Spread of Disease From Reservoir to Spillover Populations

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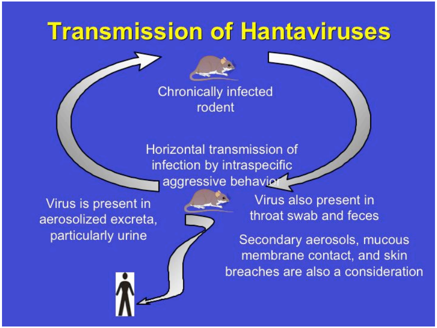
Outline

1. HANTAVIRUS: A Recent Emerging Zoonotic Disease is Carried by Wild Rodents.



We Summarize Hantavirus Infection in Humans and Its Origin

- **In Humans the disease is known as either Hemorrhagic Fever with Renal Syndrome – HFRS (Europe, Asia) Hantavirus Pulmonary Syndrome – HPS (Americas).**
- **HFRS was first recognized in 1951 when an outbreak occurred in military personnel during the Korean War (near Hataan River).**
- **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 humans in the US $\approx 40\%$. No cure or established drug treatment.**

Each Hantavirus is Associated with A Specific Wild Rodent.

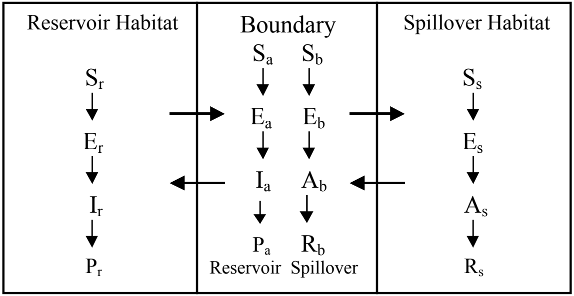
A Zoonotic Disease Involves Multiple Species, the Animal Reservoir and Spillover Infections.

- **During an outbreak, the reservoir species is identified by the large number of animals that have positive antibody titers.**
- **Spillover species, secondary rodent species, are also identified; a few animals that have positive antibody titers.**
- **Humans are also spillover species but there is no human-to-human transmission.**

Questions of Interest

1. **Disease Maintenance: Can the spillover species be a source for maintenance of the disease in the wild?**
2. **Host-Shifts: What are the important drivers for cross species transmission that result in host shifts, spillover becoming a reservoir?**

2. We Formulated an ODE Patch Model with Three Regions



Fogarty International Center # R01TW006986-02 under the NIH NSF Ecology of Infectious Diseases initiative.

Allen et al. 2009

Reservoir Species in its Preferred Habitat: (S_r, E_r, I_r, P_r).

$$
\begin{aligned}
\dot{S}_r &= b_r N_r - S_r(\beta_I I_r + \beta_P P_r) - S_r d_r(N_r) - p_i S_r + p_o S_a \\
\dot{E}_r &= S_r(\beta_I I_r + \beta_P P_r) - \delta_r E_r - E_r d_r(N_r) - p_i E_r + p_o E_a \\
\dot{I}_r &= \delta_r E_r - \gamma_r I_r - I_r d_r(N_r) - p_i I_r + p_o I_a \\
\dot{P}_r &= \gamma_r I_r - P_r d_r(N_r) - p_i P_r + p_o P_a
\end{aligned}
$$

p_i =movement into boundary
p_o =movement out of boundary
I_r = newly infectious P_r = persistently infectious
Reservoir Species in the Boundary: (S_a, E_a, I_a, P_a).

Spillover Species in its Preferred Habitat: (S_s, E_s, A_s, R_s)

$$\begin{aligned}
\dot{S}_s &= b_s N_s - \beta_A S_s A_s - S_s d_s(N_s) - p_i S_s + p_o S_b \\
\dot{E}_s &= \beta_A S_s A_s - \delta_s E_s - E_s d_s(N_s) - p_i E_s + p_o E_b \\
\dot{A}_s &= \delta_s E_s - \gamma_s A_s - A_s d_s(N_s) - p_i A_s - p_o A_b \\
\dot{R}_s &= \gamma_s A_s - R_s d_s(N_s) - p_i R_s + p_o R_b
\end{aligned}$$

A_s = acutely infectious
R_s = recovered
Spillover Species in the Boundary: (S_b, E_b, A_b, R_b)

Reservoir and Spillover Species in the Boundary – No Births and Deaths.

Reservoir:

$$\begin{aligned}
\dot{S}_a &= -S_a(\beta_{a1}I_a + \beta_{a2}P_a + \beta_{a3}A_b) + p_i S_r - p_o S_a \\
\dot{E}_a &= S_a(\beta_{a1}I_a + \beta_{a2}P_a + \beta_{a3}A_b) - \delta_a E_a + p_i E_r - p_o E_a \\
\dot{I}_a &= \delta_a E_a - \gamma_a I_a + p_i I_r - p_o I_a \\
\dot{P}_a &= \gamma_a I_a + p_i P_r - p_o P_a
\end{aligned}$$

Spillover:

$$\begin{aligned}
\dot{S}_b &= -S_b(\beta_{b1}I_a + \beta_{b2}P_a + \beta_{b3}A_b) + p_i S_s - p_o S_b \\
\dot{E}_b &= S_b(\beta_{b1}I_a + \beta_{b2}P_a + \beta_{b3}A_b) - \delta_b E_b + p_i E_s - p_o E_b \\
\dot{A}_b &= \delta_b E_b - \gamma_b A_b + p_i A_s - p_o A_b \\
\dot{R}_b &= \gamma_b A_b + p_i R_s - p_o R_b.
\end{aligned}$$

The Total Population Satisfies a Logistic Growth Assumption.

$$\begin{aligned}
\frac{dN_r}{dt} &= p_o N_a + N_r\left[b_r - p_i - d_r(N_r)\right] \\
\frac{dN_a}{dt} &= p_i N_r - p_o N_a \\
\frac{dN_s}{dt} &= p_o N_b + N_s\left[b_s - p_i - d_s(N_s)\right] \\
\frac{dN_b}{dt} &= p_i N_s - p_o N_b.
\end{aligned}$$

Solutions approach their carrying capacities.

RESERVOIR:

$$\lim_{t\to\infty} N_r(t) = K_r \text{ and } \lim_{t\to\infty} N_a(t) = \frac{p_i}{p_o} K_r = K_a$$

SPILLOVER:

$$\lim_{t\to\infty} N_s(t) = K_s \text{ and } \lim_{t\to\infty} N_b(t) = \frac{p_i}{p_o} K_s = K_b.$$

The Basic Reproduction Numbers for Reservoir, Spillover and Three-Patches are Computed.

$\vec{X} = (E_r, E_a, E_b, E_s, I_r, I_a, A_b, A_s, P_r, P_a)$

In the special case $\delta_i = 0 = \gamma_i,\ i = a, b$, an explicit expression for $\mathcal{R}_0$ can be obtained:

$$\mathcal{R}_0^r = \frac{p_o K_r(\beta_I b_r + \beta_P \gamma_r)\delta_r + p_i K_a(\beta_{a1} b_r + \beta_{a2}\gamma_r)\delta_r}{p_o(\delta_r + b_r)(\gamma_r + b_r)b_r}.$$

$$\mathcal{R}_0^s = \frac{p_o K_s \beta_A \delta_s + p_i K_b \beta_{b3}\delta_s}{p_o(\delta_s + b_s)(\gamma_s + b_s)}.$$

Diekmann, Heesterbeek, Metz, 1990; van den Driessche, Watmough, 2002; Roberts, Heesterbeek, 2003

The Basic Reproduction Number for Three Patches Depends on the Crossover Reproduction Number

$$\mathcal{R}_0 = \frac{\mathcal{R}_0^r + \mathcal{R}_0^s + \sqrt{(\mathcal{R}_0^r - \mathcal{R}_0^s)^2 + 4\mathcal{R}_0^c}}{2}.$$

Crossover Reproduction Number in the Boundary ($\delta_i = 0 = \gamma_i,\ i = a, b$):

$$\mathcal{R}_0^c = \left[\frac{p_i K_b(\beta_{b1} b_r + \beta_{b2}\gamma_r)\delta_r}{p_o(\delta_r + b_r)(\gamma_r + b_r)b_r}\right]\left[\frac{p_i \beta_{a3} K_a \delta_s}{p_o(\gamma_s + b_s)(\delta_s + b_s)}\right]$$

$$= \mathcal{R}_{sr}\mathcal{R}_{rs}.$$

Disease invasion occurs if $\mathcal{R}_0 > 1$.

The Basic Reproduction Number Determines the Global Dynamics.

Theorem

(ODE Model, $\boldsymbol{\delta_i = 0 = \gamma_i,\ i = a, b}$)

(i) *If $\boldsymbol{\mathcal{R}_0 < 1}$, then the DFE is globally asymptotically stable, and*

(iii) *If $\boldsymbol{\mathcal{R}_0 > 1}$, then the DFE is unstable and there exists a unique positive EE.*

3. Continuous-Time Markov Chain (CTMC) Model for Rodent-Hantavirus System

$\vec{Z} =$
$(S_r, E_r, I_r, P_r, S_a, E_a, I_a, P_a, S_b, E_b, A_b, R_b, S_s, E_s, A_s, R_s)$

$$\Delta\vec{Z} = (\Delta S_r, \Delta E_r, \dots, \Delta A_s, \Delta R_s)$$

Change $\Delta\vec{Z}$	Probability
$(-1, 1, 0, 0, \dots, 0)$	$\beta_A S_r I_r \Delta t + o(\Delta t)$
$(0, -1, 1, \dots, 0)$	$\delta_A E_r \Delta t + o(\Delta t)$
$\vdots$	$\vdots$

Assumptions about Parameter Values

Reservoir Parameter	Value	Spillover Parameter	Value
K_r	100	K_s	50
b_r	3	b_s	3
δ_r	26/yr	δ_s	26/yr
γ_r	4 /yr	γ_s	26/yr
δ_a	26/yr	δ_b	26/yr
γ_a	4/yr	γ_b	26/yr
β_I	0.075	β_A	0.025
β_P	0.025	β_{b_3}	0.025
β_{a_1}	0.075	β_{b_1}	0.15
β_{a_2}	0.025	β_{b_2}	0.05
β_{a_3}	0.05		

Table: Basic parameter values for the ODE and the CTMC models for reservoir and spillover species. For $p_i = 8$, $p_o = 52$, $\mathcal{R}_0^r = 1.4$, $\mathcal{R}_0^s \approx 0.04$, and $\mathcal{R}_0^c < 2 \times 10^{-4}$.

Comparison of ODE and CTMC Infectious Reservoir Population in Preferred Habitat and in Boundary

Preferred Habitat **Boundary**

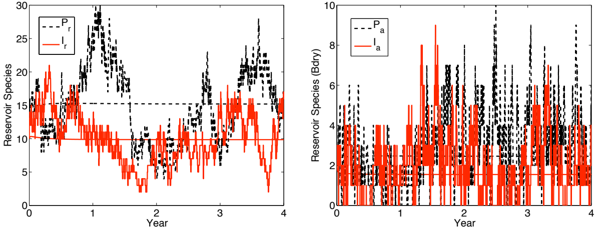


Figure: Solution to the ODE model (straight lines) and one sample path of the CTMC model (variable curves)

Probability Histograms for the Reservoir Species in Preferred Habitat

Newly Infectious **Persistently Infectious**

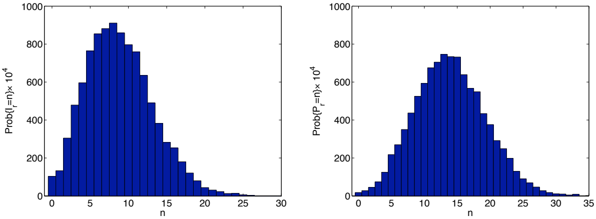
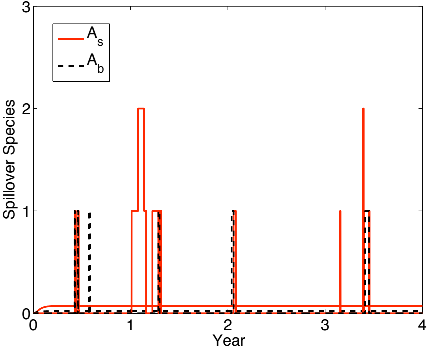


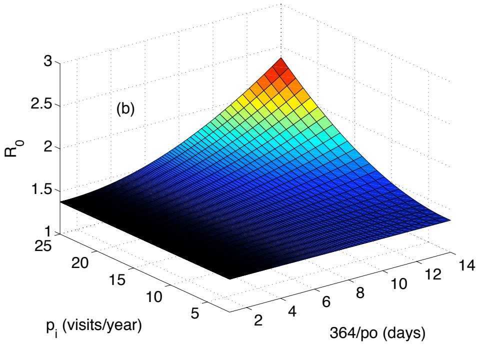
Figure: Probability histograms $\boldsymbol{I_r}$ and $\boldsymbol{P_r}$ based on 10,000 sample paths of the CTMC model; $\boldsymbol{\hat{\mu}_{I_r} = 8.8}$, $\boldsymbol{\hat{\sigma}_{I_r} = 4.3}$ and $\boldsymbol{\hat{\mu}_{P_r} = 14.0}$, $\boldsymbol{\hat{\sigma}_{P_r} = 5.4}$.

ODE and CTMC for the Acute Infection of Spillover Species in Preferred Habitat and Boundary.



The model shows sporadic infection in spillover species. Spillover events may lead to “host shifts” and emergence of new diseases.

The Value of $\mathcal{R}_0$ as a function of p_i (rate move into boundary) and $364/p_o$ (average number days in bdry)



4. We Formulate a Branching Process Model

We apply Galton Watson Branching Process to approximate the probability of an outbreak, given $I_r(0) = 1$, $I_a(0) = 1$, or $A_b(0) = 1$. Assume events are independent. In each region, the population densities are at their disease-free states.

Preferred Habitats:

$$S_r = K_r, \quad S_s = K_s$$

Boundary Habitat:

$$S_a = K_a, \quad S_b = K_b.$$

$$\boxed{K_a = \frac{p_i}{p_o} K_r \quad K_b = \frac{p_i}{p_o} K_s}$$

We will Formulate Probability Generating Functions (P.G.F.) for the Offspring

At the disease-free state consider the offspring distribution for $\vec{X} = (E_r, I_r, P_r, E_a, I_a, P_a, E_b, A_b, E_s, A_s)$ if one individual is introduced, E_r or I_r, etc. Given $\vec{X}(0) = (\delta_{1j}, \dots, \delta_{nj})$, then

$$f_j(s_1, \dots, s_{10})$$

$$= \sum_{i_1,\dots,i_{10}} \text{Prob}\{\vec{X} = (i_1, \dots, i_{10})\} s_1^{i_1} \cdots s_{10}^{i_{10}}$$

$j = 1, \dots, 10$, $f_j(1, \dots, 1) = 1$.

EXAMPLE: Branching Process Applied to the Spillover Species in its Preferred Habitat– NO Dispersal

$$E_s = 1: \; f_1(s_1, s_2) = \frac{\delta_s s_2 + b_s}{\delta_s + b_s}$$

$$A_s = 1: \; f_2(s_1, s_2) = \frac{\beta_A K_s s_1 s_2 + \gamma_s + b_s}{\beta_A K_s + \gamma_s + b_s}$$

Expectation Matrix $M = (\partial f_j / \partial s_i)_{s_1 = 1 = s_2}$

$$M = \begin{pmatrix} 0 & \frac{\delta_s}{\delta_s + b_s} \\ \frac{\beta_A K_s}{\beta_A K_s + \gamma_s + b_s} & \frac{\beta_A K_s}{\beta_A K_s + \gamma_s + b_s} \end{pmatrix}$$

Lahodney, Allen (in progress)

EXAMPLE: Probability of Disease Extinction for Spillover Species

$$m = \rho(M) < 1 \quad \text{iff} \quad \mathcal{R}_0^s = \frac{\beta_a K_s \delta_s}{(\gamma_s + b_s)(\delta_s + b_s)} < 1$$

(i) **If $m < 1(\mathcal{R}_0^s < 1)$, the branching process is called subcritical and the probability of extinction is one.**

(ii) **If $m > 1(\mathcal{R}_0^s > 1)$, the branching process is called supercritical and the probability of extinction is less than one,**

$$q_1^{a_1} q_2^{a_2},$$

where (q_1, q_2) is the smallest fixed point of $f_i(q_1, q_2) = q_i$, $0 \leq q_i \leq 1$, $i = 1, 2$, $E_s(0) = a_1$ and $A_s(0) = a_2$.

EXAMPLE: Explicit Expressions for the Fixed Points when $\mathcal{R}_0^s > 1$

$$
\begin{aligned}
q_1 &= \frac{\delta_s}{\delta_s + b_s}\frac{1}{\mathcal{R}_0^s} + \frac{b_s}{\delta_s + b_s} \\
q_2 &= \frac{1}{\mathcal{R}_0^s}
\end{aligned}
$$

if the process is supercritical, $\mathcal{R}_0^s > 1$. In general, an explicit expression for a fixed point for multi-type processes may not be possible to compute. We compute the fixed point numerically for our three-patch hantavirus model.

General Theory of Multi-Type Branching Process

Let f_j, $j = 1, \ldots, 10$ be the p.g.f. for a multi-type branching process and let m be the spectral radius of the expectation matrix

$$M = \left(\partial f_j / \partial s_i\right)\big|_{s_1=1,\ldots,s_{10}=1}.$$

(i) **If $m < 1$, the process is subcritical and the probability of extinction equals one.**

(ii) **If $m > 1$, the process is supercritical and the probability of extinction is approximately**

$$q_1^{a_1} q_2^{a_2} \ldots q_{10}^{a_{10}},$$

where $(q_1, \ldots, q_{10})$ is the unique minimal fixed point of f_j, $0 \le q_i \le 1, E_r(0) = a_1, \ldots, A_s(0) = a_{10}$.

Formulating a Branching Process for Spillover and Reservoir

For the spillover species $\vec{Y} = (E_s, A_s, E_b, A_b)$, $\Delta\vec{Y} = (\Delta E_b, \Delta A_b, \Delta E_s, \Delta A_s)$.

Change $\Delta\vec{Y}$	Probability
$(0,0,1,0)$	$\beta_A A_s K_s \Delta t$
$(0,0,-1,1)$	$\delta_s E_s \Delta t$
$(0,0,-1,0)$	$b_s E_s \Delta t$
$(1,0,-1,0)$	$p_i E_s \Delta t$
$(-1,0,1,0)$	$p_o E_b \Delta t$
$(0,0,0,-1)$	$(\gamma_s + b_s) A_s \Delta t$
$(0,1,0,-1)$	$p_i A_s \Delta t$
$(0,-1,0,1)$	$p_o A_b \Delta t$
$(1,0,0,0)$	$K_b(\beta_{b1} I_a + \beta_{b2} P_a + \beta_{b3} A_b)\Delta t$
$(-1,1,0,0)$	$\delta_b E_b \Delta t$
$(0,-1,0,0)$	$\gamma_b A_b \Delta t$

We Formulate the P.G.F. for Offspring for the Spillover Species

$$\vec{X} = (E_r, I_r, P_r, E_a, I_a, P_a, E_b, A_b, E_s, A_s)$$

$$. \qquad (s_1, s_2, s_3, s_4, s_5, s_6, s_7, s_8, s_9, s_{10})$$

$$E_b = 1: \; f_7 = \frac{\delta_b s_8 + p_o s_9}{\delta_b + p_o}$$

$$A_b = 1: \; f_8 = \frac{\beta_{a3} K_a s_8 s_4 + \beta_{b3} K_b s_8 s_7 + \gamma_b + p_o s_{10}}{\beta_{a3} K_a + \beta_{b3} K_b + \gamma_b + p_o}$$

$$E_s = 1: \; f_9 = \frac{\delta_s s_{10} + b_s + p_i s_7}{\delta_s + b_s + p_i}$$

$$A_s = 1: \; f_{10} = \frac{\beta_A K_s s_9 s_{10} + p_i s_8 + b_s + \gamma_s}{\beta_A K_s + p_i + b_s + \gamma_s}$$

Probability of an Outbreak in Hantavirus Model with Spillover and Reservoir

For the parameter values in the Table, $m = \rho(M) > 1$. The minimal fixed point for f_j is calculated. For one infectious individual, the probability of an outbreak is $1 - q_j$:

Three curves $1 - q_j$ are graphed as a function of $K_a = (p_i/p_o)K_r$.
Reservoir in Preferred Habitat, $I_r = 1$: $1 - q_2$
Reservoir in Boundary, $I_a = 1$: $1 - q_5$
Spillover in Boundary, $A_b = 1$: $1 - q_8$

The Probability of an Outbreak Increases as $\boldsymbol{K_a}$ increases.

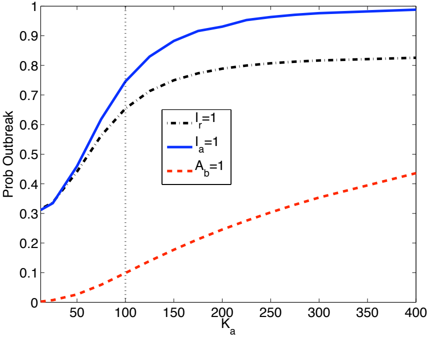


Figure: **Parameter values as in the Table with $\boldsymbol{K_a = (p_i/p_o)K_r = 1000/p_o}$ ($\boldsymbol{K_r = 100}$ and $\boldsymbol{p_i = 10}$).**

Conclusion
Questions on Disease Maintenance and Host-Shifts

1. **Disease maintenance?** It is possible for the spillover species to contribute to the maintenance of the disease in the wild when the density of (or transmission between) the reservoir and spillover species in regions of overlap increase significantly. Presence of spillover increases $\mathcal{R}_0$ and decreases probability of disease extinction (amplification effect).
2. **Host-shifts?** Cross species transmission can lead to host-shifts when a new viral strain is able to reproduce in a new host. Evolution must lead to $\mathcal{R}_0^s > 1$. More likely between closely related hosts.

Streicker et al. 2010