



Probability of a Zoonotic Spillover in a Fluctuating Environment

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September 27, 2019

Acknowledgements

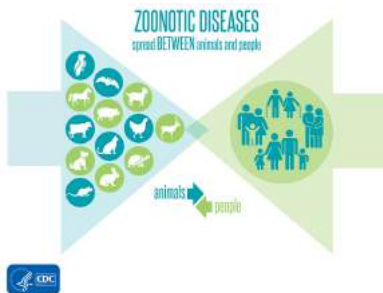
- **NMSU:** Dr. Paul Tian and Dr. John Harding
- **National Science Foundation**
- **Texas Tech PhD Students:** Aadrita Nandi and Kaniz Fatema Nipa



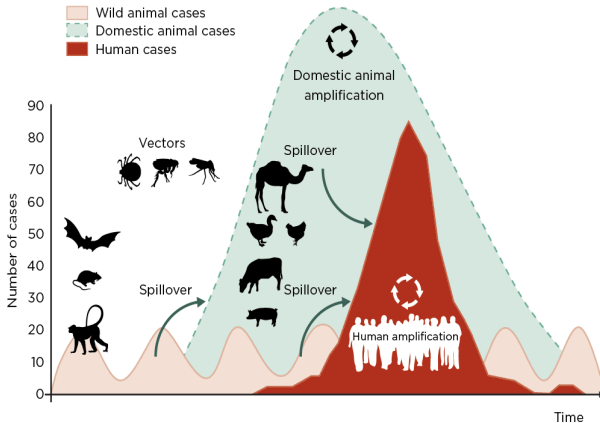
- **Ref:** A Nandi & LJS Allen. 2019. Probability of a Zoonotic Spillover in a Fluctuating Environment. To be Submitted.
- **Ref:** KF Nipa & LJS Allen. 2019. The effect of demographic variability and periodic fluctuations on disease outbreaks in a vector-host epidemic model. Under review.

I Zoonoses: Diseases Spread from Animals to Humans

- More than 60% of infectious diseases in humans are zoonotic.
- Priority zoonotic diseases in USA include:
Zoonotic influenza viruses, Salmonellosis, West Nile virus, Plague, Emerging coronaviruses (MERS, SARS), **Rabies**, Brucellosis, Lyme Disease



Seasonal Effect on Spillover of Zoonotic Infections



Spillover from Animal Reservoir and Humans

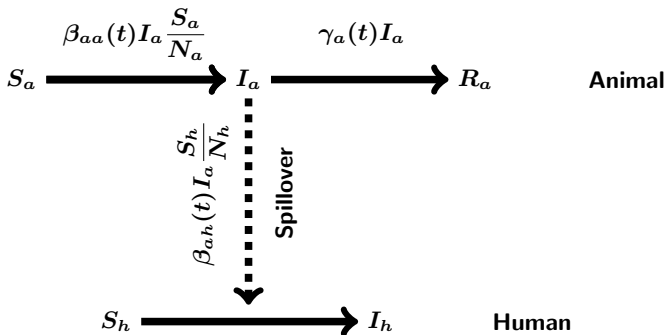


Figure: Compartmental diagram of the SIR ODE model for a spillover event from an animal reservoir to humans.

ODE Model for Animals and Humans

$$\text{Animal} \quad \left\{ \begin{array}{l} \frac{dS_a}{dt} = -\beta_{aa}(t) \frac{S_a I_a}{N_a} \\ \frac{dI_a}{dt} = \beta_{aa}(t) \frac{S_a I_a}{N_a} - \gamma_a(t) I_a \\ \frac{dR_a}{dt} = \gamma_a(t) I_a \end{array} \right.$$

$$\text{Human} \quad \left\{ \begin{array}{l} \frac{dS_h}{dt} = -\beta_{ah}(t) \frac{S_h I_a}{N_h} \\ \frac{dI_h}{dt} = \beta_{ah}(t) \frac{S_h I_a}{N_h} \end{array} \right.$$

$$\text{DFE: } \bar{S}_a = N_a, \bar{S}_h = N_h$$

Continuous **periodic** functions of time:

$$\beta_i(t) = \beta_i(t + T), \quad i = aa, ah, \quad \gamma_a(t) = \gamma_a(t + T)$$

Time-Nonhomogeneous Stochastic Model of Spillover

Discrete random variables:

$$S_a, I_a, R_a \in \{0, 1, \dots, N_a\}, \quad S_h, I_h, R_h \in \{0, 1, \dots, N_h\}$$

Table: Transition Probabilities Until First Human Spillover

Description	Event	Probability
Animal infection	$(S_a, I_a) \rightarrow (S_a - 1, I_a + 1)$	$\beta_{aa}(t) i_a \frac{s_a}{N_a} \Delta t$
Animal recovery	$(I_a, R_a) \rightarrow (I_a - 1, R_a + 1)$	$\gamma_a(t) i_a \Delta t$
Human infection	$(S_h, I_h) \rightarrow (S_h - 1, I_h + 1)$	$\beta_{ah}(t) i_a \frac{s_h}{N_h} \Delta t$
No Change	$(S_a, I_a, S_h, I_h) \rightarrow (S_a, I_a, S_h, I_h)$	$1 - \Sigma(t) \Delta t$

$$\Sigma(t) = \beta_{aa}(t) i_a \frac{s_a}{N_a} + \gamma_a(t) i_a + \beta_{ah}(t) i_a \frac{s_h}{N_h}$$

$$I_a(0) = i, \quad S_a(0) = N_a - i, \quad S_h(0) = N_h, \quad I_h(0) = 0.$$

Sample Paths of Infected Animals Until First Spillover

Five sample paths of I_a given $I_a(0) = 1$ or $I_a(1) = 1$ until extinction or until the first human spillover for **periodic** β_{aa} , β_{ah} and γ_a .

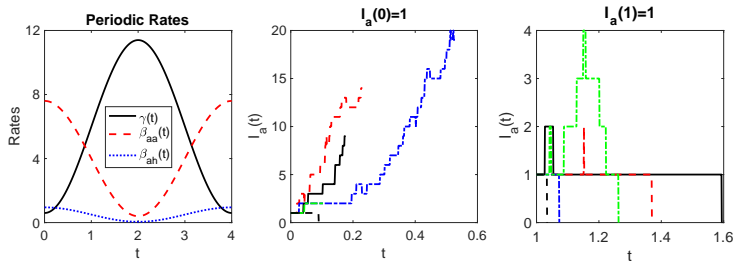


Figure: Five sample paths of I_a , $T = 4$.

Branching Process Approximation

- **Apply a branching process approximation (birth-death-killing process) to obtain an analytical estimate of the probability of the first human spillover event, when $I_\alpha(\tau) = 1$ and $\tau \in [0, T]$.**
- **Apply the backward Kolmogorov differential equations and generating functions.**

Ref: Karlin and Tavaré, 1982; Singh et al. 2014; Bacaër and Dads, 2014; Voinson et al. 2018

Estimate Probability of Disease Extinction in Animals

- Probability i infected animals, introduced at time τ , infect k animals but no humans by time t :

$$p_{i,k}(\tau, t) = \mathbb{P}\{I_a(t) = k | I_a(\tau) = i \text{ and } I_h(s) = 0, \tau \leq s \leq t\}.$$

- Generating Functions near DFE $\bar{S}_a = N_a$ and $\bar{S}_h = N_h$

$$G_i(u, \tau, t) = \mathbb{E} \left[u^{I_a(t)} | I_a(\tau) = i \right] = \sum_{k=0}^{\infty} p_{i,k}(\tau, t) u^k$$

$$G_1(0, \tau, 0) = p_{1,0}(\tau, 0) = P_{ext}(\tau)$$

- Probability of extinction in time $[\tau, 0]$:

$$\frac{dP_{ext}}{d\tau} = -(\beta_{aa}(\tau) + \gamma_a(\tau) + \beta_{ah}(\tau))[f(P_{ext}, \tau) - P_{ext}],$$

$$f(u, \tau) = \frac{\beta_{aa}(\tau)u^2 + \gamma_a(\tau)}{\beta_{aa}(\tau) + \gamma_a(\tau) + \beta_{ah}(\tau)}$$

Probability of First Spillover Event to Humans

- **Probability of No Spillover in time $[\tau, 0]$:**

$$\frac{dP_{ext}}{d\tau} = -(\beta_{aa}(\tau) + \gamma_a(\tau) + \beta_{ah}(\tau))[f(P_{ext}, \tau) - P_{ext}]$$

$$P_{ext}(0) = 0.$$

- **Let $\tau = -t$ and solve on $[0, t]$.**

$$\frac{dP(t)}{dt} = (\beta_{aa}(-t) + \gamma(-t) + \beta_{ah}(-t))[f(P(t), -t) - P(t)],$$

$$P(0) = 0 \tag{1}$$

- **Reflection of $P(t)$ is Probability of No Spillover in time $[0, t]$: $P_{ext}(t)$.**

The Probability of First Spillover is

$$\mathbb{P}_{spill}(t) = 1 - P_{ext}(t)$$

Convergence to a Periodic Solution

Theorem

Assume the transmission and recovery rates are positive and periodic functions with period T . Then the solution of the initial value problem (1) satisfies

$$P(t) \in (0, 1), \quad t > 0$$

and converges monotonically and uniformly to a periodic solution $\Phi(t)$ on $[0, T]$. In particular,

$$P(t + kT) \rightarrow \Phi(t)$$

as the integer $k \rightarrow \infty$ for $0 \leq t \leq T$.

Constant Probability of Spillover

Theorem

Assume the transmission and recovery rates are positive and continuous:

$$\begin{aligned}\beta_i(t) &= \bar{\beta}_i g(t), i = aa, ah \\ \gamma_a(t) &= \bar{\gamma}_a g(t).\end{aligned}$$

with a common factor $g(t)$. If $I_a(0) = 1$, then

$$\lim_{t \rightarrow \infty} \mathbb{P}_{spill}(t) = 1 - q,$$

where q is the unique fixed point of $f(q) = q$ on $(0, 1)$,

$$q = \frac{(\bar{\beta}_{aa} + \bar{\gamma}_a + \bar{\beta}_{ah}) - \sqrt{(\bar{\beta}_{aa} + \bar{\gamma}_a + \bar{\beta}_{ah})^2 - 4\bar{\beta}_{aa}\bar{\gamma}_a}}{2\bar{\beta}_{aa}}.$$

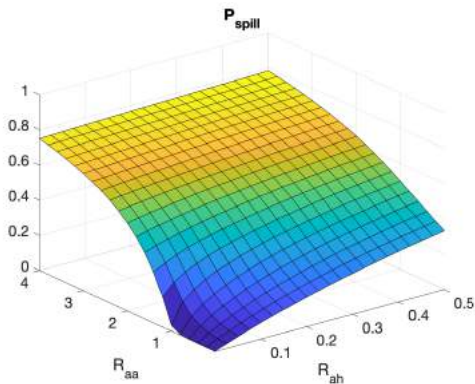
$$f(q, t) = \frac{\beta_{aa}(t)q^2 + \gamma_a(t)}{\beta_{aa}(t) + \gamma_a(\tau) + \beta_{ah}(t)}$$

Constant Probability of Spillover for Constant Rates

$$\mathcal{R}_{aa} = \frac{\beta_{aa}}{\gamma_a}, \quad \mathcal{R}_{ah} = \frac{\beta_{ah}}{\gamma_a}$$

$$q = \frac{\mathcal{R}_{aa} + 1 + \mathcal{R}_{ah} - \sqrt{(\mathcal{R}_{aa} + 1 + \mathcal{R}_{ah})^2 - 4\mathcal{R}_{aa}}}{2\mathcal{R}_{aa}}$$

$$\mathbb{P}_{spill} = 1 - q$$



Hypothetical Parameter Values for Zoonotic Infection

Parameter	Value
N_a	10000
N_h	10000
$\bar{\gamma}_a$	6/season
$\bar{\beta}_{aa}$	4/season
$\bar{\beta}_{ah}$	1/season
T	4 seasons

Animal Basic Reproduction Number: $\bar{\mathcal{R}}_a = \frac{\bar{\beta}_{aa}}{\bar{\gamma}_a} = \frac{2}{3}$

Periodic Parameters

$$\beta_i(t) = \bar{\beta}_i \left[1 + \epsilon_i \cos \left(\frac{\pi}{2} t \right) \right], \quad i = aa, ah$$

$$\gamma_a(t) = \bar{\gamma}_a \left[1 + \epsilon_g \cos \left(\frac{\pi}{2} t \right) \right]$$

Constant Probability of Spillover for Periodic Rates

$$\beta_i(t) = \bar{\beta}_i \left[1 + 0.9 \cos \left(\frac{\pi}{2} t \right) \right] = \bar{\beta}_i g(t), \quad i = aa, ah$$

$$\gamma_a(t) = \bar{\gamma}_a \left[1 + 0.9 \cos \left(\frac{\pi}{2} t \right) \right] = \bar{\gamma}_a g(t),$$

then

$$\lim_{t \rightarrow \infty} \mathbb{P}_{spill}(t) = 1 - q = 0.25$$

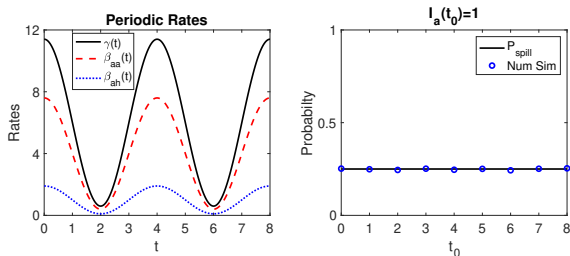


Figure: Probability of spillover $\mathbb{P}_{spill}(t_0)$ verified with 10,000 sample paths $t_0 = 0, 1, 2, \dots, 8$.

Periodic Probability of Human Spillover

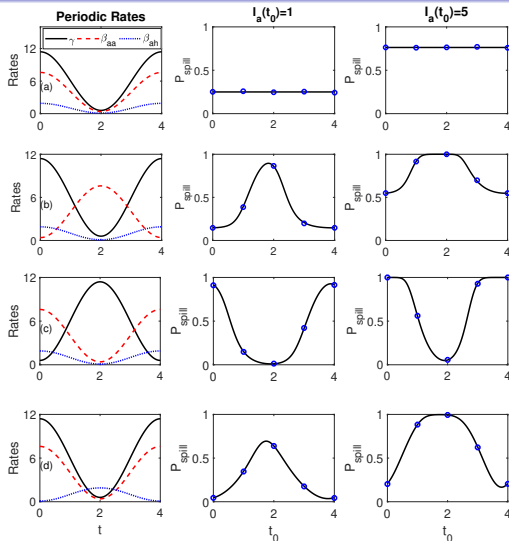


Figure: $\mathbb{P}_{spill}(t_0) = \mathbb{P}_{spill}(t_0 + T) = 1 - [P_{ext}(t_0)]^i$, $I(t_0) = i$, $i = 1, 5$, $\epsilon_k = \pm 0.9$, $k = aa, ah, g$.

Compare Constant Probability of Spillover with Average of the Periodic Probability of Spillover

The average of the periodic probability of spillover:

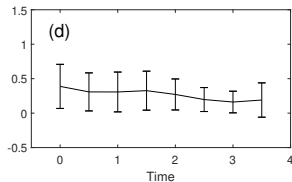
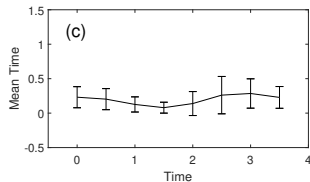
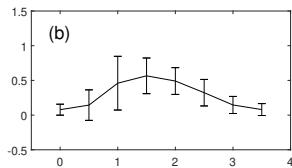
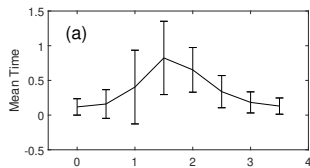
$$\bar{P}_{spill} = \frac{1}{T} \int_0^T \mathbb{P}_{spill}(t) dt.$$

Table: \bar{P}_{spill} based on parameter values in previous Figure with $I(t_0) = 1$.

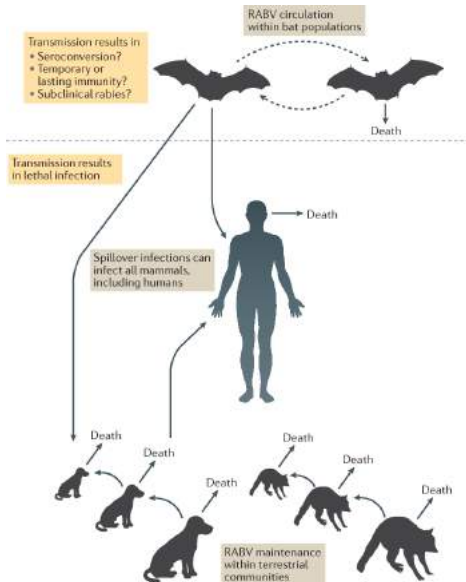
Figure	\bar{P}_{spill}
(a)	0.250
(b)	0.397
(c)	0.373
(d)	0.304

The Mean Time Until First Spillover to Humans

The mean and standard deviation for time until spillover from the previous Figure (a), (b), (c), and (d).



Rabies Spillover from Wild Dogs to Humans



Rabies Spillover from Bite of a Rabid Dog

Probability of first human infection I_h from an infected or exposed dog.
 Disease-related deaths, μ_i , no recovery, and a proportion of exposed individuals that develop clinical symptoms, γ_i , $i = a, h$.

$$\begin{aligned}
 \text{Dogs} \quad \left\{ \begin{array}{l} \frac{dS_a}{dt} = -\beta_{aa}(t) \frac{S_a I_a}{N_a} + \sigma_a (1 - \gamma_a) E_a \\ \frac{dE_a}{dt} = \beta_{aa}(t) \frac{S_a I_a}{N_a} - \sigma_a (1 - \gamma_a) E_a - \sigma_a \gamma_a E_a \\ \frac{dI_a}{dt} = \sigma_a \gamma_a E_a - \mu_a I_a \end{array} \right. \\
 \\
 \text{Humans} \quad \left\{ \begin{array}{l} \frac{dS_h}{dt} = -\beta_{ah}(t) \frac{S_h I_a}{N_h} + \sigma_h (1 - \gamma_h) E_h \\ \frac{dE_h}{dt} = \beta_{ah}(t) \frac{S_h I_a}{N_h} - \sigma_h (1 - \gamma_h) E_h - \sigma_h \gamma_h E_h \\ \frac{dI_h}{dt} = \sigma_h \gamma_h E_h - \mu_h I_h \end{array} \right.
 \end{aligned}$$

Parameter Values for Rabies in China

Table: Parameters for Rabies Model in China (Ruan, 2017)

Parameter	Dog	Parameter	Human	Units
N_a	500 [†]	N_h	2000 [†]	Pop. Size
γ_a	0.49, 1 [‡]	γ_h	0.5, 1 [‡]	Proportion
σ_a	0.957	σ_h	0.5	(month) ⁻¹
μ_a	1	μ_h	1	(month) ⁻¹
$\bar{\beta}_{aa}$	3.62	$\bar{\beta}_{ah}$	0.0362 [†]	(month) ⁻¹
T	12			month

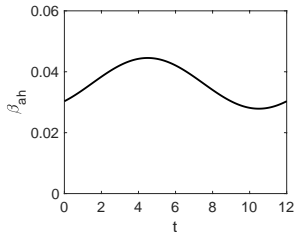
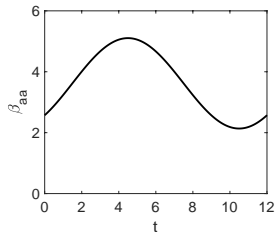
For constant parameters $\bar{\mathcal{R}}_{aa} = \frac{\bar{\beta}_{aa}\gamma_a}{\mu_a} = 1.77$

[†]local population sizes, depends on pop sizes [‡]assumed

Transmission Rates for Rabies Vary Annually

$$\beta_{aa}(t) = 3.62 \left[1 + 0.41 \sin \left(\frac{\pi t}{6} + 5.5 \right) \right]$$

$$\beta_{ah}(t) = 0.0362 \left[1 + 0.23 \sin \left(\frac{\pi t}{6} + 5.5 \right) \right]$$



Probability of First Spillover from Dogs to Humans

The dog rabies outbreak begins with an exposed or infectious dog, The probability of spillover for two cases (i) all exposed individuals develop rabies or (ii) only 50% of individuals develop clinical signs of rabies.

$\mathbb{P}_{spill}(t_0)$ similar to $\beta_{aa}(t)/\beta_{ah}(t)$ but is shifted **Left**.

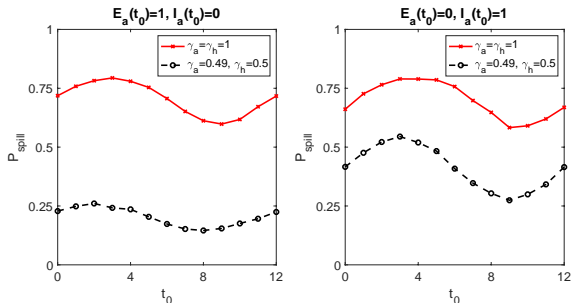
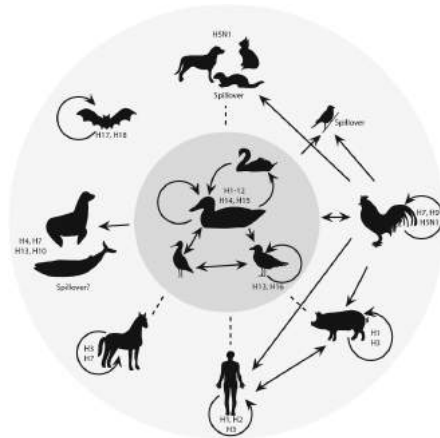


Figure: Probability of rabies spillover from dogs to humans for (i) $\gamma_a = 1 = \gamma_h$ —x— and (ii) $\gamma_a = 0.49, \gamma_h = 0.5$ —o—

Highly Pathogen Avian Influenza (HPAI) Spillover

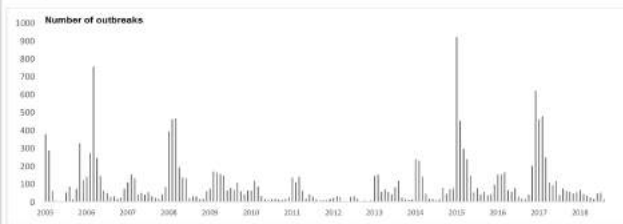
Avian influenza viruses are classified by hemagglutinin (H, 16 subtypes) and neuraminidase (N, 9 subtypes). HPAI associated with H5 and H7.



HPAI Outbreaks in Domestic Birds Worldwide

World Organization for Animal Health (OIE, 8/2018) data show annual outbreaks,

Figure 3 shows the number of outbreaks in domestic birds since 2005 by month. Major peaks can be observed in 2006 (N=1,841), 2008 (N=1,954), 2015 (N=2,454) and 2017 (N=1,830).



Spillover Model HPAI from Domestic Birds to Humans

Seasonality in direct transmissibility of H5N1 in poultry.

$$\text{Domestic Birds} \left\{ \begin{array}{l} \frac{dS_a}{dt} = \Lambda_a - \beta_{aa}(t) \frac{I_a S_a}{N_a} - \mu_a S_a \\ \frac{dI_a}{dt} = \beta_{aa}(t) \frac{I_a S_a}{N_a} - (\mu_a + \nu_a) I_a \end{array} \right.$$

$$\text{Humans} \left\{ \begin{array}{l} \frac{dS_h}{dt} = -\beta_{ah} \frac{I_a S_h}{N_h} \\ \frac{dI_h}{dt} = \beta_{ah} \frac{I_a S_h}{N_h} - \nu_h I_h \end{array} \right.$$

Parameter Values for HPAI

Table: Parameter Values for Poultry and Humans for HPAI (Tuncer & Martcheva, 2010)*

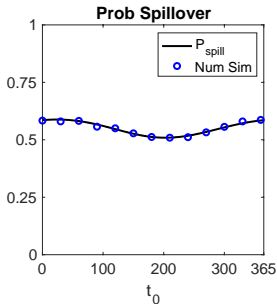
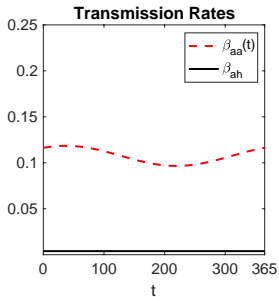
Parameter	Poultry	Parameter	Human
$N_a \dagger$	40000	$N_h \dagger$	200
Λ_a	N_a/T	T	365 days
$\bar{\beta}_{aa}$	0.1075	β_{ah}	$3.89 \times 10^{-3} \ddagger$
ν_a	0.05		
μ_a	$0.5/T$		

Basic reproduction number for animal:

$$\bar{\mathcal{R}}_{aa} = 2.09, \quad \mathcal{R}_{ah} = 0.0757$$

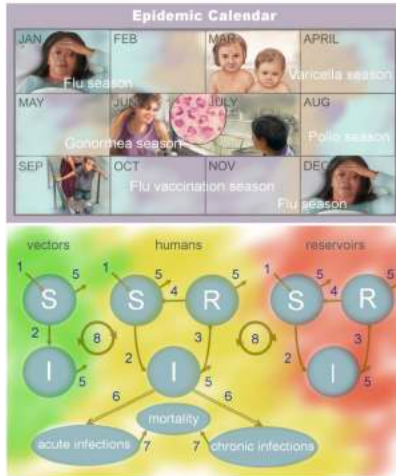
*Parameter fit to data on cumulative number of human cases. \dagger local population size $\ddagger \beta_{ah} \times 10^8$

Probability of HPAI from Domestic Birds to Humans



$$\beta_{aa}(t) = 0.1075 \left[1 + 0.1015 \sin \left(\frac{2\pi t}{365} + 107.75 \right) \right]$$

II Seasonal Periodicity and Disease Outbreaks



Ref: Martinez. 2018. The calendar of epidemics: seasonal cycle of infectious diseases. PLoS Path

Vector-Host Model with Periodic Transmission Rates

$$\text{Host} \begin{cases} \frac{dS}{dt} &= -\beta_s(t)V \frac{S}{N_s} + bN_s - bS + \gamma I \\ \frac{dI}{dt} &= \beta_s(t)V \frac{S}{N_s} - \gamma I - bI \end{cases}$$

$$\text{Vector} \begin{cases} \frac{dM}{dt} &= -\beta_m(t)I \frac{M}{N_m} + cN_m - cM \\ \frac{dV}{dt} &= \beta_m(t)I \frac{M}{N_m} - cV \end{cases}$$

Time-periodic coefficients, period p :

$$\beta_m(t) = \beta_m(t + p), \quad \beta_s(t) = \beta_s(t + p)$$

ODE Basic Reproduction Number for Constant or for Periodic Coefficients

Constant Coefficients: $\beta_m = \bar{\beta}_m, \beta_s = \bar{\beta}_s$

$$\bar{\mathcal{R}}_0 = \rho(\bar{\mathcal{F}}\bar{\mathcal{V}}^{-1}) = \sqrt{\frac{\bar{\beta}_m \bar{\beta}_s}{c(b + \gamma)}}$$

Periodic Coefficients: Compute λ so that the dominant Floquet multiplier of the monodromy matrix

$$\rho(\Phi_{(\mathcal{F}/\lambda - \mathcal{V})}(p)) = 1.$$

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

Ref: Diekmann, Heesterbeek and Metz 1990; van den Driessche and Watmough 2002; Ma and Ma 2006; Bacaër and Guernaoui 2006; Wang and Zhao 2008; Wesley and Allen 2009; Cushing and Ackleh, 2012; Tian and Wang, 2014; Cushing and Diekmann 2016; van den Driessche 2018 . . .

Stochastic Vector-Host Models

Discrete random variables:

$$\Delta X(t) = (\Delta I(t), \Delta V(t), \Delta S(t), \Delta M(t))$$

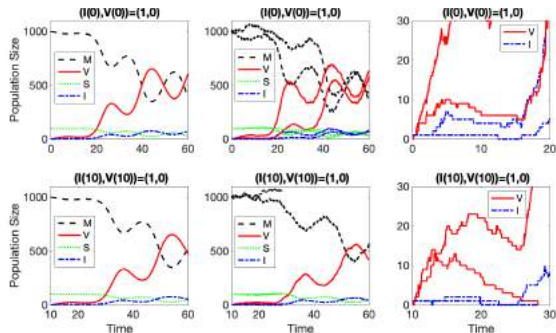
Table: Time-Nonhomogeneous Transition Probabilities

Event	Description	$\Delta X(t)$	Probability
1	Host infection	$(1, 0, -1, 0)$	$\beta_s(t)sv/N_s\Delta t$
2	Infected host death	$(-1, 0, 0, 0)$	$bi\Delta t$
3	Host recovery	$(-1, 0, 1, 0)$	$\gamma i\Delta t$
4	Vector infection	$(0, 1, 0, -1)$	$\beta_m(t)mi/N_m\Delta t$
5	Infected vector death	$(0, -1, 0, 0)$	$cv\Delta t$
6	Healthy host birth	$(0, 0, 1, 0)$	$bN_s\Delta t$
7	Healthy vector birth	$(0, 0, 0, 1)$	$cN_m\Delta t$
8	Healthy host death	$(0, 0, -1, 0)$	$bs\Delta t$
9	Healthy vector death	$(0, 0, 0, -1)$	$cm\Delta t$
10	No change	$(0, 0, 0, 0)$	$1 - \Sigma(t)\Delta t$

$$\Sigma(t) = \beta_s(t)sv/N_s + b(i + s + N_s) + \gamma i + \beta_m(t)mi/N_m + c(v + m + N_m).$$

Two Sample Paths and ODE Solution

$$\beta_m(t) = 2(1 + 0.9 \cos(\pi t/10)), \quad \beta_s(t) = 0.04(1 + 0.9 \cos(\pi t/10))$$



Probability of an outbreak depends on the time of introduction of an infected host, $t = 0$ or $t = 10$:

$$\mathbb{P}_{\text{outbreak}}(0) = 0.87 \quad \text{and} \quad \mathbb{P}_{\text{outbreak}}(10) = 0.63.$$

ODE Basic Reproduction Number is the Threshold for the Branching Process Approximation

Multitype Branching Process Approximation:

If $\mathcal{R}_0 \leq 1$, then the probability of disease extinction equals one, but if $\mathcal{R}_0 > 1$, then the probability disease extinction is a positive periodic function of t :

$$\mathbb{P}_{ext}(t) = 1 - \mathbb{P}_{outbreak}(t)$$

$$\mathbb{P}_{outbreak}(t) = \mathbb{P}_{outbreak}(t + p)$$

Ref: N Bacaër, EH Ait Dads. 2014. On the probability of extinction in a periodic environment. JMB

Multitype Branching Process Approximation

Generating Functions for I and V near the DFE, $S = N_s$, $M = N_m$:

$$\begin{aligned} G_{(i,v)}(u_1, u_2, \tau, t) &= \mathbb{E} \left[u_1^{I(t)} u_2^{V(t)} \mid (I(\tau), V(\tau)) = (i, v) \right] \\ &= \sum_{j,k \geq 0} p_{(i,v),(j,k)}(\tau, t) u_1^j u_2^k \end{aligned}$$

$$G_{e_i}(0, 0, \tau, 0) = p_{e_i,(0,0)}(\tau, 0)$$

$$\frac{\partial G_{e_1}}{\partial \tau} = -(\beta_m(\tau) + b + \gamma)[f_I(G_{e_1}, G_{e_2}, \tau) - G_{e_1}]$$

$$\frac{\partial G_{e_2}}{\partial \tau} = -(\beta_s(\tau) + c)[f_V(G_{e_1}, G_{e_2}, \tau) - G_{e_2}].$$

$$f_I(u_1, u_2, \tau) = \frac{\beta_m(\tau)u_1u_2 + \gamma + b}{\beta_m(\tau) + \gamma + b},$$

$$f_V(u_1, u_2, \tau) = \frac{\beta_s(\tau)u_1u_2 + c}{\beta_s(\tau) + c},$$

Parameter Values for Vector-Host Model

Parameter	Description	Value
N_s	total number of hosts	100
N_m	total number of vectors	1000
$\bar{\beta}_s$	vector to host transmission	0.04
$\bar{\beta}_m$	host to vector transmission	2.0
γ	recovery rate of host	0.1
b	birth and death rate of host	0.02
c	birth and death rate of vector	0.1

Seasonal Transmission Parameters, $p = 20$.

$$\beta_m(t) = \bar{\beta}_m \left(1 + 0.9 \cos \left(\frac{2\pi t}{p} \right) \right)$$

$$\beta_s(t) = \bar{\beta}_s \left(1 + 0.9 \sin \left(\frac{2\pi t}{p} \right) \right)$$

Periodic Probability of a Disease Outbreak

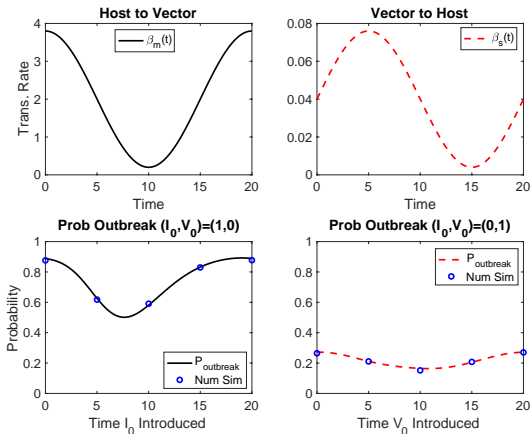


Figure: Periodic probability of a disease outbreak, verified with 10,000 sample paths at $t = 0, 5, 10, 15, 20$, $\mathcal{R}_0 = 2.49$.

Basic Reproduction Number and $\mathbb{P}_{outbreak}$

Constant Coefficients

$$\mathbb{P}_{outbreak} = \text{constant}$$

$\bar{\mathcal{R}}_0$	$\mathbb{P}_{outbreak}$ $(i, v) = (1, 0)$	$\mathbb{P}_{outbreak}$ $(i, v) = (0, 1)$
2.58	0.80	0.24

Periodic Coefficients

$$\mathbb{P}_{outbreak}(t) = \mathbb{P}_{outbreak}(t + p)$$

Average Probability of an Outbreak:

$$\bar{\mathbb{P}}_{outbreak} = \frac{1}{p} \int_0^p \mathbb{P}_{outbreak}(t) dt$$

$\bar{\mathcal{R}}_0$	$\bar{\mathbb{P}}_{outbreak}$ $(i, v) = (1, 0)$	$\bar{\mathbb{P}}_{outbreak}$ $(i, v) = (0, 1)$
2.49	0.73	0.21

Summary and Public Health Implications

- **Branching processes (BP) provide an analytical approximation for the probability of zoonotic spillover when parameters such as transmission or recovery vary seasonally.**
- **The probability of spillover depends on the time at which infection is introduced into the animal population.**
- **BP also provide information about time-dependent probability of a disease outbreak or probability of invasion when parameters vary seasonally.**
- **For public intervention and conservation, it is important to identify drivers of seasonal effects and incorporate them into realistic stochastic/deterministic models.**