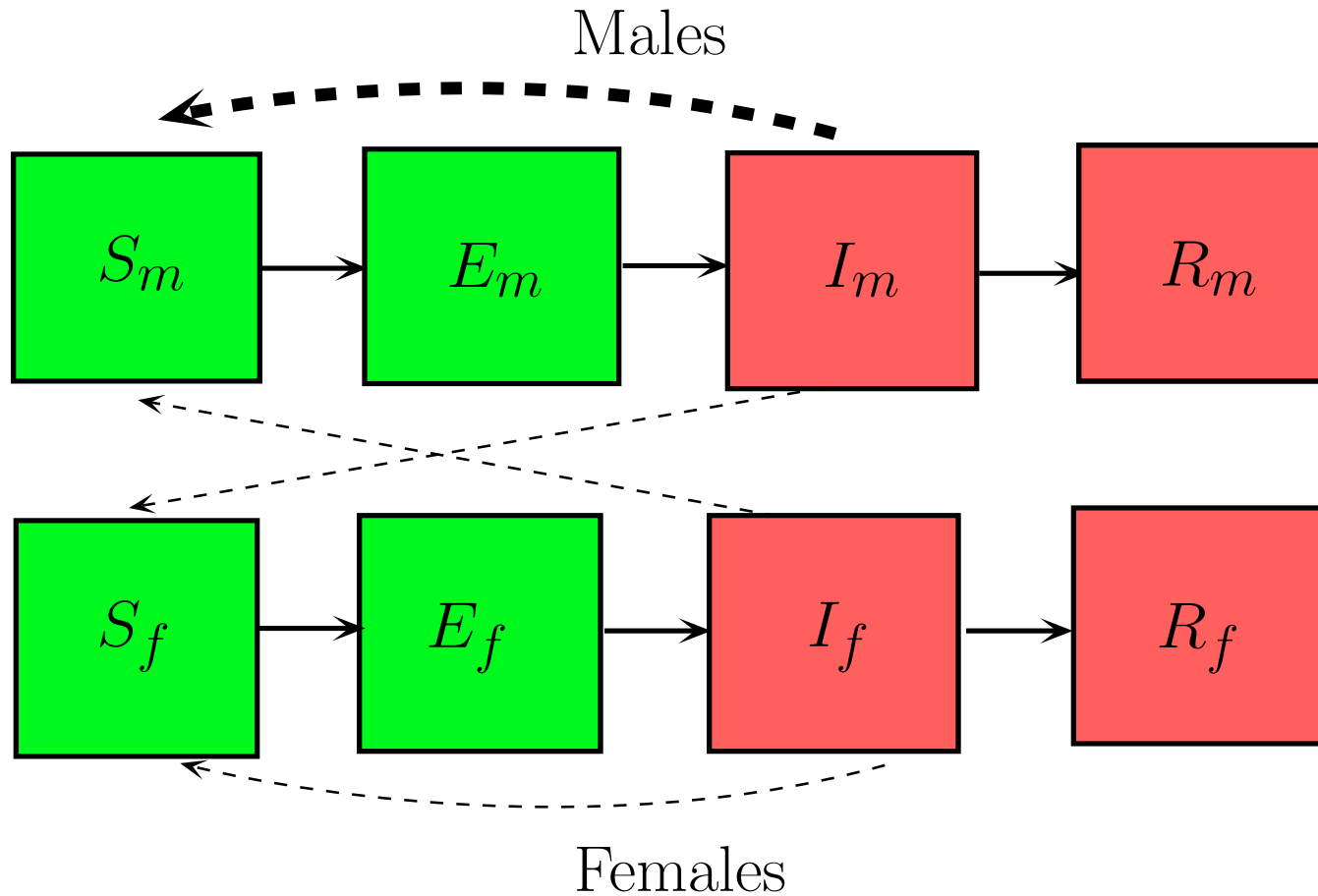
### Biology

- Equal numbers of males and females – same male and female birth functions.
- Mating is random – no partner association.
- Rodents become reproductive soon after birth – no juveniles.

### Epizology

- Hantavirus has little or no effect on rodent survival – no disease-related deaths.
- Disease transmission is horizontal – no vertical transmission from mother to offspring.
- Male seroprevalence is much higher than females – male aggressive behavior results in larger contact rates between two males.

The Compartmental Diagram for the SEIR Male/Female Model Illustrates the Relationship Between the States.



# 1. The Basic SEIR Male/Female Model is a System of Eight Differential Equations, One Equation for Each State.

Males:

$$\frac{dS_m}{dt} = \frac{B(N_m, N_f)}{2} - S_m d(N) - S_m(\beta_f I_f + \beta_m I_m),$$

$$\frac{dE_m}{dt} = -E_m d(N) + S_m(\beta_f I_f + \beta_m I_m) - \delta E_m,$$

$$\frac{dI_m}{dt} = \delta E_m - I_m d(N) - \gamma_m I_m,$$

$$\frac{dR_m}{dt} = \gamma_m I_m - R_m d(N),$$

Similar equations apply to the Females.

Reference: Allen, McCormack, and Jonsson. *Bull Math Biol* 2006.

## We also Formulated a Model that Consists of 8 Itô Stochastic Differential Equations.

Males:

$$\frac{dS_m}{dt} = \frac{B(N_m, N_f)}{2} - S_m d(N) - S_m(\beta_f I_f + \beta_m I_m) + \sum_{j=1}^8 a_{1j} \frac{dW_j}{dt}$$

$$\frac{dE_m}{dt} = -E_m d(N) + S_m(\beta_f I_f + \beta_m I_m) - \delta E_m + \sum_{j=1}^8 a_{2j} \frac{dW_j}{dt}$$

$$\frac{dI_m}{dt} = \delta E_m - I_m d(N) - \gamma_m I_m + \sum_{j=1}^8 a_{3j} \frac{dW_j}{dt}$$

$$\frac{dR_m}{dt} = \gamma_m I_m - R_m d(N) + \sum_{j=1}^8 a_{4j} \frac{dW_j}{dt}$$

where  $W_j$ ,  $j = 1, 2, \dots, 8$  are eight independent Wiener processes and  $A = (a_{ij})$ . A similar set of SDEs apply to the female population.

## The Coefficients $A = (a_{ij})$ of the Wiener process are Determined From the Covariance Matrix.

Matrix  $A$  is the  $8 \times 8$  unique symmetric positive definite matrix and  $\Sigma$  is the covariance matrix.

$$A = \sqrt{\Sigma}$$

$$\Sigma = \begin{pmatrix} \Sigma_m & \mathbf{0} \\ \mathbf{0} & \Sigma_f \end{pmatrix}$$

Matrix  $\Sigma_m$  is

$$\begin{pmatrix} \frac{B}{2} + S_m(d + \beta I_f + \beta_m I_m) & -S_m(\beta I_f + \beta_m I_m) & 0 & 0 \\ -S_m(\beta I_f + \beta_m I_m) & E_m(\delta + d) + S_m(\beta I_f + \beta_m I_m) & -\delta E_m & 0 \\ 0 & -\delta E_m & \delta E_m + I_m(\gamma_m + d) & -\gamma_m I_m \\ 0 & 0 & -\gamma_m I_m & \gamma_m I_m + R_m d \end{pmatrix}$$

where  $d \equiv d(N)$  is the density-dependent death rate.

## There are Important Differences in the Epizootology of Males and Females.

- Fighting between males results in greater contacts and spread of hantavirus.

$$\beta_m > \beta_f$$

- The incubation period is assumed to be the same for males and females

$$\frac{1}{\delta}$$

- The infectious period is longer in males than in females.

$$\frac{1}{\gamma_m} > \frac{1}{\gamma_f}$$

# Population Growth is Logistic.

$$\frac{dN}{dt} = B(N_m, N_f) - Nd(N)$$

$$\text{Males } N_m = S_m + E_m + I_m + R_m$$

$$\text{Females } N_f = S_f + E_f + I_f + R_f$$

$$\text{Total } N = N_m + N_f.$$

The Birth and Death Functions are

$$B(N_m, N_f) = \frac{2bN_mN_f}{N}, \quad d(N) = a + \left(\frac{b}{2} - a\right) \frac{N}{K},$$

where  $b$  is the average litter size and  $K$  = carrying capacity.

$$\lim_{t \rightarrow \infty} N(t) = K$$

## We Derived a Formula for the Basic Reproduction Number for the SEIR Male/Female Model, $\mathcal{R}_0$ .

If  $\mathcal{R}_0 > 1$ , an outbreak occurs.

If  $\mathcal{R}_0 < 1$ , there is no outbreak.

$$\mathcal{R}_0 = \frac{\beta_m \delta K / 4}{\pi_m (b/2 + \delta)} + \frac{\beta_f \delta K / 4}{\pi_f (b/2 + \delta)} + \frac{\delta K / 4 \sqrt{[\beta_m \pi_f + \beta_f \pi_m]^2 - 4\beta_f(\beta_m - \beta_{m,f})\pi_f \pi_m}}{\pi_m \pi_f (b/2 + \delta)}$$

where  $\pi_f = \frac{b}{2} + \gamma_f$  and  $\pi_m = \frac{b}{2} + \gamma_m$ .

The carrying capacity  $K$  is a factor of  $\mathcal{R}_0$ .

**In the Special Case  $\beta_{mf} = \beta_m$ , the Basic Reproduction Number Simplifies.**

The sum of two basic reproduction numbers, one for males and one for females:

$$\mathcal{R}_0 = \frac{\beta_m \delta K / 2}{(b/2 + \gamma_m)(b/2 + \delta)} + \frac{\beta_f \delta K / 2}{(b/2 + \gamma_f)(b/2 + \delta)}.$$

At the unique **Endemic Equilibrium**, the **Proportion of Animals Antibody Positive or Seroprevalence** is

$$\frac{\bar{I}_m + \bar{I}_f + \bar{R}_m + \bar{R}_f}{K} = \frac{\delta}{b/2 + \delta} \left( 1 - \frac{1}{\mathcal{R}_0} \right). \quad (1)$$

An estimate for  $\mathcal{R}_0$  in this special case can be obtained from formula (1).

## Overall Hantavirus Seroprevalence is Low, Leading to a Reproduction Number Which is Close to One.

For *O. pallustris*, carrier for Bayou virus in eastern Texas: Let the time unit be two months, the gestation period (25 days) plus the time to reach sexual maturity (40 to 45 days). The incubation period is two to three weeks,  $\frac{1}{\delta} \approx \frac{1}{4} - \frac{3}{8}$ . The average litter size is 4,  $b \approx 4$ . Overall seroprevalence is about 16%.

Applying formula (1), the approximate value of  $\mathcal{R}_0$  is

$$\mathcal{R}_0 \approx 1.32 - 1.39$$

# We Illustrate The Basic Model Dynamics with Several Examples for Different Values of $K$ Female, Male

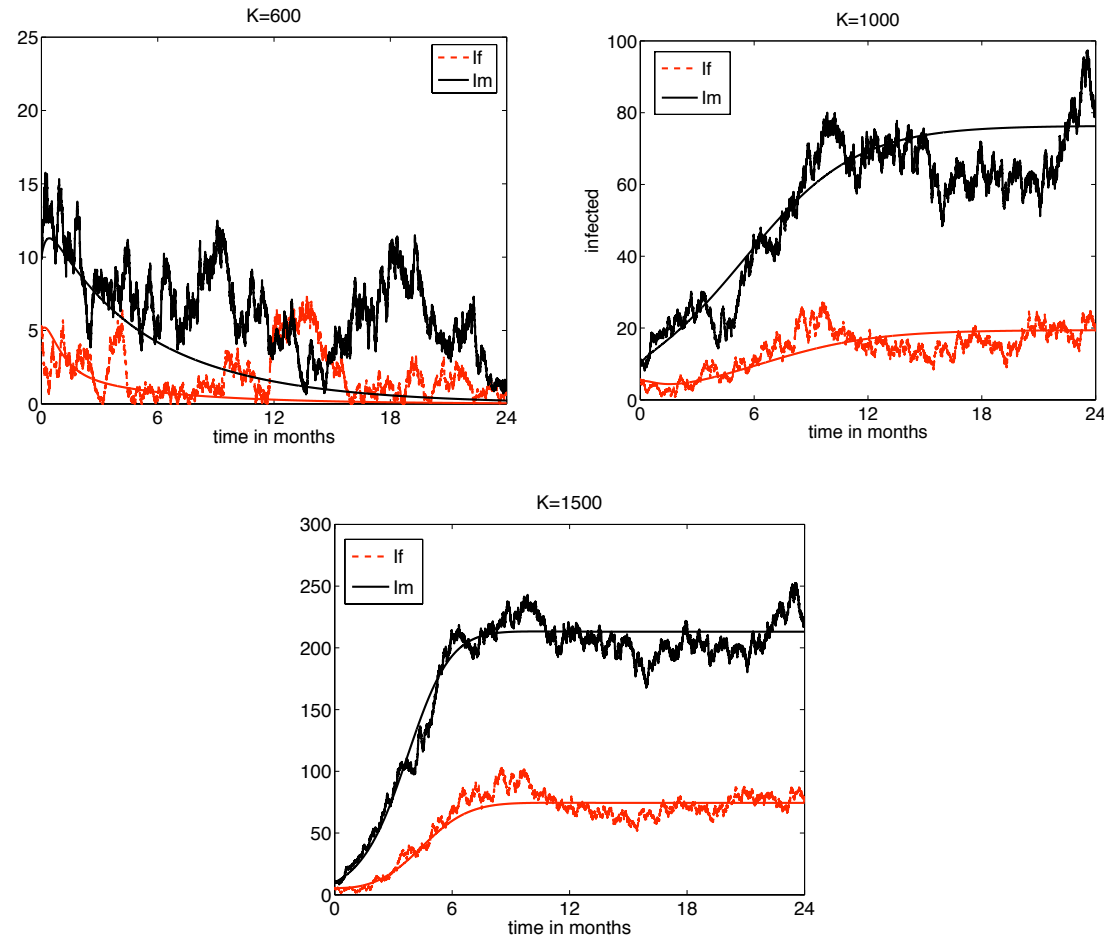


Figure 1:  $K = 600, 1000, 1500, \mathcal{R}_0 = 0.83, 1.38, 2.08$

## 2. Next We Assume Periodic Seasonal Variation and Random Environmental Variation Directly Impact the Carrying Capacity $K$ .

The outbreak of Sin Nombre virus in 1993 in New Mexico was associated with increased densities of deer mice. Densities increased from less than one deer mouse per hectare prior to 1991 to 20 to 30 per hectare during the spring of 1993.

$$\frac{dK}{dt} = \alpha_1 [K_e - K] + \alpha_2 \cos(\omega t) + \alpha_3 \frac{dW}{dt}$$

$\alpha_1 [K_e - K]$  represents return to carrying capacity  $K_e$ .

$\alpha_2 \cos(\omega t)$  represents annual periodic variation.

$\alpha_3 dW/dt$  represents random environmental variation

$$\alpha_3 dW \sim N(0, \alpha_3^2 dt)$$

Allen, Allen, Jonsson. *AMS Contemp Math. Series.* 2006

# The Deterministic Solution Exhibits Periodicity with Seasonal Variation.

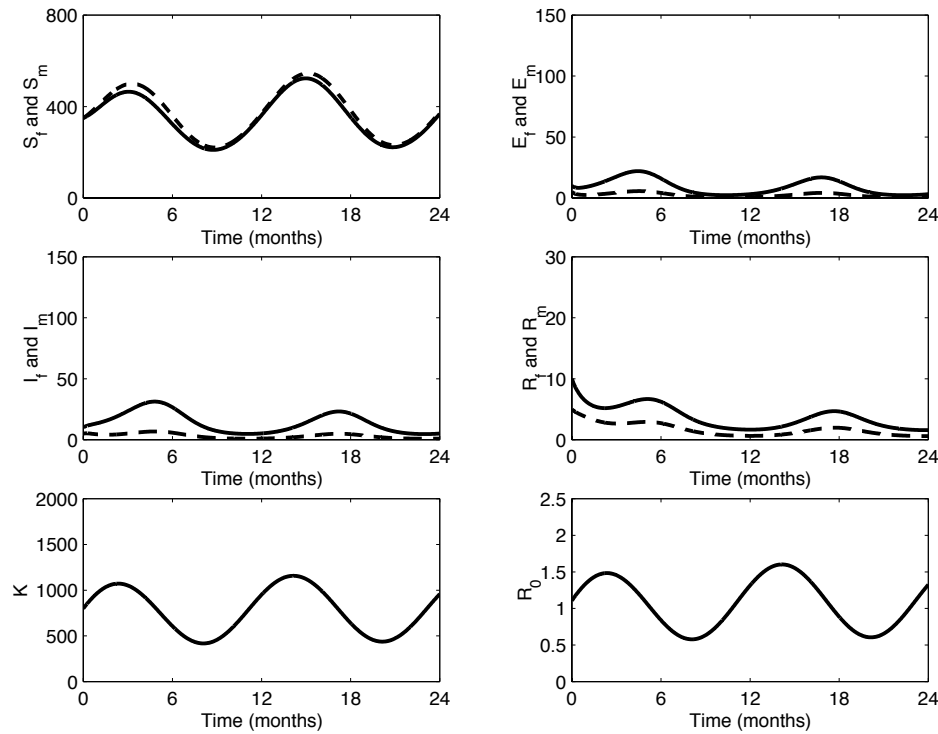


Figure 2:  $\alpha_1 = 0.5$ ,  $\alpha_2 = K_e\omega/2$ ,  $\alpha_3 = 300$ , and  $K_e = 800$ .

# A Stochastic Sample Path Generally Follows the Peak Values of the Carrying Capacity but an Outbreak may Not Always Occur.

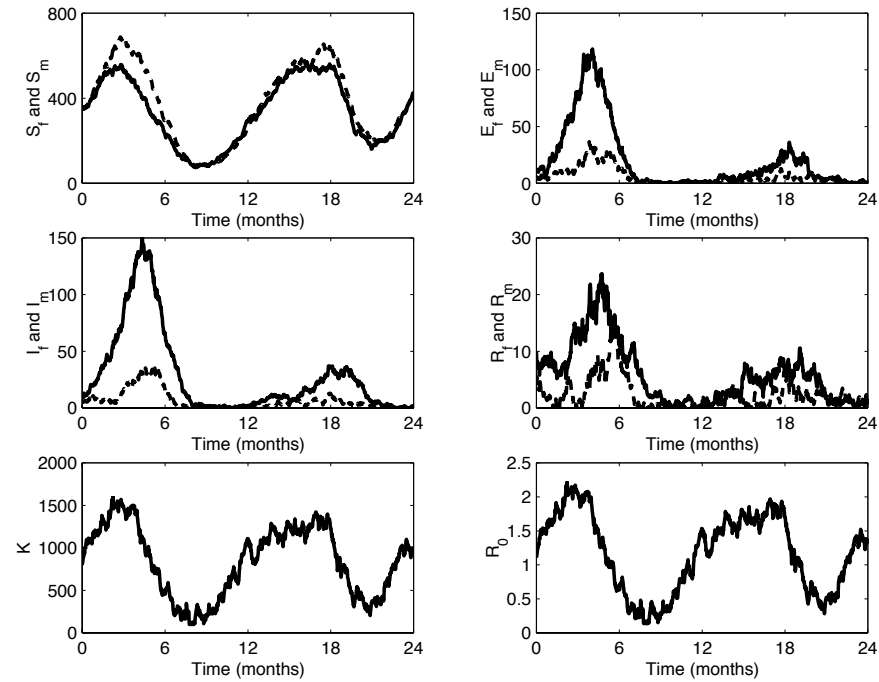


Figure 3:  $\alpha_1 = 0.5$ ,  $\alpha_2 = K_e \omega / 2$ ,  $\alpha_3 = 300$ , and  $K_e = 800$ .

The first outbreak runs its course naturally, with  $\mathcal{R}_0 > 1$  throughout the epidemic. In contrast, the second outbreak is cut short as a rapid drop in  $\mathcal{K}$  reduces  $\mathcal{R}_0 < 1$ .

### 3. For the Third Type of Model We Consider an SEIR Multi-Host Model— $n$ Hosts

Male Host  $i$ :

$$\frac{dS_m^i}{dt} = \frac{B^i(N_m^i, N_f^i)}{2} - S_m^i d^i(N^i) - S_m^i \sum_{k=1}^n (\beta_f^k I_f^k + \beta_m^k I_m^k)$$

$$\frac{dE_m^i}{dt} = -E_m^i d^i(N^i) + S_m^i \sum_{k=1}^n (\beta_f^k I_f^k + \beta_m^k I_m^k) - \delta^i E_m^i$$

$$\frac{dI_m^i}{dt} = \delta^i E_m^i - I_m^i d^i(N^i) - \gamma_m^i I_m^i$$

$$\frac{dR_m^i}{dt} = \gamma_m^i I_m^i - R_m^i d^i(N^i)$$

One rodent serves as the primary **Reservoir Host**. Others are referred to as **Spillover Species**.

## The Basic Reproduction Number Increases with Multiple Hosts.

Suppose the basic reproduction number with  $n$  hosts is

$$\mathcal{R}_0^n = \rho(M_n),$$

where  $M_n$  is the next generation matrix.

Then, if the parameters remain the same, but one more host is added to the system,

$$M_{n+1} = \begin{pmatrix} M_n & A \\ B & C \end{pmatrix},$$

where  $A, B, C$  are nonnegative matrices.

$$\mathcal{R}_0^n = \rho(M_n) \leq \rho(M_{n+1}) = \mathcal{R}_0^{n+1}.$$

## 4. Our Last Model Considers the Effect of Spatial Heterogeneity in a Two-Patch SEIR Model-Males Disperse.

$$\frac{dS_m^1}{dt} = \frac{B^1(N_m^1, N_f^1)}{2} - S_m^1 d^1(N^1) - S_m^1 (\beta_f^1 I_f^1 + \beta_m^1 I_m^1) + gm \left( \frac{S_m^2}{K_2} - \frac{S_m^1}{K_1} \right)$$

$$\frac{dE_m^1}{dt} = -E_m^1 d^1(N^1) + S_m^1 (\beta_f^1 I_f^1 + \beta_m^1 I_m^1) - \delta^1 E_m^1 + gm \left( \frac{E_m^2}{K_2} - \frac{E_m^1}{K_1} \right)$$

$$\frac{dI_m^1}{dt} = \delta^1 E_m^1 - I_m^1 d^1(N^1) - \gamma_m^1 I_m^1 + gm \left( \frac{I_m^2}{K_2} - \frac{I_m^1}{K_1} \right)$$

$$\frac{dR_m^1}{dt} = \gamma_m^1 I_m^1 - R_m^1 d^1(N^1) + gm \left( \frac{R_m^2}{K_2} - \frac{R_m^1}{K_1} \right)$$

Itô SDEs can be derived for the two patch model.

## Two Patches with Different Carrying Capacities in Each Patch.

**Example 1:**  $K_1 = 1000$ ,  $K_2 = 600$ ,  $\mathcal{R}_0^1 = 1.384$ ,  $\mathcal{R}_0^2 = 0.831$ .

$$\mathcal{R}_0 = 1.377$$

**Example 2:**  $K_1 = 1000$ ,  $K_2 = 1500$ ,  $\mathcal{R}_0^1 = 1.384$ ,  $\mathcal{R}_0^2 = 2.0765$ .

$$\mathcal{R}_0 = 2.0757$$

The overall  $\mathcal{R}_0$  lies between the two patch reproduction numbers.

**Example 1:  $K_1 = 1000$ ,  $K_2 = 600$**

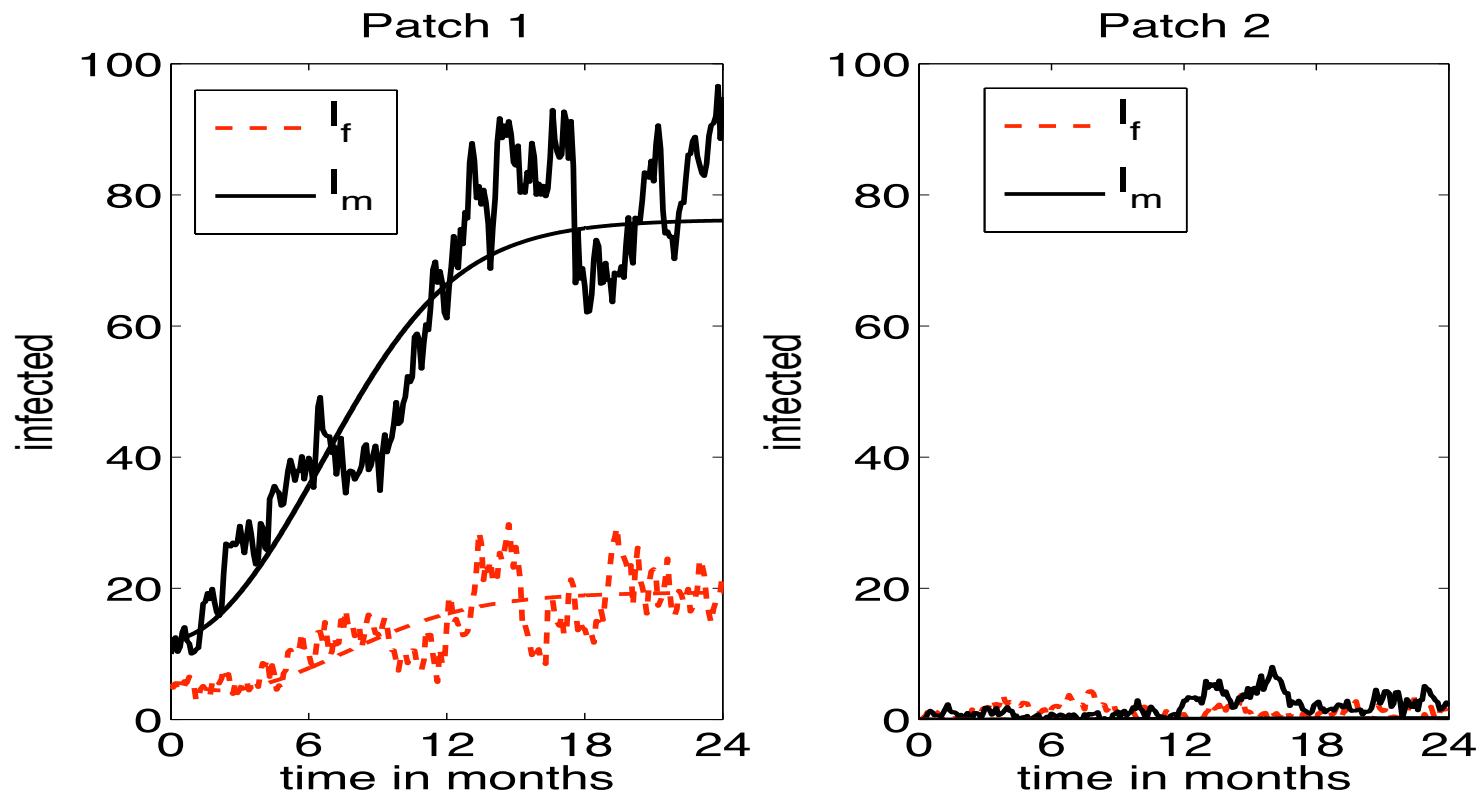


Figure 4: Disease spread to an unfavorable habitat is not maintained.

**Example 2:  $K_1 = 1000$ ,  $K_2 = 1500$**

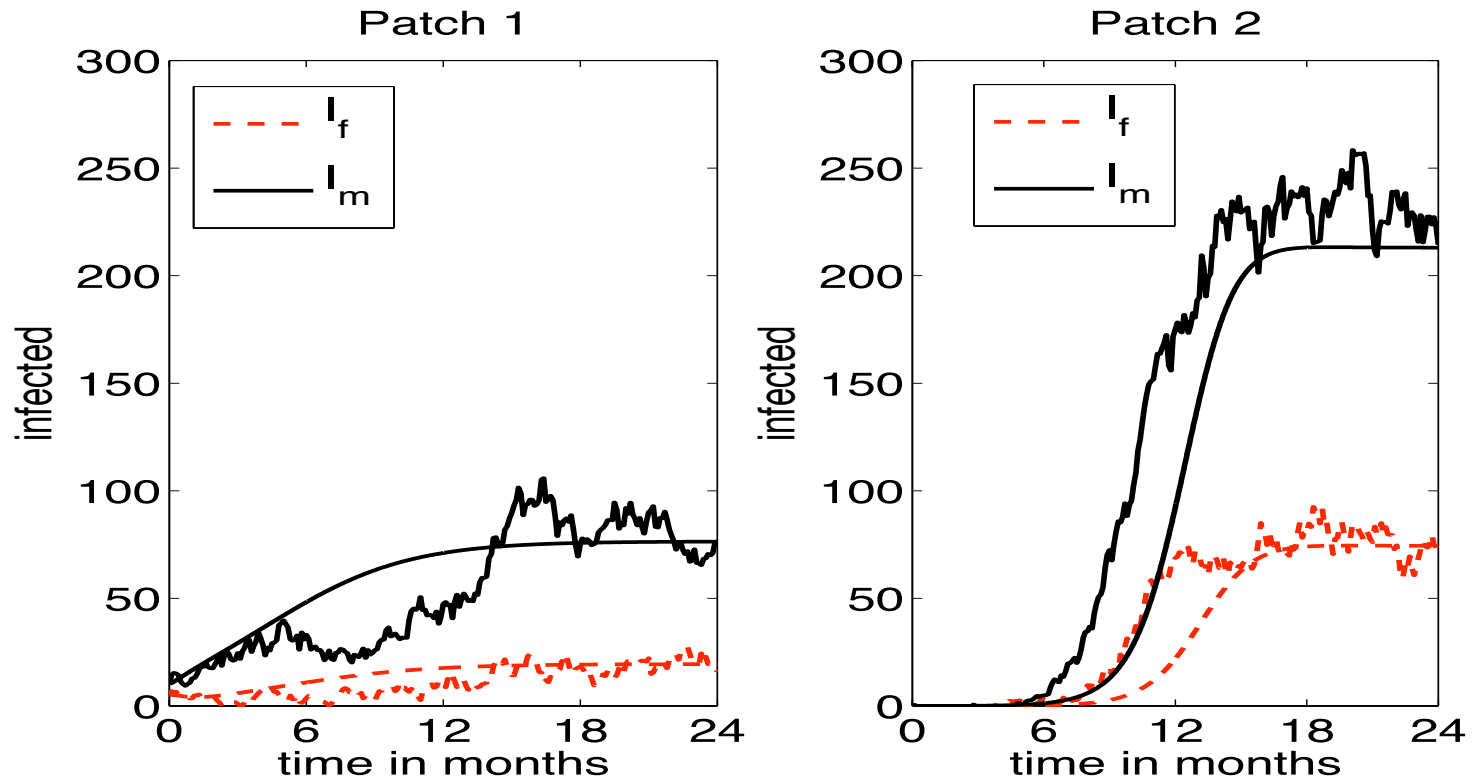


Figure 5: Disease spread to favorable habitat results in an outbreak.

## Summary

- **Basic Deterministic and Stochastic Epidemic Models** for hantavirus account for the higher contact rate and longer period of infectivity in males as well as variability in births, deaths and infection.
- **Variable Carrying Capacity** driven by changes in the environment can account for outbreaks.
- **Multi-Host Models** with spillover species might play an important role in disease persistence.
- **Heterogeneous Patch Models** with some patches better habitat for rodents can be sites where outbreaks occur.