Deterministic Models for the Spread of Cholera

Pauline van den Driessche

Department of Mathematics & Statistics
Department of Computer Science
University of Victoria
Victoria, B.C., Canada

pvdd@math.uvic.ca

Thanks to NSERC, Mprime, collaborators Zhisheng Shuai and others

University of Victoria

What is Cholera?

- An infection of the small intestine caused by the bacterium *Vibrio cholerae*
- Infection causes mild diarrhea in most cases
- But some cases develop severe diarrhea and vomiting which if untreated may lead to death within a few hours due to dehydration and electrolyte imbalance

How is Cholera Transmitted?

- Human-environment (water)-human transmission Indirect, Slow
- Other transmission pathways Direct, Fast

- Incubation period is short, usually 2-3 days

Methods of control: purify water, provide sanitation, vaccination (oral vaccine is 50-60% effective)

Treatment: rehydration and antimicrobial

John Snow traced the source of a cholera outbreak in England in 1854 to a contaminated water pump

John Snow's memorial and pub

Where does Cholera Occur? http:healthmap.org 08.05.2013

University of Victoria

- 1817-1824: First recorded pandemic: started in the Bay of Bengal and spread to most of the world

  ....

- Zimbabwe outbreak in 2008-2009 (with 98,585 reported cases and 4,287 deaths, Mukandavire et al. *PNAS* 2011)

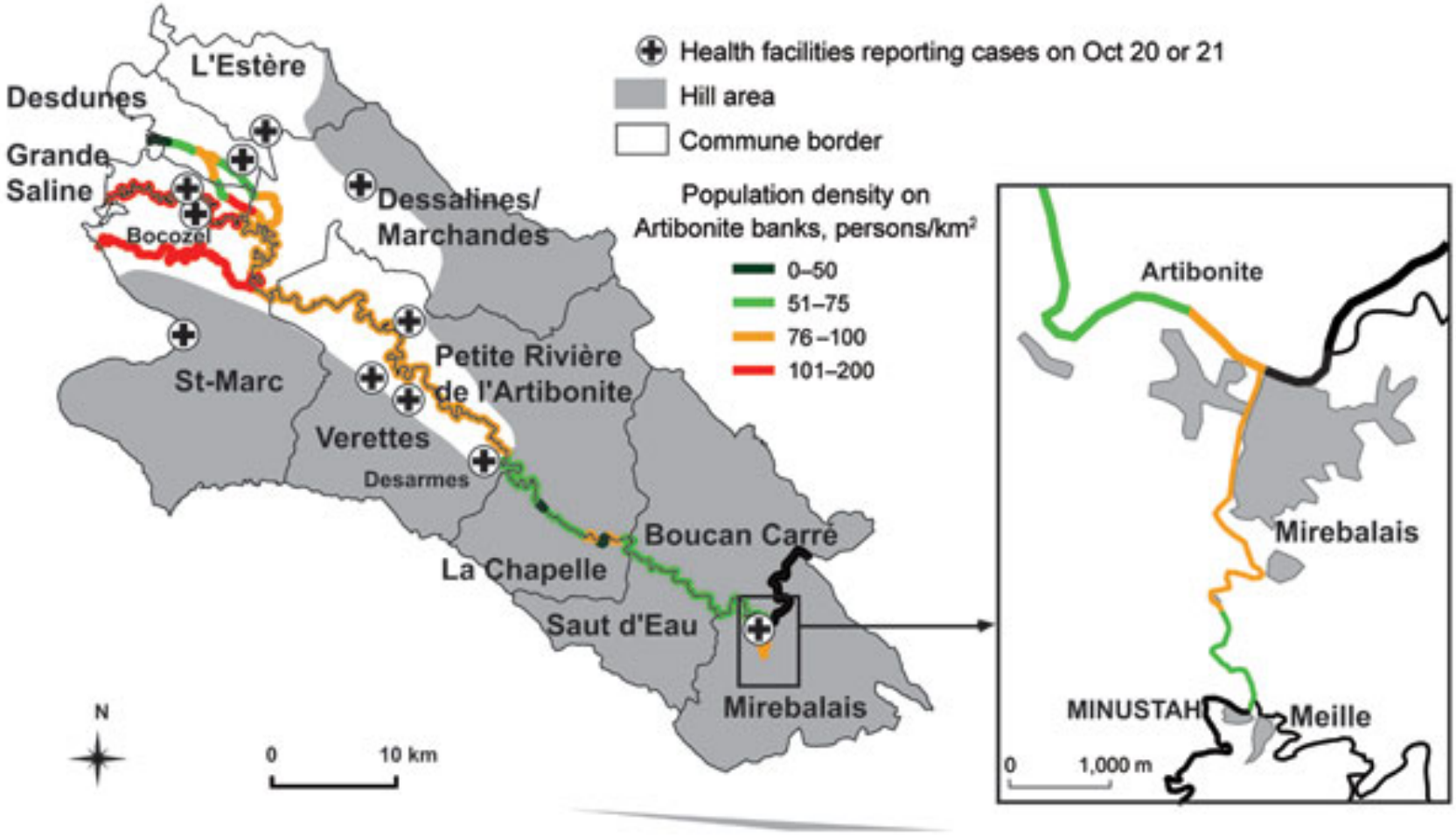
- Haiti outbreak since October 2010, with 712,330 reported cases and 8,655 deaths as of 24 November 2014, giving 1.2% fatality ratio
  (*ProMed data*)

- WHO estimates 3m-5m cholera cases per year with 100,000 deaths spread over 40-50 countries, mainly in underdeveloped countries,
  thus modeling of cholera was largely neglected at least until the
  Haiti outbreak

Map of Haiti

University of Victoria

Map of the Artibonite River



Possible source of outbreak: The United Nations Stabilization Mission in Haiti (MINUSTAH)

Piarroux et al. *Emerging Infectious Diseases* 2011

University of Victoria

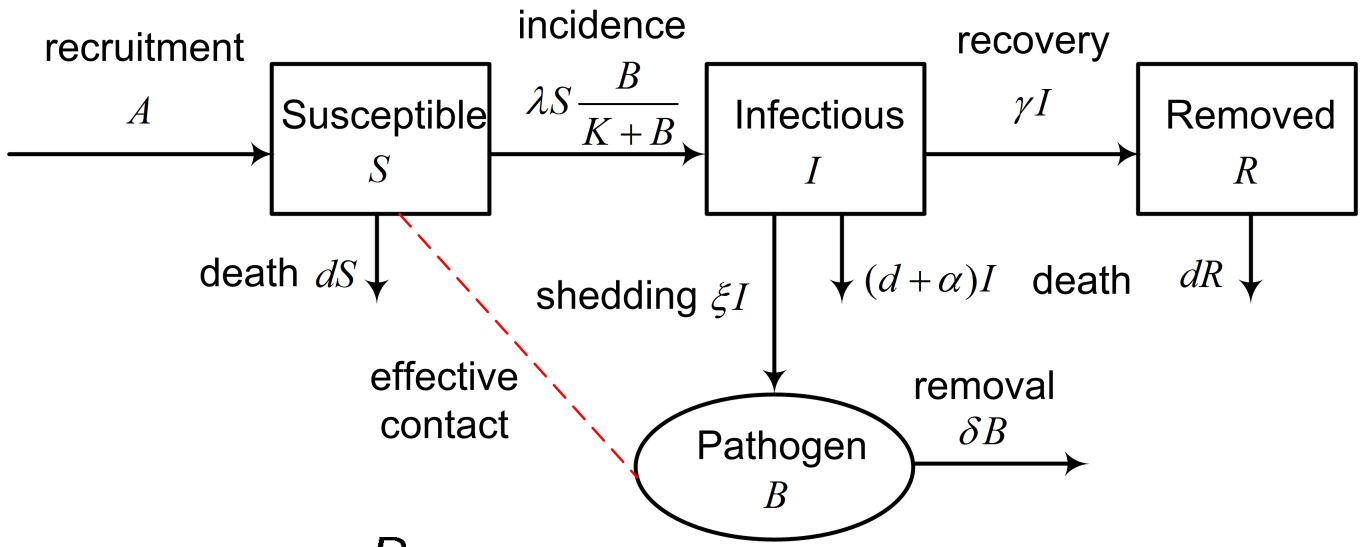
How to Model the Spread of Cholera?

"All models are wrong, but some are useful" George E.P. Box

"A scientific theory should be as simple as possible, but no simpler" Albert Einstein

Some ODE deterministic models assuming spatial homogeneity

Basic Model: Indirect Transmission, Saturating Incidence



$$\frac{dS}{dt} = A - \lambda S \frac{B}{K+B} - dS$$

$$\frac{dI}{dt} = \lambda S \frac{B}{K+B} - (d+\gamma+\alpha)I$$

$$\frac{dR}{dt} = \gamma I - dR$$

$$\frac{dB}{dt} = \xi I - \delta B$$

Codeço *BMC Infectious Diseases* 2001

Calculation of $\mathcal{R}_0$ for Codeço's model

There is a disease free equilibrium (DFE) at $S = A/d, I = R = B = 0$

$$\begin{aligned} \frac{dI}{dt} &= \lambda S \frac{B}{K+B} - (d+\gamma+\alpha)I \\ \frac{dB}{dt} &= \xi I - \delta B \end{aligned}$$

By the next generation matrix method:

$$F = \begin{bmatrix} 0 & \frac{A\lambda}{dK} \\ 0 & 0 \end{bmatrix} \qquad V = \begin{bmatrix} d+\gamma+\alpha & 0 \\ -\xi & \delta \end{bmatrix}$$

giving

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{A\lambda\xi}{dK\delta(d+\gamma+\alpha)}$$

The DFE is locally asymptotically stable if $\mathcal{R}_0 < 1$, whereas it is unstable if $\mathcal{R}_0 > 1$ [vdD & Watmough 2002]

Remark

If shedding is though of as a new infection, then ξ is placed in the F matrix giving

$$F = \begin{bmatrix} 0 & \frac{A\lambda}{dK} \\ \xi & 0 \end{bmatrix} \qquad V = \begin{bmatrix} d+\gamma+\alpha & 0 \\ 0 & \delta \end{bmatrix}$$

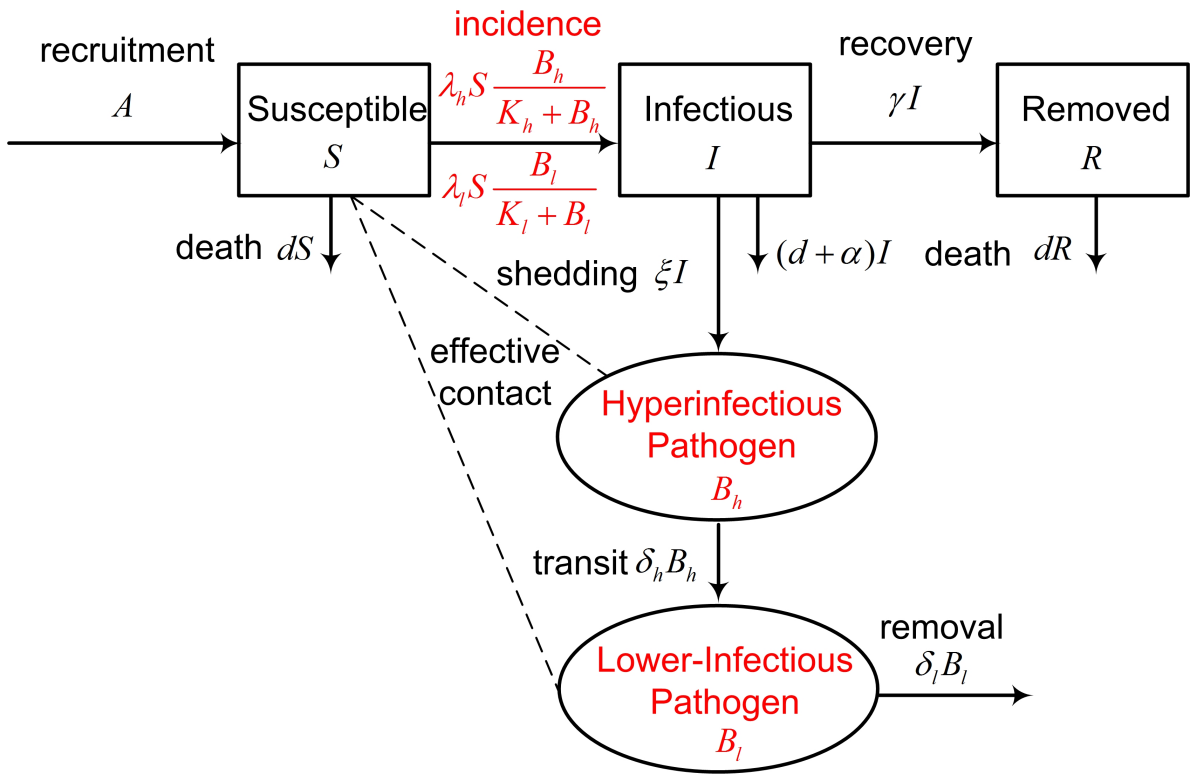
and

$$\mathcal{R}_0 = \sqrt{\frac{A\lambda\xi}{dK\delta(d+\gamma+\alpha)}}$$

agreeing with the previous value (no square root) at the threshold value 1

Hyperinfectivity Model

Infectivity of freshly shed vibrios can be up to 700-fold greater than not freshly shed vibrios [Sengupta et al. *FEMS Microbiol Lett* 1998]



Hartley et al. *PLOS Medicine* 2006

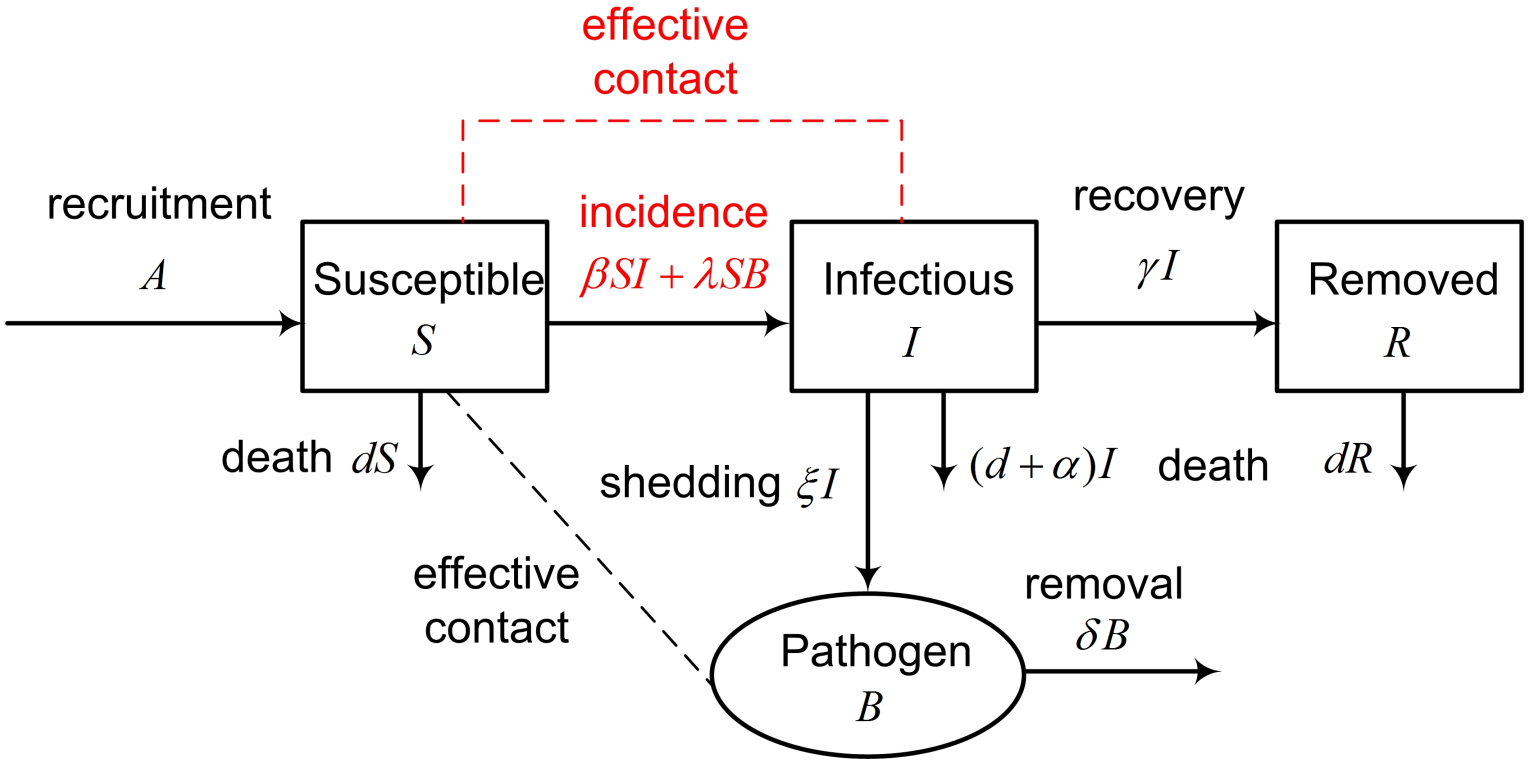
University of Victoria

Direct/Indirect Transmission Model: Mass Action Incidence

In certain situation, fast transmission may contribute 41-95% of all transmission [Mukandavire et al. *PNAS* 2011]

Fast transmission: βSI (mass action)
Slow transmission: λSB (mass action)

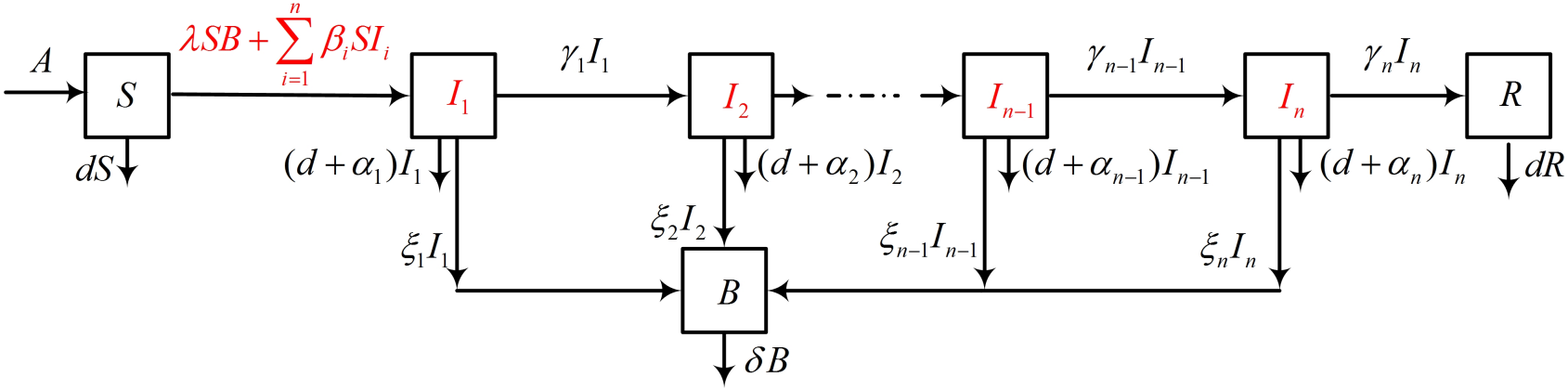
Hyperinfectivity ignored



Tien & Earn *Bull Math Biol* 2010

Direct/Indirect Transmission Model: Mass Action Incidence Stage-Progression Model

The infectious individuals are categorized into n different compartments according to infectivity and infection age



Tien & Earn *Bull Math Biol* 2010

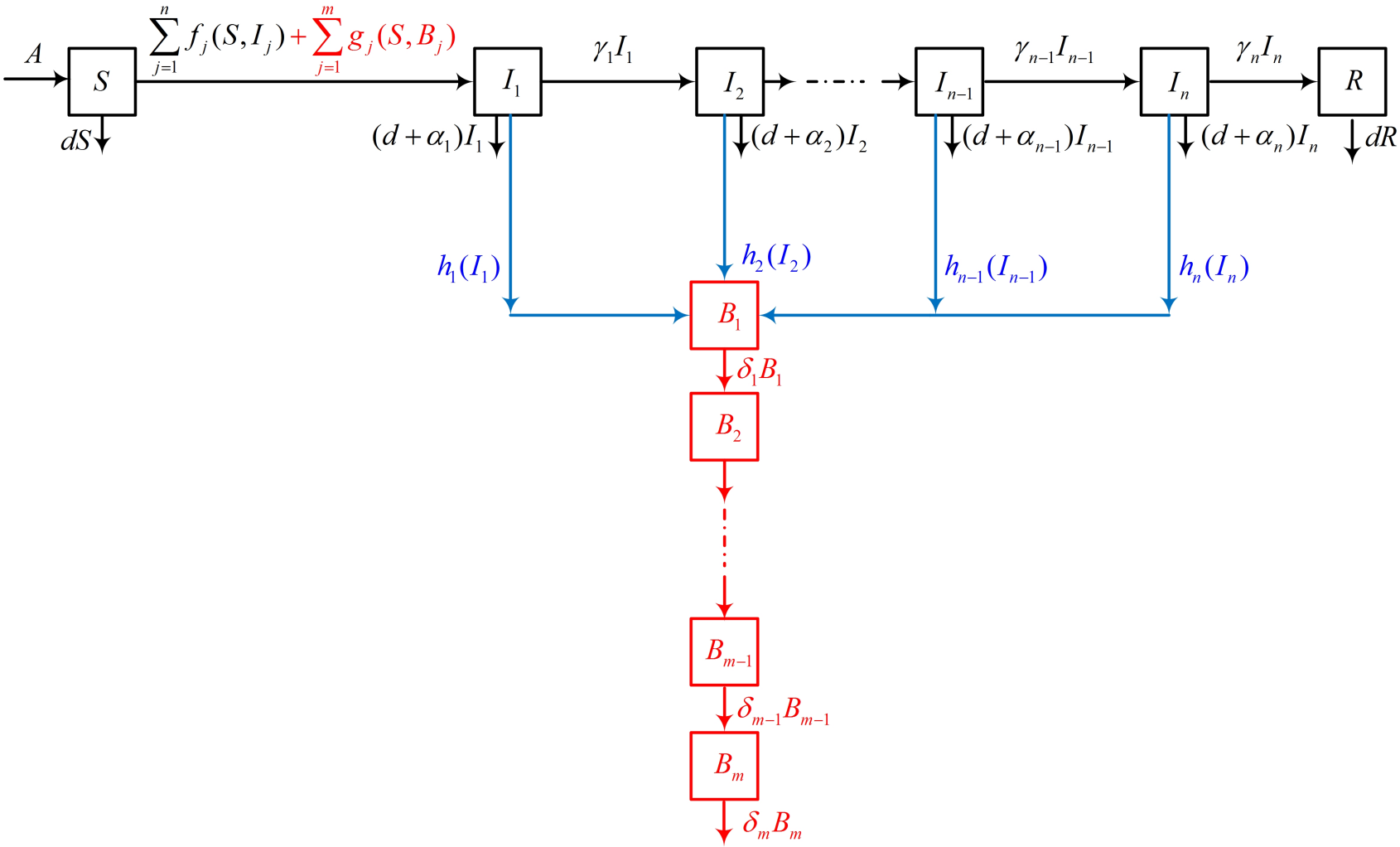
University of Victoria

More General Cholera Model

[Shuai & vdD *Math Biosc (2011) 234:118-126*]

- Infectious individuals have multiple infectious stages $I_1, I_2, \ldots, I_n$
- Pathogen has multiple infectious states $B_1, B_2, \ldots, B_m$
- Fast transmission (contact between S and I_i) and Slow transmission (contact between S and B_k)
- Nonlinear incidence functions $f_i(S, I_i)$ and $g_k(S, B_k)$ under some biologically reasonable assumptions that include mass action incidence, saturating incidence, frequency dependent incidence for one infectious stage
- Nonlinear shedding functions $h_i(I_i)$ including linear
- For different n, m, f_i, g_k, h_i our model includes those described on previous slides and by Tian & Wang *Math Biosc* 2011

Flow Diagram



University of Victoria

Model Formulation

A cholera model is formulated as the following $n + m + 1$ ODEs:

$$
\begin{aligned}
\frac{dS}{dt} &= A - \sum_{j=1}^{n} f_j(S, I_j) - \sum_{j=1}^{m} g_j(S, B_j) - dS \\
\frac{dI_1}{dt} &= \sum_{j=1}^{n} f_j(S, I_j) + \sum_{j=1}^{m} g_j(S, B_j) - (d + \gamma_1 + \alpha_1) I_1 \\
\frac{dI_i}{dt} &= \gamma_{i-1} I_{i-1} - (d + \gamma_i + \alpha_i) I_i \qquad \text{for } i = 2, \ldots, n \\
\frac{dB_1}{dt} &= \sum_{j=1}^{n} h_j(I_j) - \delta_1 B_1 \\
\frac{dB_k}{dt} &= \delta_{k-1} B_{k-1} - \delta_k B_k \qquad \text{for } k = 2, \ldots, m
\end{aligned}
$$

with nonnegative initial conditions $S(0), I_i(0), B_k(0) \geq 0$

Feasible Region and Equilibria

Take biologically reasonable assumptions on f, g, h including sufficient smoothness, increasing in S, I_i, B_i and concave down in I_i, B_i

- There is a positively invariant feasible region

$$\Gamma = \left\{ (S, I_1, \ldots, I_n, B_1, \ldots, B_m) \in \mathbb{R}_+^{n+m+1} \;\middle|\; S + I_1 + \cdots + I_n \leq \frac{A}{d} \right.$$
$$\left. B_k \leq M_k, k = 1, \ldots, m \right\}$$

- The disease-free equilibrium (DFE) denoted by $P_0 = (S_0, 0, \ldots, 0)$ with $S_0 = \frac{A}{d}$ lies on $\partial\Gamma$

- An endemic equilibrium (EE) in $\overset{\circ}{\Gamma}$, if it exists, is denoted by $P^* = (S^*, I_1^*, \ldots, I_n^*, B_1^*, \ldots, B_m^*)$

Basic Reproduction Number

The disease free equilibrium (DFE) is

$$S_0 = \frac{A}{d}, I_i = B_k = 0$$

Assume $p_i = \frac{\partial f_i}{\partial I_i}(S_0, 0)$, $q_k = \frac{\partial g_k}{\partial B_k}(S_0, 0)$, and $r_i = h_i'(0)$ are nonnegative and set $\nu_i = d + \gamma_i + \alpha_i$

Using the next generation matrix method, the basic reproduction number is derived as

$$\mathcal{R}_0 = \frac{p_1}{\nu_1} + .. + \frac{p_n \gamma_1 \cdots \gamma_{n-1}}{\nu_1 \cdots \nu_n} + \left(\frac{q_1}{\delta_1} + \cdots + \frac{q_m}{\delta_m}\right)\left(\frac{r_1}{\nu_1} + \cdots + \frac{r_n \gamma_1 \cdots \gamma_{n-1}}{\nu_1 \cdots \nu_n}\right)$$

direct transmission indirect transmission

The DFE is locally asymptotically stable if $\mathcal{R}_0 < 1$, whereas it is unstable if $\mathcal{R}_0 > 1$ [vdD & Watmough 2002]

Global Stability of the DFE and Persistence

Theorem

(*a*) *If* $\mathcal{R}_0 < 1$ *then the DFE is globally asymptotically stable in the feasible region* Γ

(*b*) *If* $\mathcal{R}_0 > 1$ *then the system is uniformly persistent and there exists at least one endemic equilibrium*

Let $\omega^T \geq 0$ be a left eigenvector of $V^{-1}F$ corresponding to $\rho(V^{-1}F) = \mathcal{R}_0$
Then $Q = \omega^T V^{-1} x$ where x is the vector of infected compartments is a Lyapunov function for the system when $\mathcal{R}_0 < 1$

(no guessing in finding Q !)

This result holds for mass action, saturating and frequency dependent incidence functions f_i, g_k

Global Stability of the Endemic Equilibrium S^*, I_i^*, B_k^*

Theorem

If $\mathcal{R}_0 > 1$, then the system has a unique endemic equilibrium that is globally asymptotically stable in the interior of the feasible region

Proof uses the Lyapunov function

$$V = c_1 \int_{S^*}^{S} \frac{\Phi(\xi) - \Phi(S^*)}{\Phi(\xi)}\, d\xi + \sum_{i=1}^{n} c_i \left(I_i - I_i^* - I_i^* \ln \frac{I_i}{I_i^*} \right) + \sum_{k=1}^{m} c_{n+k} \left(B_k - B_k^* - B_k^* \ln \frac{B_k}{B_k^*} \right)$$

where $\Phi : (0, S_0] \to \mathrm{R}_+$ is increasing and satisfies certain inequalities

Constants $c_i > 0$ are chosen by using Kirchhoff's Matrix Tree theorem [1847] and the tree cycle identity [Li & Shuai *JDE* 2010] giving

$$\frac{dV}{dt} \leq 0 \quad \forall \quad (S, I_1, \cdots I_n, B_1, \cdots, B_m) \in \overset{\circ}{\Gamma}$$

Conclusions for this Cholera Model

For the ODE cholera model $\mathcal{R}_0$ is a sharp threshold

$$\mathcal{R}_0 = \frac{p_1}{\nu_1} + \cdots + \frac{p_n \gamma_1 \cdots \gamma_{n-1}}{\nu_1 \cdots \nu_n} + \left(\frac{q_1}{\delta_1} + \cdots + \frac{q_m}{\delta_m} \right) \left(\frac{r_1}{\nu_1} + \cdots + \frac{r_n \gamma_1 \cdots \gamma_{n-1}}{\nu_1 \cdots \nu_n} \right)$$

- If $\mathcal{R}_0 < 1$ then the disease dies out
- If $\mathcal{R}_0 > 1$ the disease persists at an endemic level

To control cholera: reduce $\mathcal{R}_0$ below 1

- vaccination (decrease p_i, q_k)
  herd immunity vaccinate more than $1 - 1/\mathcal{R}_0$ of the host population
- provide clean water (decrease q_k)
- improve sanitation (decrease r_i and/or increase δ_i)

Target/type reproduction numbers can be used to assess different strategies, Shuai et al. *J. Math Biol.* 2013,
but accurate data is needed to evaluate control strategies

Final Size of an Epidemic

Assume

- Recruitment and death are zero ($A = d = \alpha_i = 0$) so wlog $N = 1$
- Mass action direct transmission ($f_i(S, I_i) = \beta_i S I_i$)
- Linear pathogen shedding rate ($h_i(I_i) = \xi_i I_i$)
- Indirect transmission is either mass action or saturating incidence ($g_k(S, B_k) = \lambda_k S B_k$ or $\lambda_k S \frac{B_k}{K_k + B_k}$)

Lemma

Under the above assumptions $I_i(t), B_k(t) \to 0$ *as* $t \to \infty$ *(disease burns out)*

Mass Action $g_k(S, B_k) = \lambda_k S B_k$

If a small number of infectious individuals or pathogens is initially introduced then the final size of an epidemic is

$$1 - R(\infty) = \exp(-\mathcal{R}_0 R(\infty))$$

where

$$\mathcal{R}_0 = \frac{\beta_1}{\gamma_1} + \frac{\beta_2}{\gamma_2} + \cdots + \frac{\beta_n}{\gamma_n} + \left(\frac{\lambda_1}{\delta_1} + \cdots + \frac{\lambda_m}{\delta_m}\right)\left(\frac{\xi_1}{\gamma_1} + \cdots + \frac{\xi_n}{\gamma_n}\right)$$

This is equivalent to

$$\ell n \frac{S_0}{S(\infty)} = \mathcal{R}_0[1 - \frac{S(\infty)}{N}]$$

with $S_0 \simeq N = 1, R(\infty) = 1 - S(\infty)$

Saturating Incidence $g_k(S, B_k) = \lambda_k S \frac{B_k}{K_k + B_k}$

An attempt to model in a continuous way the fact that a relatively high level of pathogen is needed to develop cholera

The final size of an epidemic satisfies the inequality

$$1 - R(\infty) \geq \exp(-\mathcal{R}_0 R(\infty))$$

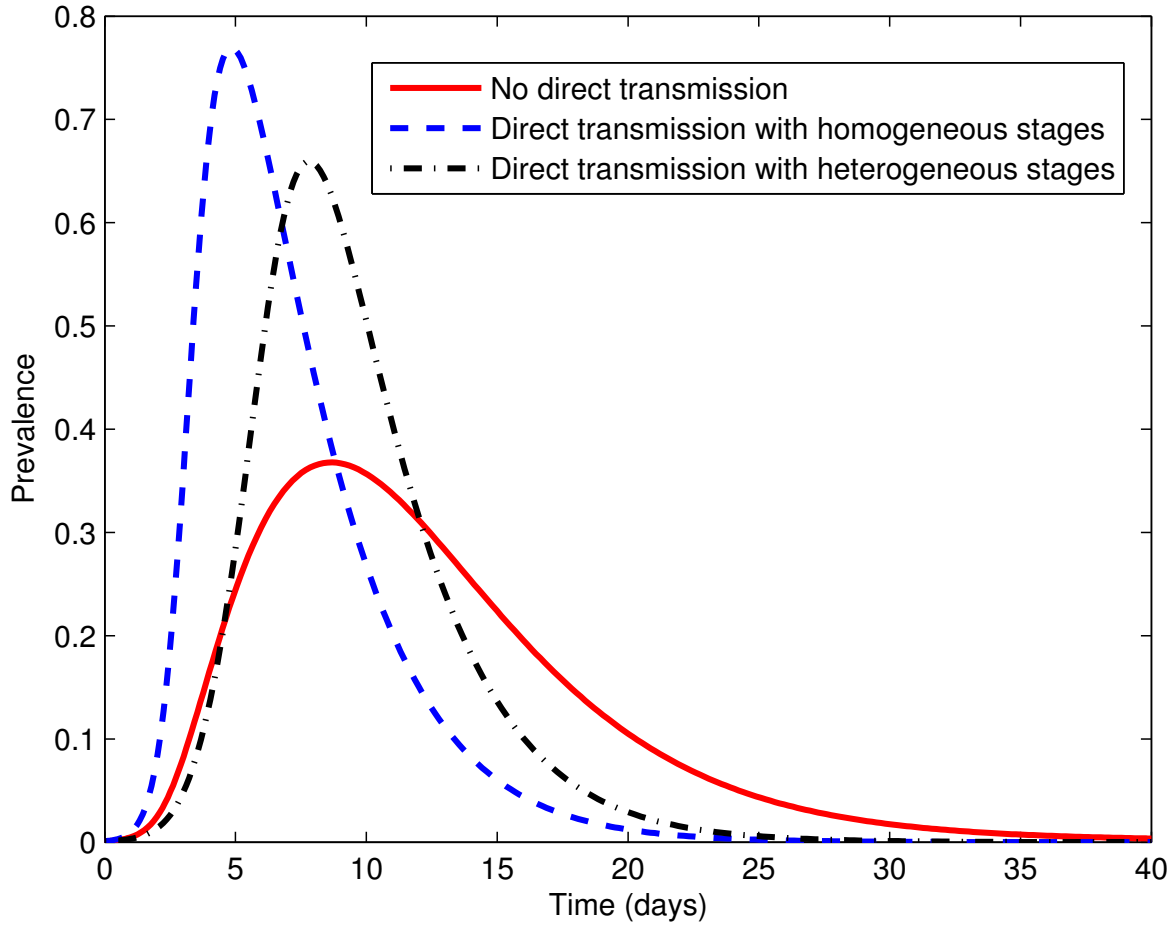
where $\mathcal{R}_0$ is as before but with δ_k replaced with $\delta_k K_k$
giving an upper bound on $R(\infty)$

Simulations

For simulations consider saturating incidence with $n = m = 2$
Infectivity of hyperinfectious state B_1 is 700 times that of B_2
Parameters are taken from cholera data in
Hartley et al. *PLOS Medicine* 2006
giving $\mathcal{R}_0 = 15.83$

Simulations show

- Direct transmission provides a fast route for cholera spread and produces a higher peak in prevalence
- Heterogeneity in infectious hosts may decelerate disease spread and reduce the peak

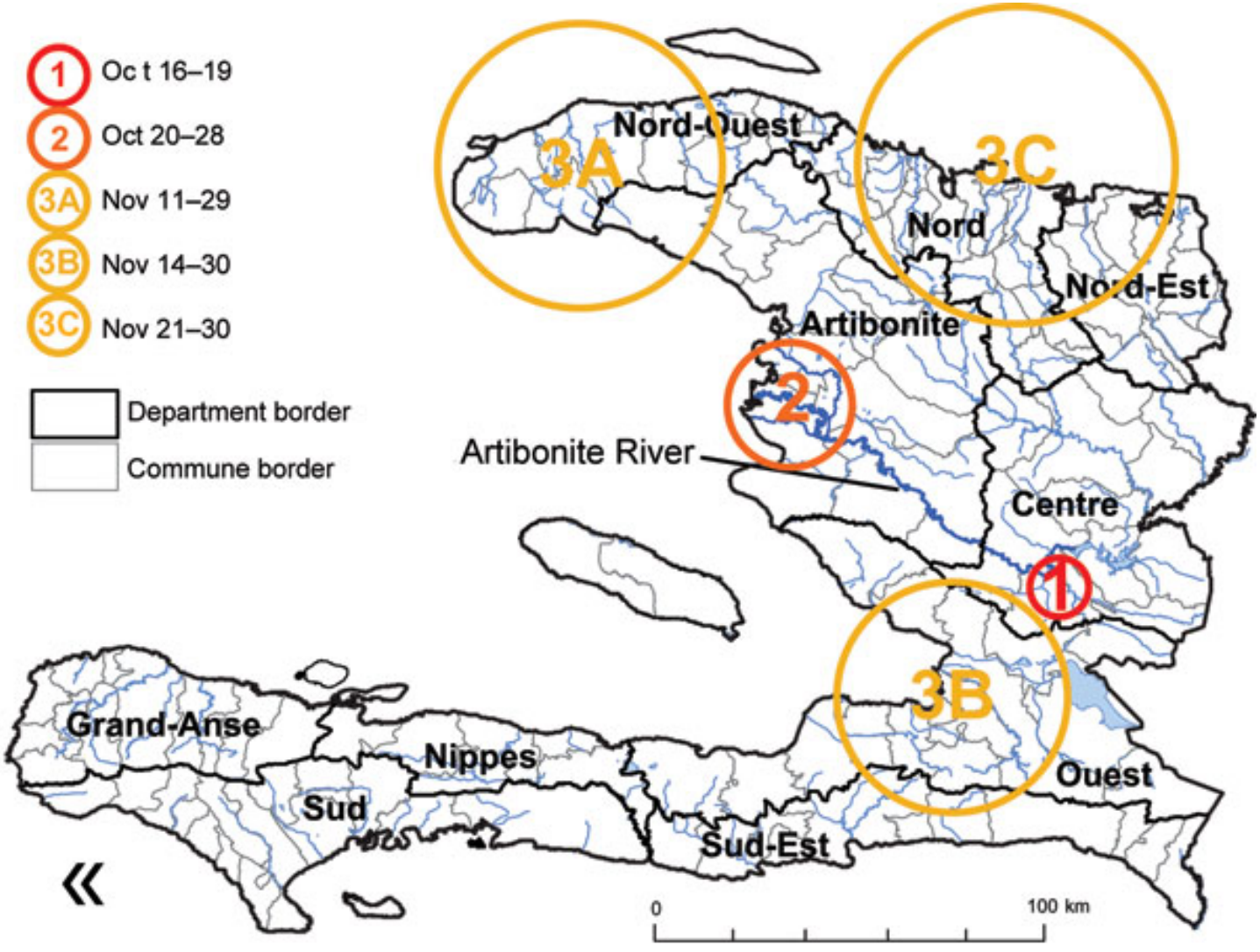


Outbreak of a cholera epidemic keeping $\mathcal{R}_0 = 15.83$ and same initial conditions

More realistic cholera models should include spatial heterogeneity, age structure, optimal disease control, $\cdots$

Now consider spatial heterogeneity

Cholera Outbreak in Haiti as of November 2010



Piarroux et al. *Emerging Infectious Diseases* 2011

University of Victoria

How to Include Spatial Heterogeneity in a Cholera Model?

- A multigroup model with cross infection between groups

Tuite et al. *Ann. Internal Medicine* 2011 incorporate 10 groups corresponding to the populations in the 10 departments of Haiti and numerically simulate control strategies (vaccination and clean water)

Theoretical work with Zhisheng Shuai, SIAP 2013

- A partial differential equation (PDE) model for spread by humans and/or by a river Bertuzzo et al. *J. Royal Society Interface* 2010
- A discrete patch (metapopulation) ODE model for spread due to human and/or water movement

Work with Maria Eisenberg (U Michigan), Zhisheng Shuai (U Central Florida), and Joe Tien (Ohio State U)
Math. Bios. 2013, J. Math Biol. 2014

Challenges in Modeling Cholera and Other Neglected Infectious Diseases

- How much epidemiological realism to include in a model
- How to obtain accurate data for model parameters
- How to include social aspects, such as lack of public information,
  lack of access to heath clinics
- How to include economic aspects, such as optimizing treatment strategies
- ....

Answers depend in part on the particular question being addressed

THANK YOU