Rapid loss of immunity is necessary to explain historical cholera epidemics

Ed Ionides & Aaron King

University of Michigan
Departments of Statistics and Ecology & Evolutionary Biology
Bengal: cholera’s homeland
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Cholera: unsolved puzzles

- **Mode of transmission**
  - contaminated water: environmental reservoir
  - food-borne/direct fecal-oral
  - transient hyperinfectious state (<18 hr)

- **Seasonality**
  - two peaks per year
  - regional climate drivers: monsoon rainfall and winter
  - multi-year climate drivers: El Niño-Southern Oscillation (ENSO)

- **Immunity**
  - volunteer studies: >3 yr immunity following severe infection
  - community study of reinfections in Matlab, Bangladesh: risk of reinfection equal to risk of primary infection
  - 1.6 yr average duration between primary infection and reinfection
  - retrospective statistical analyses (Koelle & Pascual 2004): 7–10 yr immunity following severe infection
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Dacca cholera mortality

0 1000 3000 5000
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Inapparent infections

- most cholera infections are mild or asymptomatic
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- reports of the asymptomatic:symptomatic ratio range from 3 to 100
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- it is easy to underestimate the degree to which one underestimates a quantity one cannot observe
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- **Needed:** an approach that allows indirect inference about unobserved variables
Inapparent infections

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- reports of the asymptomatic:symptomatic ratio range from 3 to 100
- it is easy to underestimate the degree to which one underestimates a quantity one cannot observe
- **Needed:** an approach that allows indirect inference about unobserved variables
- historical cholera mortality records are a rich source of information, but have been difficult to fully exploit
Historical cholera mortality

Dacca
Historical cholera mortality
Historical cholera mortality
Historical cholera mortality
SIRS model

\[ P \xrightarrow{b} S \xrightarrow{\lambda(t)} I \xrightarrow{\gamma} R_1 \xrightarrow{k\epsilon} \ldots \xrightarrow{k\epsilon} R_k \]

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<thead>
<tr>
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SIRS model

\[ \lambda(t) = \left( e^{\beta_{\text{trend}} t} \beta_{\text{seas}}(t) + \xi(t) \right) \frac{l(t)}{P(t)} + \omega \]
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\( \beta_{trend} = \text{trend in transmission} \)
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\[ \lambda(t) = \left( e^{\beta_{trend} t} \beta_{seas}(t) + \xi(t) \right) \frac{l(t)}{P(t)} + \omega \]

\[ \beta_{seas}(t) = \text{seasonality in transmission} \]

semimechanistic approach: use flexible function
SIRS model

\[ \lambda(t) = \left( e^{\beta_{trend} t} \beta_{seas}(t) + \xi(t) \right) \frac{l(t)}{P(t)} + \omega \]

\[ \xi(t) = \text{environmental stochasticity} \]
SIRS model

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\[ \omega = \text{environmental reservoir} \]
\[ \lambda(t) = \left( e^{\beta_{\text{trend}} t} \beta_{\text{seas}}(t) + \xi(t) \right) \frac{l(t)}{P(t)} + \omega \]

\[ P(t) = \text{censused population size} \]
SIRS model

\[
\frac{dS}{dt} = \frac{dP(t)}{dt} + \delta P(t) - (\lambda(t) + k\epsilon R_k + \delta) S
\]

\[
\frac{dI}{dt} = \lambda(t) S - (m + \gamma + \delta) I(t)
\]

\[
\frac{dR_1}{dt} = \gamma I - (k\epsilon + \delta) R_1
\]

\[
\vdots
\]

\[
\frac{dR_k}{dt} = k\epsilon R_{k-1} - (k\epsilon + \delta) R_k
\]

Stochastic force of infection:

\[
\lambda(t) = \left(e^{\beta_{\text{trend}} t} \beta_{\text{seas}}(t) + \xi(t)\right) \frac{I(t)}{P(t)} + \omega
\]
Likelihood maximization by iterated filtering

- new frequentist approach
  (Ionides, Bretó, & King, PNAS 2006)
- can accommodate:
  - continuous-time models
  - nonlinearity
  - stochasticity
  - unobserved variables
  - measurement error
  - nonstationarity
  - covariates
- based on well-studied sequential Monte Carlo methods
  (particle filter)
- “plug and play” property
- Implemented in pomp, an open-source R package
  (www.r-project.org)
Duration of immunity
SIRS model

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SIRS model predictions

- estimated cholera fatality (across districts): $0.0039 \pm 0.0021$. 

- In the historical period, fatality in severe cases was c. 60%.

- Model prediction: lots of silent shedders.

- Evidence for silent shedders is mixed and weak.

- Q: Is it necessary that all exposed individuals become infectious?
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- **Q:** Is it necessary that all exposed individuals become infectious?
Two-path model

\[ P \quad b \rightarrow S \quad c\lambda(t) \rightarrow I \quad m \rightarrow M \quad \gamma \rightarrow R_1 \quad k\varepsilon \rightarrow \ldots \rightarrow k\varepsilon \rightarrow R_k \]

\[ (1 - c)\lambda(t) \rightarrow Y \quad \rho \]

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Two-path model

\[ P \xrightarrow{b} S \xrightarrow{c\lambda(t)} I \xrightarrow{\gamma} R_1 \xrightarrow{k_1\varepsilon} \ldots \xrightarrow{k_{\varepsilon}} R_k \]

- Parameter symbols:
  - Force of infection: \( \lambda(t) \)
  - Probability of severe infection: \( c \)
  - Recovery rate: \( \gamma \)
  - Disease death rate: \( m \)
  - Mean long-term immune period: \( 1/\varepsilon \)
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\[ \frac{dI}{dt} = c\lambda(t) S - (m + \gamma + \delta) I(t) \]

\[ \frac{dY}{dt} = (1 - c)\lambda(t) S - (\rho + \delta) Y \]

\[ \frac{dR_1}{dt} = \gamma I - (k\epsilon + \delta) R_1 \]

\[ \vdots \]

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## Model comparison

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<th>model</th>
<th>log likelihood</th>
<th>AIC</th>
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<tr>
<td>two-path</td>
<td>-3775.8</td>
<td>7591.6</td>
</tr>
<tr>
<td>SIRS</td>
<td>-3794.3</td>
<td>7622.6</td>
</tr>
<tr>
<td>SARMA((2,2)×(1,1))</td>
<td>-3804.5</td>
<td>7625.0</td>
</tr>
<tr>
<td>Koelle &amp; Pascual (2004)</td>
<td>-3840.1</td>
<td>—</td>
</tr>
<tr>
<td>seasonal mean</td>
<td>-3989.1</td>
<td>8026.1</td>
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## Goodness of fit

<table>
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<tr>
<th>district</th>
<th>$r^2$</th>
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<tbody>
<tr>
<td>Bakergang</td>
<td>0.856</td>
<td>Jessore</td>
<td>0.754</td>
</tr>
<tr>
<td>Bankura</td>
<td>0.559</td>
<td>Khulna</td>
<td>0.735</td>
</tr>
<tr>
<td>Birbhum</td>
<td>0.509</td>
<td>Malda</td>
<td>0.596</td>
</tr>
<tr>
<td>Bogra</td>
<td>0.570</td>
<td>Midnapur</td>
<td>0.666</td>
</tr>
<tr>
<td>Burdwan</td>
<td>0.589</td>
<td>Mohrshidabad</td>
<td>0.631</td>
</tr>
<tr>
<td>Calcutta</td>
<td>0.756</td>
<td>Mymensingh</td>
<td>0.805</td>
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<tr>
<td>Chittagong</td>
<td>0.712</td>
<td>Nadia</td>
<td>0.734</td>
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<tr>
<td>Dacca</td>
<td>0.848</td>
<td>Noakhali</td>
<td>0.701</td>
</tr>
<tr>
<td>Dinajpur</td>
<td>0.078</td>
<td>Pabna</td>
<td>0.690</td>
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<tr>
<td>Faridpur</td>
<td>0.785</td>
<td>Rangpur</td>
<td>0.594</td>
</tr>
<tr>
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<td>0.569</td>
<td>Rashahi</td>
<td>0.690</td>
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<tr>
<td>Howrath</td>
<td>0.769</td>
<td>Tippera</td>
<td>0.767</td>
</tr>
<tr>
<td>Jaipaguri</td>
<td>0.109</td>
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<td>0.839</td>
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Goodness of fit

$r^2$
Simulated vs. actual data

SIRS model
Simulated vs. actual data

two-path model
Parameter estimates

- Cholera fatality: $0.07 \pm 0.05$
- Probability of severe infection: $\hat{c} = 0.008 \pm 0.005$
- $R_0 = 1.10 \pm 0.27$
- Duration of long-term immunity: 2.6 $\pm$ 1.8 yr
- Duration of short-term immunity: 0.3–8.3 wk
- Geographical variability in force of infection
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\[ R_0(t) \]

\[ c(0, \text{max(seas)}) \]

\[ J \quad F \quad M \quad A \quad M \quad J \quad J \quad A \quad S \quad O \quad N \quad D \quad J \]

\[ 0.0 \quad 2.5 \quad 5.0 \quad 7.5 \quad 10.0 \]

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Geographical patterns

environmental reservoir
Geographical patterns
transmission, Jan–Feb

\( b_0 \)
Geographical patterns transmission, Mar–Apr
Geographical patterns

transmission, May–Jun
Geographical patterns

transmission, Jul–Aug

b₃
Geographical patterns

transmission, Sep–Oct
Geographical patterns
transmission, Nov–Dec
Contrasting views of endemic cholera dynamics

View of Koelle & Pascual (2004):

- long-term immunity (7–10 yr)
- modest asymptomatic ratio (c. 70:1)
- spatial heterogeneity slows epidemic
- seasonal drop in transmission stops epidemic
- waning of immunity interacts with climate drivers on multi-year scale
Contrasting views of endemic cholera dynamics

New view:

- rapidly waning immunity
- high asymptomatic ratio (>160:1)
- susceptible depletion slows and stops epidemic
- loss of immunity replenishes susceptibles rapidly
- waning of immunity interacts with climate drivers on seasonal scale
- multi-year climate drivers?
Public health implications

- What determines the switch probability $c$?

- Serological profile data suggest declines with age.

- Dose/hyperinfectiousness.

- Foodborne/direct fecal-oral mode is most important.

- Lower doses provide short-term immunity.

- Unintended consequences of neglect of household transmission?

- Presence of vibriophage in environment?
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Public health implications

McCormack et al. (1969)

Figure 5. Age specific attack rate per 1,000 population in the control groups of the PSCRL Matlab vaccine trial area.
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Alternative hypotheses?

- inhomogeneities
- behavioral effects
Extensions

- Recent data (1966–2005, Matlab, Bangladesh)
- Discrete population continuous time models
- Other diseases
  - malaria
  - measles
  - influenza
R. G. Feachem (1982) on the seasonal patterns of cholera epidemics in Bengal:

_They are such a dominant feature of cholera epidemiology, and in such contrast to the other bacterial diarrhoeas which peak during the monsoon in mid-summer, that their explanation probably holds the key to fundamental insights into cholera transmission, ecology, and control._
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to understand seasonality, we must allow for the interaction of short-term immunity with seasonal environmental drivers
Thanks to . . .

- Mercedes Pascual
- Menno Bouma
- Carles Bretó
- Katia Koelle
- Diego Ruiz Moreno
- Andy Dobson
- the R project (www.r-project.org)
- NSF/NIH Ecology of Infectious Diseases
Thank you!