Climate variability and the population dynamics of diarrheal diseases

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and

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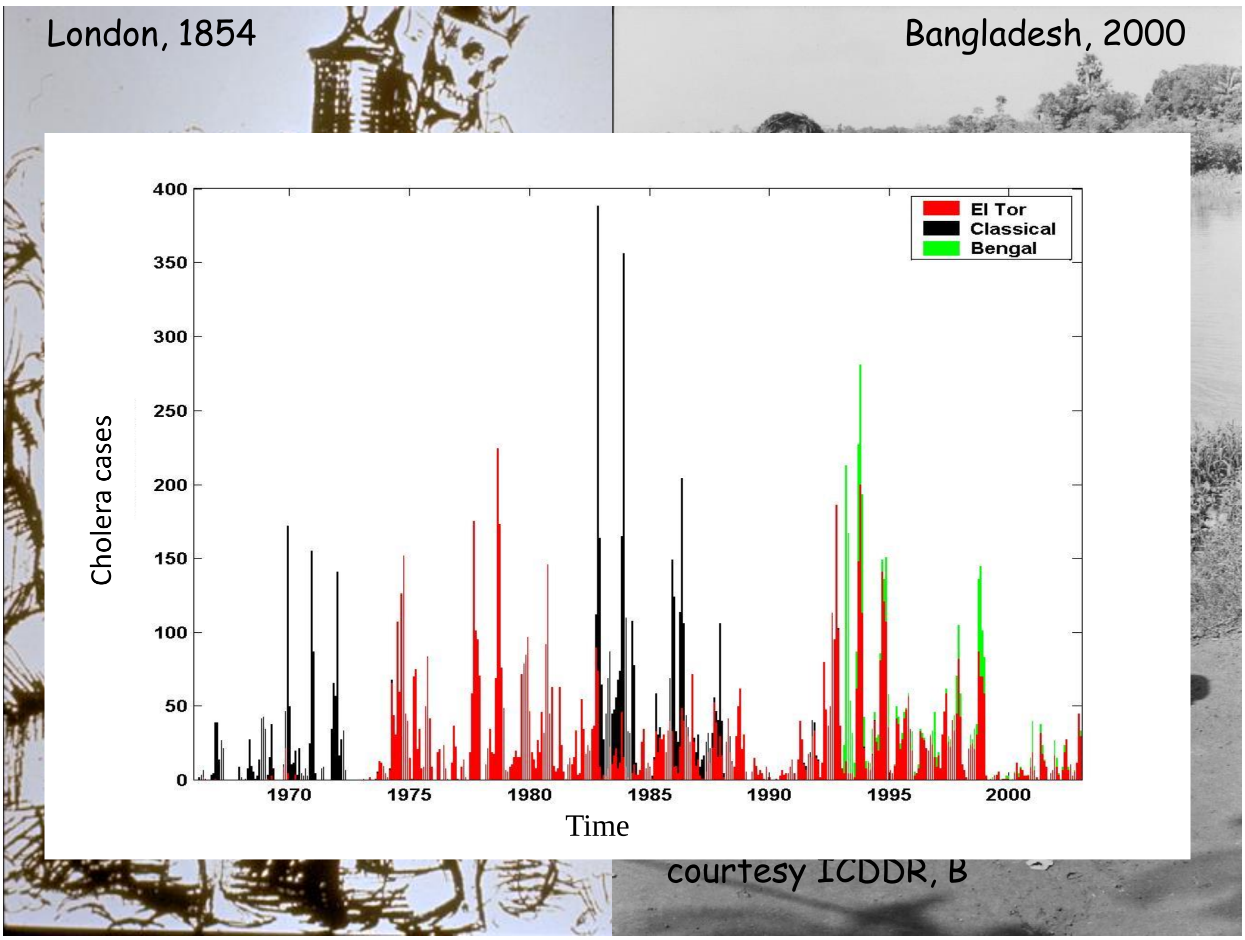
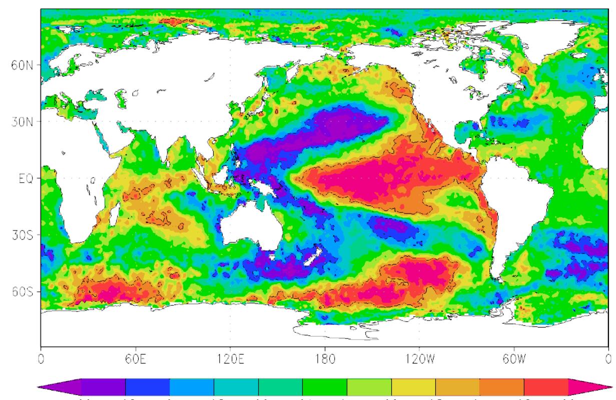

London, 1854
Bangladesh, 2000
Cholera cases
Time
El Tor
Classical
Bengal
400
350
300
250
200
150
100
50
0
1970
1975
1980
1985
1990
1995
2000
courtesy ICDDR, B


From National Geographic web site

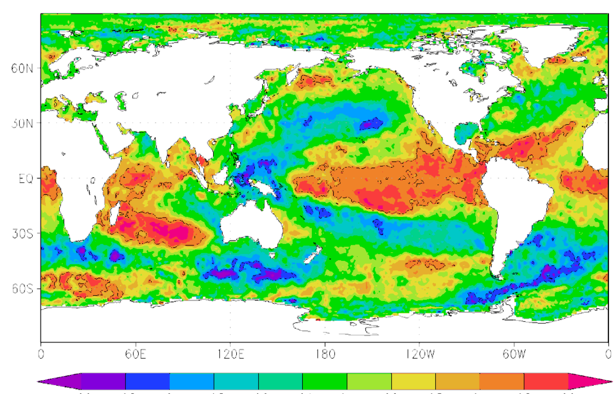
Matlab

Matlab ASOND El Tor Cholera and DJF SST
Rank Correlation 1983–2009



Dhaka

Dhaka ASOND El Tor Cholera and DJF SST
Rank Correlation 1984–2007



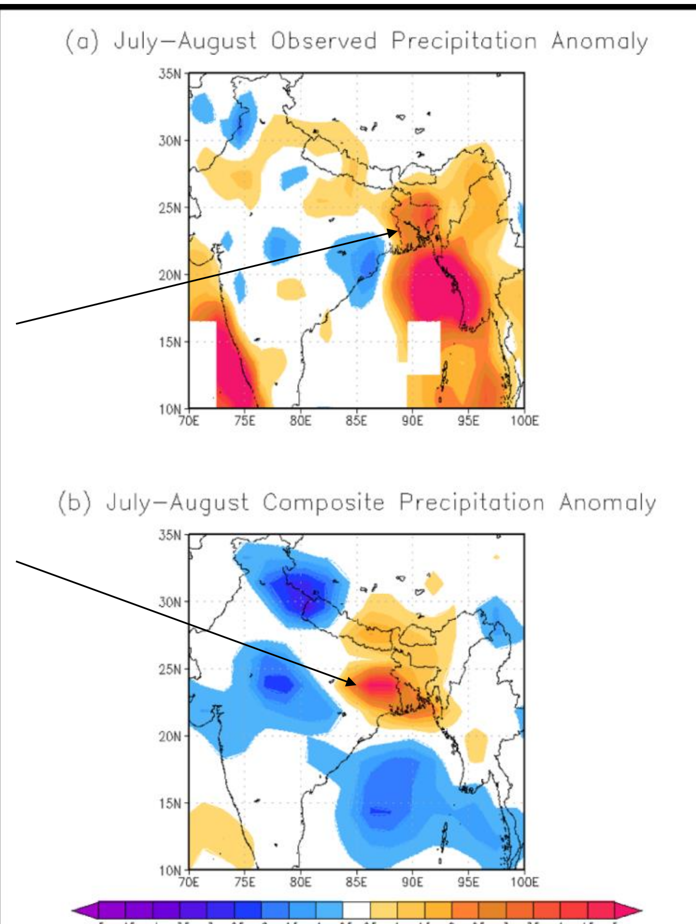
SST data: HadSST1:
Rayner et al. 2003

El Tor Cholera

Link between cholera and ENSO

- Observed precipitation enhanced following El Niño

- Model captures much of the observed empirical signal



Cash, Rodo and Kinter ,
J. Climate 2008

Climate variability

→

Spatial heterogeneity in vulnerability
(in large urban environments of the developing world)

feedbacks within the disease system itself
(epidemiological processes that depend on the current or past state of the system → immunity; control measures)

forecasting

Limitation of temporal 'correlative' approaches:

1 – Spatial (and other forms) of population heterogeneity

2 – Nonlinear responses to environmental forcing

3 – Everything is seasonal… explanations for seasonality are hard

Highly localized sensitivity to climate forcing drives endemic cholera in a megacity

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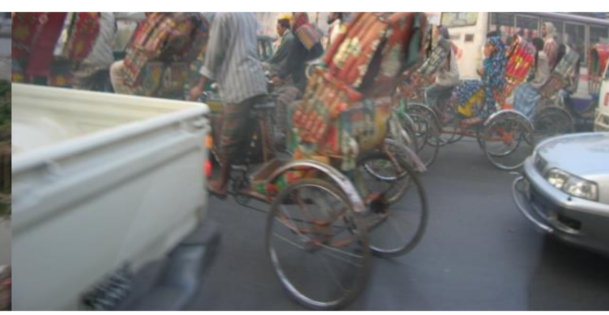
[a]University of Michigan, Ann Arbor, MI; [b]Fogarty International Center, National Institutes of Health, Bethesda, MD 20892; [c]University of North Caroli Chapel Hill, NC; and [d]International Centre for Diarrheal Disease Research, Dhaka 1000, Bangladesh



Motivation

Image courtesy of http://news.bbc.co.uk

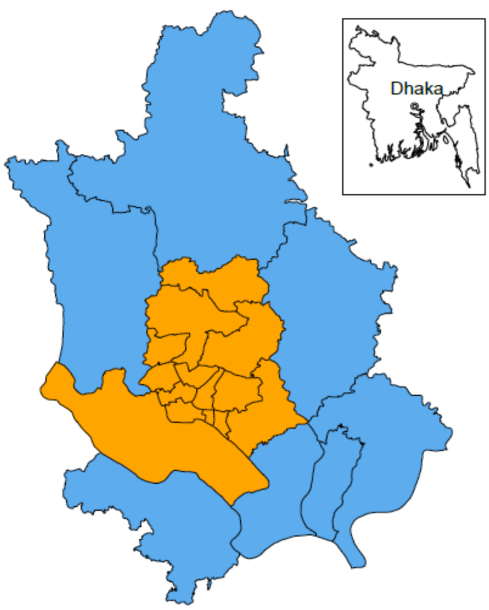
Image courtesy of http://www.purefilteredwater.com/

- Spatial effects have not been considered before in the response of cholera to climate variability. We may expect global climate drivers such as ENSO to operate at regional scales.

- We still have a poor understanding of proximal mechanisms that mediate the effect of global climate drivers in urban environments

- Statistical models in the literature cannot be used effectively for prediction because of their short lead times (ranging from 0 to 1 months)

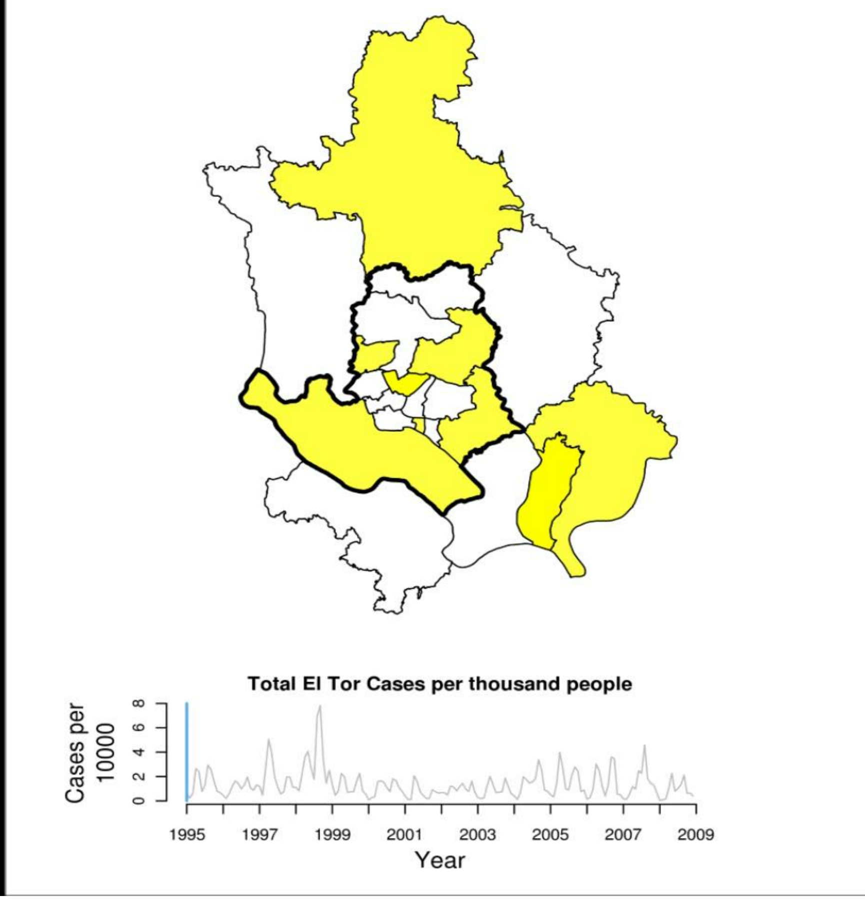
Data Description

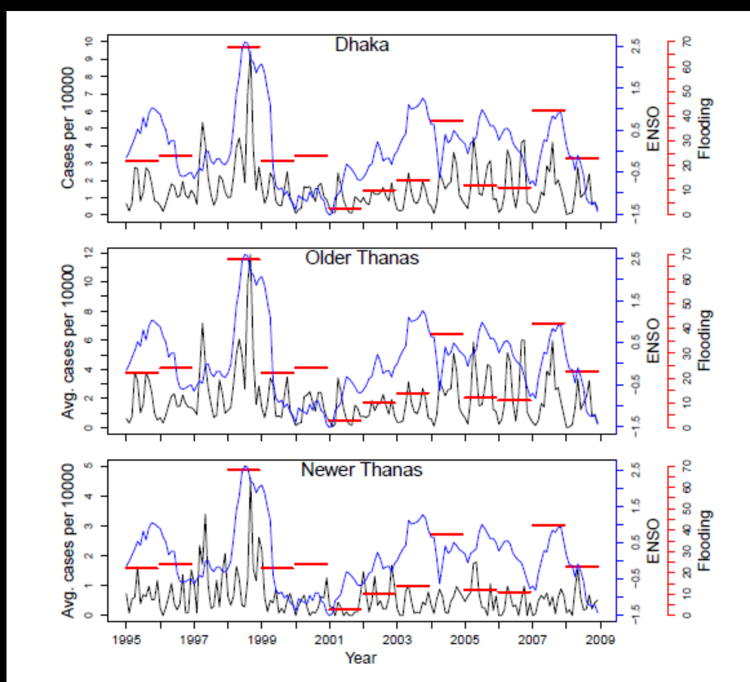


- Dhaka, the capital of Bangladesh, contains more than 14 million people (almost tripled in last 25 years, projected to double in next 25).

- The data we analyze is the number of cases of cholera of the O1 El Tor biotype over 14 years (1995-2008), broken down by thana (i.e. administrative region).

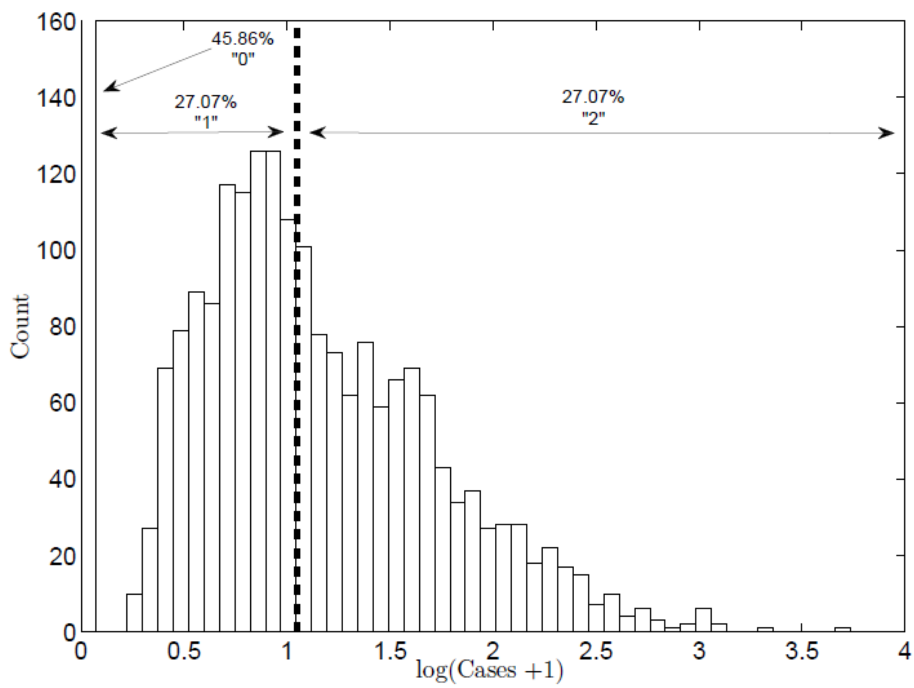
Movie


Total El Tor Cases per thousand people
Cases per 10000
0
2
4
6
8
1995
1997
1999
2001
2003
2005
2007
2009
Year

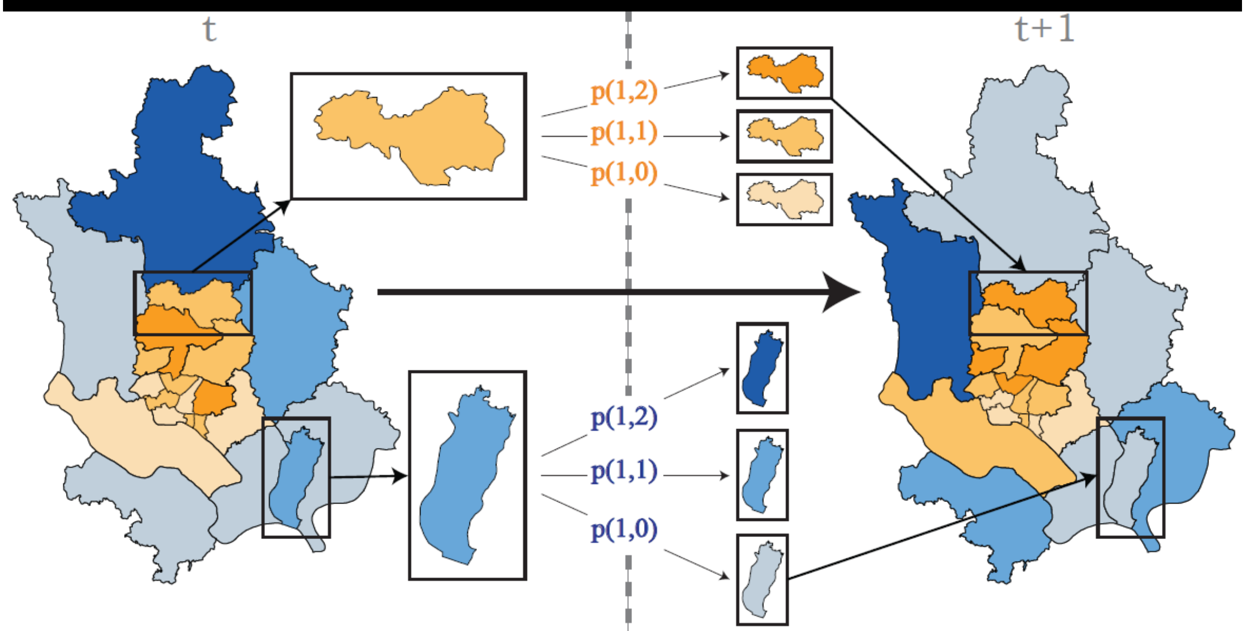


Reiner et al., PNAS 2012

Data Transformation



Probabilistic model (discrete state Markov chain model): probabilities a function of group , season, neighbors' states, and climate covariates.



Model Description

	0	1	2
0	$p(0,0)$	$p(0,1)$	$p(0,2)$
1	$p(1,0)$	$p(1,1)$	$p(1,2)$
2	$p(2,0)$	$p(2,1)$	$p(2,2)$

Markov Chain Model

- We start with a simple Markov Chain model to describe the data.
- This model assumes the only difference between any two observations is what the value of the thanas were the month before.

Model Description

Older

	0	1	2
0	$p(0,0)$	$p(0,1)$	$p(0,2)$
1	$p(1,0)$	$p(1,1)$	$p(1,2)$
2	$p(2,0)$	$p(2,1)$	$p(2,2)$

Newer

	0	1	2
0	$p(0,0)$	$p(0,1)$	$p(0,2)$
1	$p(1,0)$	$p(1,1)$	$p(1,2)$
2	$p(2,0)$	$p(2,1)$	$p(2,2)$

Multiple Markov Chain Model

- We add complexity by allowing the transition matrices to be different depending on the area of the city where the thana is located.

Model Description

NN=0

Older

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Newer

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

NN=1

Older

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Newer

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

NN=2

Older

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Newer

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Multi-Dimensional Markov Chain Model

- To account for local spatial effects, we expand the model to allow for a different transition matrix depending on the maximum state of the nearest neighbors of that thana.
- All thanas must now be simultaneously tracked, hence we now have a multi-dimensional model (21 dimensions, one for each thana).

Model Description

Spring

NN=2

Older

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Newer

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

NN=2

Older

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Newer

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

NN=2

Older

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Newer

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Summer

NN=0

Older

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Newer

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

NN=0

Older

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Newer

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

NN=0

Older

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

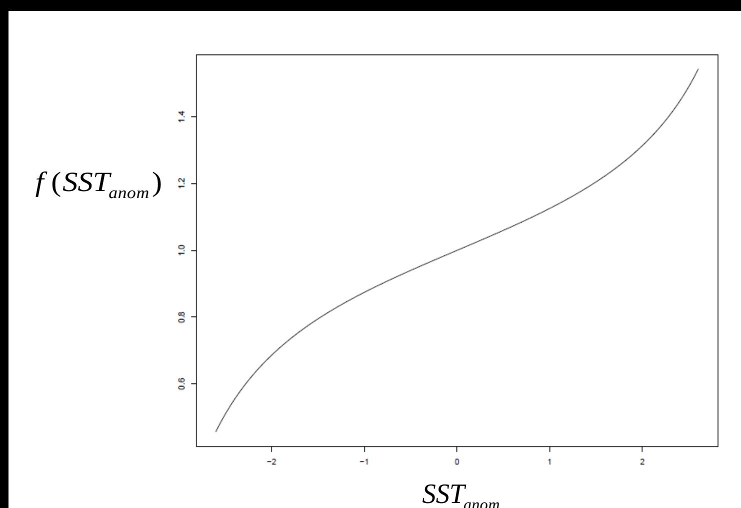
Newer

	0	1	2
0	$p_{0,0}$	$p_{0,1}$	$p_{0,2}$
1	$p_{1,0}$	$p_{1,1}$	$p_{1,2}$
2	$p_{2,0}$	$p_{2,1}$	$p_{2,2}$

Multi-Dimensional Inhomogeneous Markov Chain (MDIMC) Model

- Allowing the transitions to vary by season, our model is no longer temporally homogeneous, but allows for the known two-peak-per-year dynamics to emerge. Unfortunately there are way too many variables in this model. Only Spring and Summer are shown here in a four season model. One could imagine a different set of matrices for each month.

$$P_{ENSO}(i,j) = P(i,j) * [1 + f(SST_{anom})]$$



$$\mathbf{P}\left(X_{k,t} = j | X_{k,t-1} = i, \max_{l \in \mathcal{N}(k)} X_{l,t-1} = v, \mathrm{ENSO} = s\right) =$$

$$= \mathbb{P}_{i,j,\mathcal{D}(k)} \times \mathrm{Neigh}(i,j,v,\mathcal{D}(k)) \times \mathrm{Seas}(i,j,t,\mathcal{D}(k)) \times \mathrm{Nino}(j,s,\mathcal{D}(k))$$

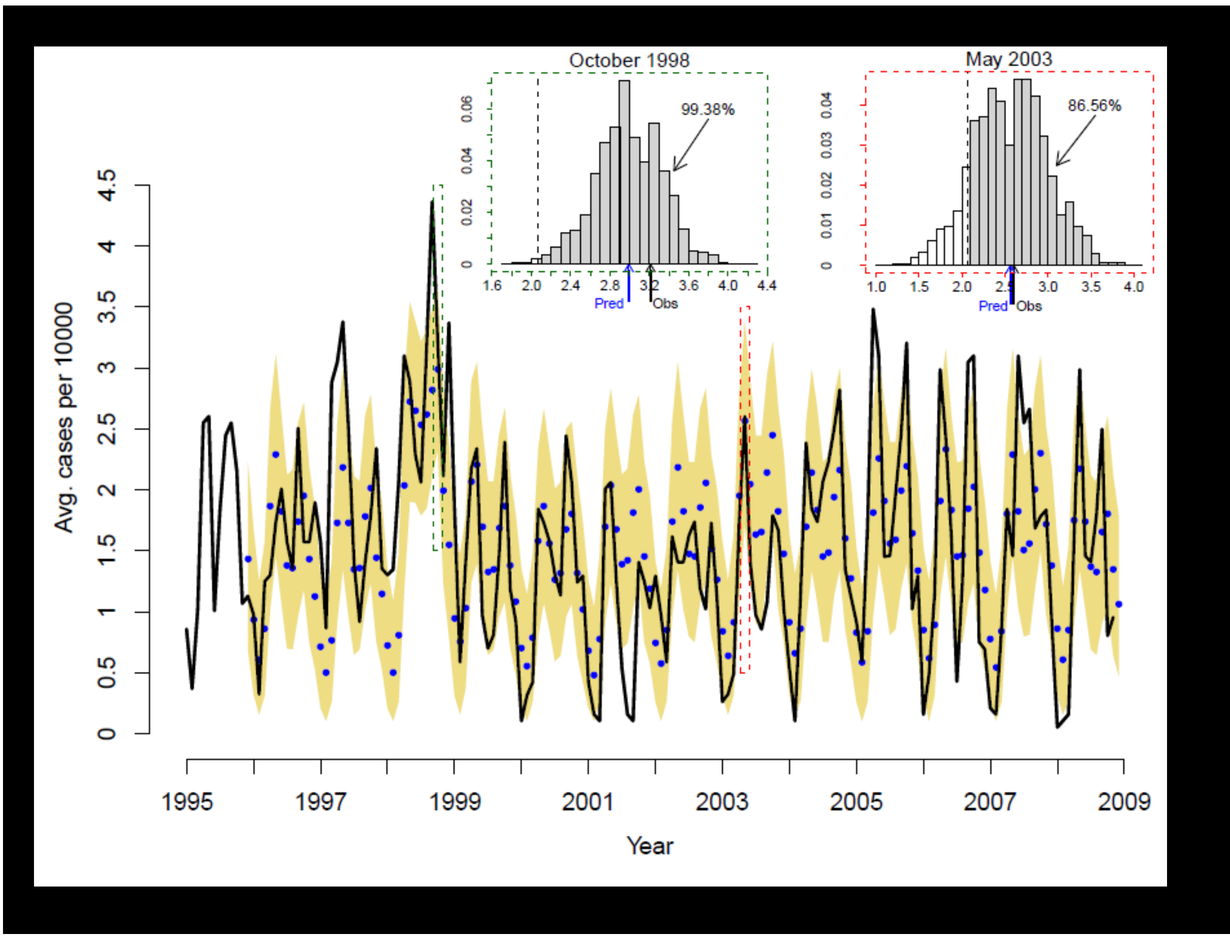
- Spatial heterogeneity: the dynamics between groups are significantly different (p-value=0.0001)
- Local effect: the state of neighboring districts matters (p-value =0.01) but a weaker effect
- Interaction between spatial structure and climate forcing: the parameters governing the effect of ENSO are significantly different between the groups (p-value= 0.03); and similarly for flooding (p-value= 0.015)

> ENSO is a significant covariate (p=value < 0.0001); lag of 11 months for the spring months and 9 months for the fall ones.

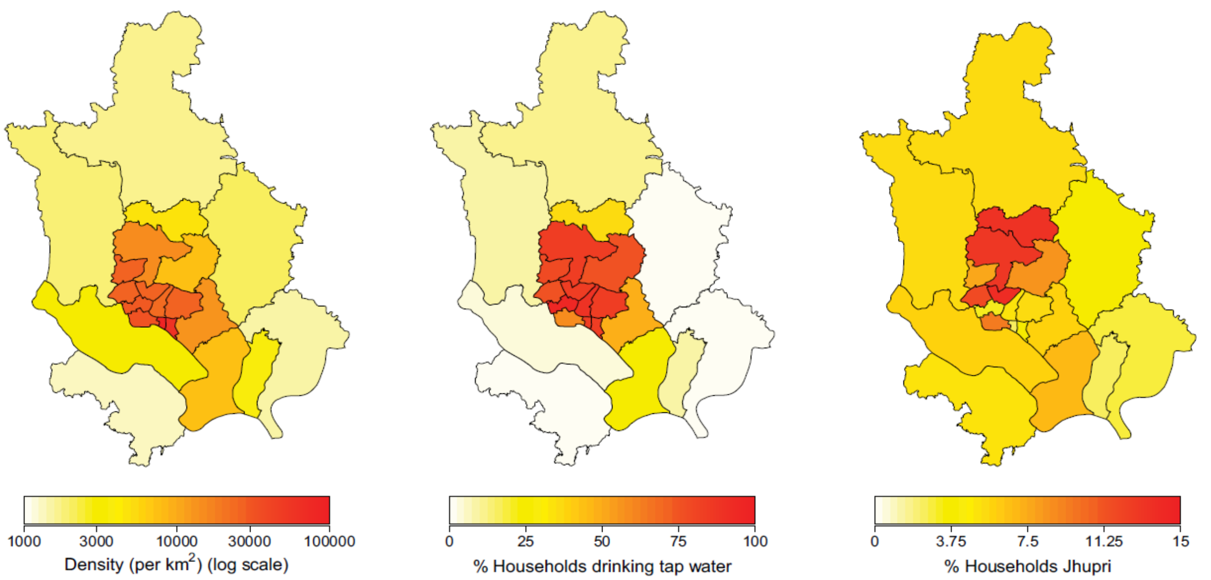
> Flooding is also significant (p-value < 0.0001)

> Flooding still significant when tested in the presence of ENSO (p-value = 0.008) and vice-versa (p-value < 0.0001)

Reiner *et al*. (*PNAS 2012*)


October 1998
99.38%
Pred
Obs
May 2003
86.56%
Pred
Obs
Avg. cases per 10000
Year
1995
1997
1999
2001
2003
2005
2007
2009

Socio-economic conditions



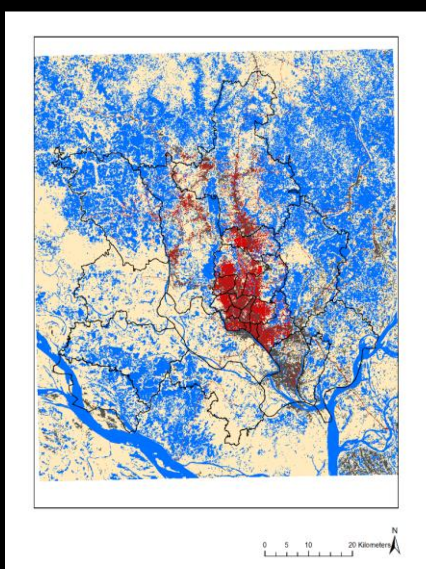
Summary so far:

- ➢ Cholera outbreaks in Dhaka (and Bangladesh) are driven by climate variability (ENSO and flooding). The effect of El Niño is partly through precipitation and associated flooding.

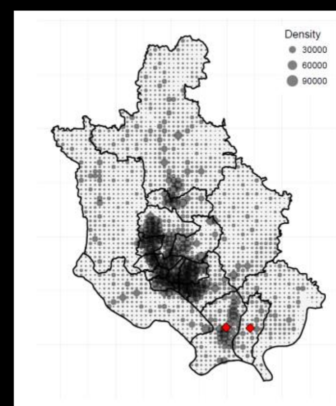
- ➢ Population susceptibility shows pronounced geographic variation within Dhaka, with a part of the city acting as a susceptible core, in a way that highlights the key role of sanitary and associated socio-economic conditions.

A remote-sensing view of the city

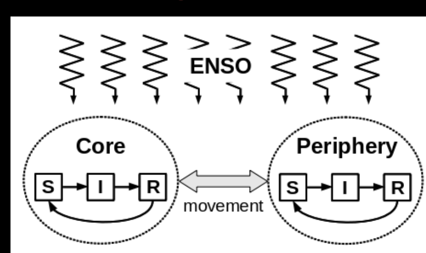
water
urban
rural



Population density

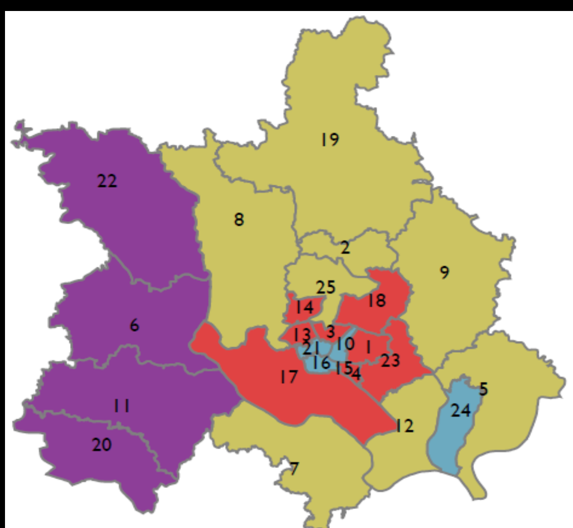


Zooming out



Perez *et al. Advances in Water Resources 2017*

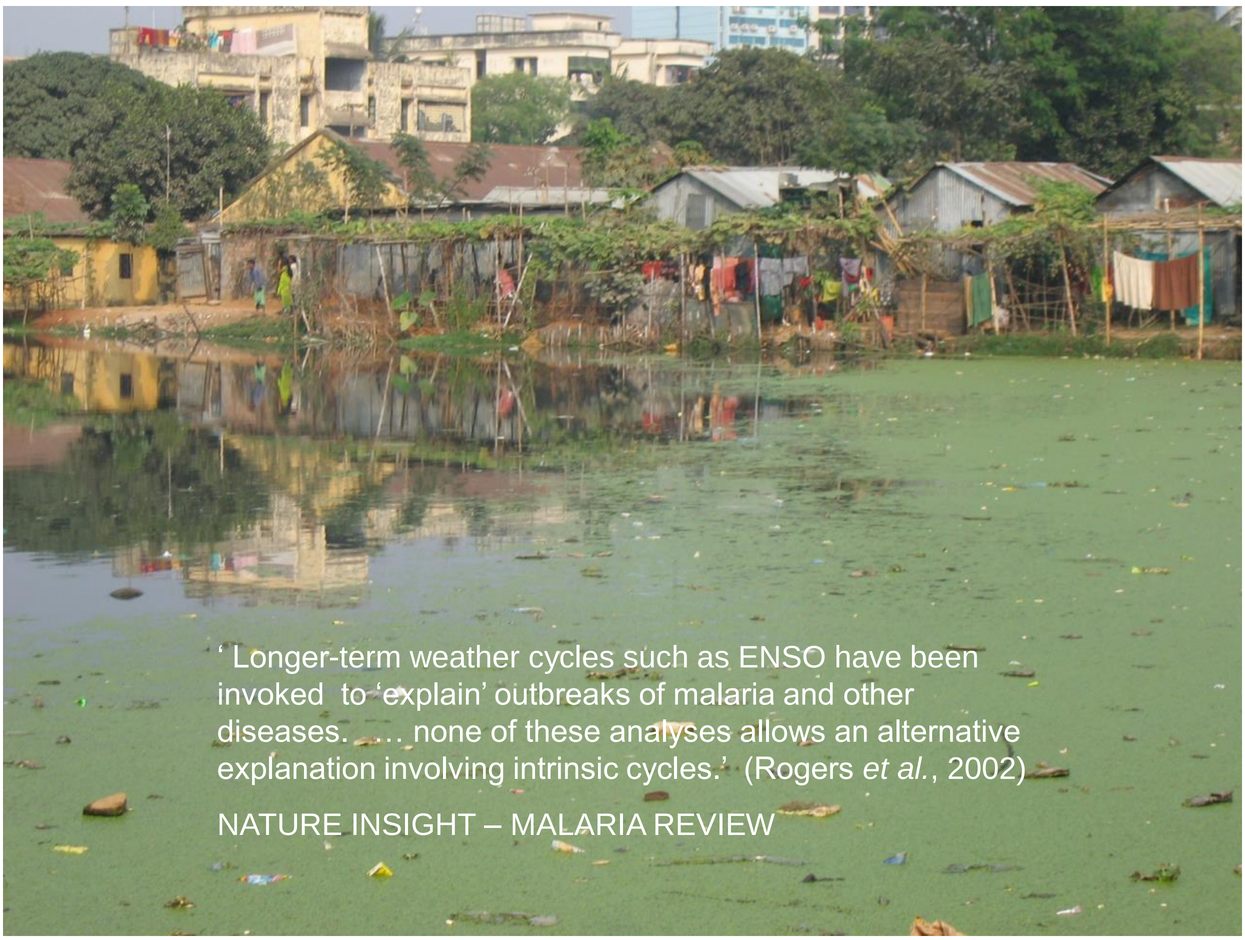
Search algorithms to identify 'groups ' of locations with similar dynamics …



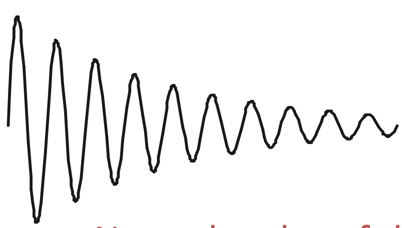
There are $\mathcal{S}_{25}^{(2)} = 16,777,215$ distinct groupings.

Bayesian approach to classify districts based on a dynamical model and time series data:

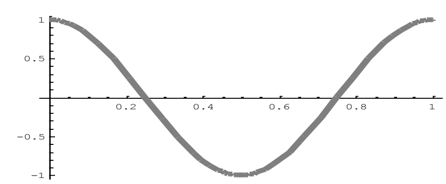
Baskerville EB, Bedford T, Reiner RC, Pascual M (2013) Nonparametric Bayesian grouping methods for spatial time-series data. arXiv:1306.5202.


' Longer-term weather cycles such as ENSO have been invoked to 'explain' outbreaks of malaria and other diseases. …. none of these analyses allows an alternative explanation involving intrinsic cycles.' (Rogers *et al.*, 2002)
NATURE INSIGHT – MALARIA REVIEW

when two cycles interact…



Natural cycles of the disease



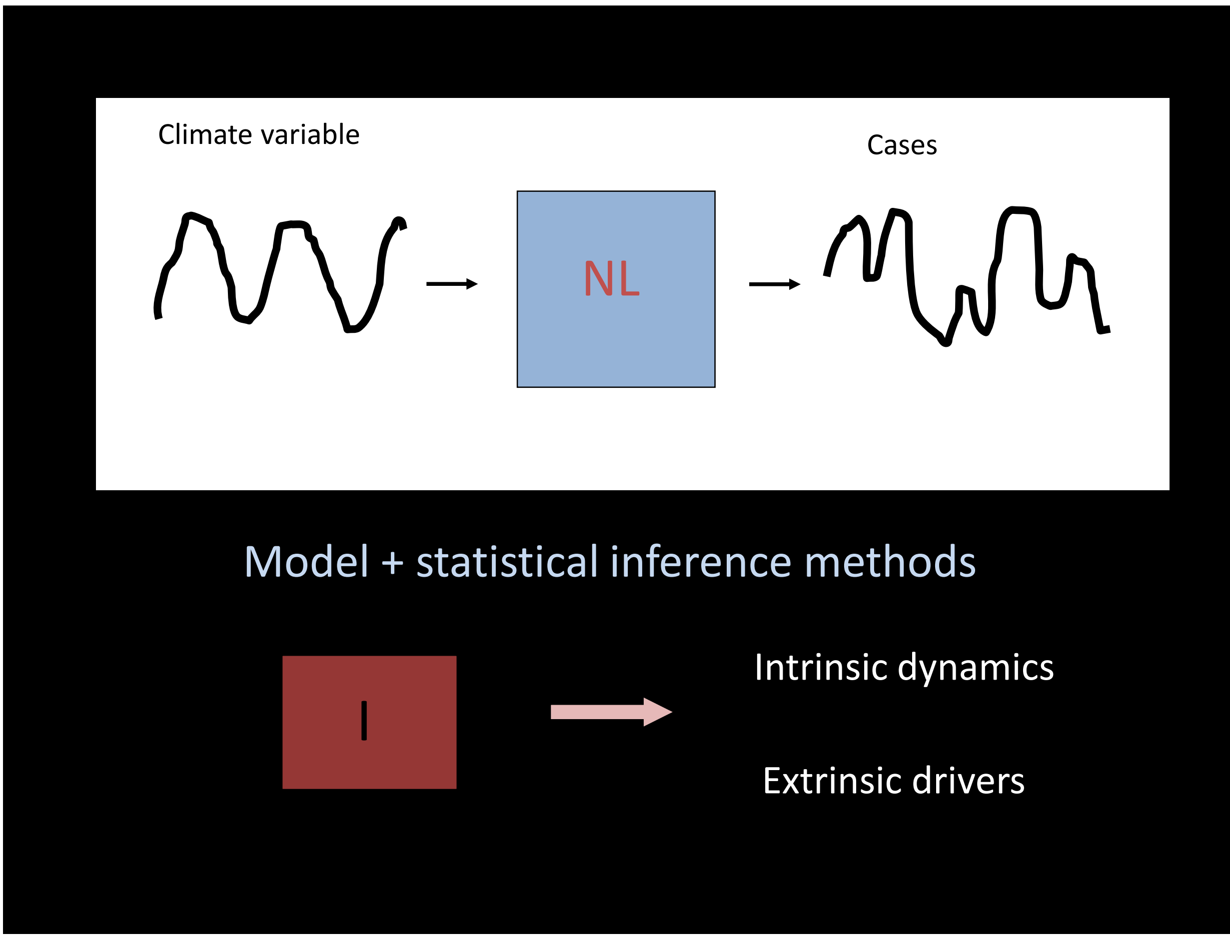
Seasonal transmission

Annual cycles

Biennial cycles or <u>cycles of longer period</u>

Multiple coexisting cycles

Chaos


Climate variable
Cases
NL
Model + statistical inference methods
I
Intrinsic dynamics
Extrinsic drivers

Parameter inference and model comparison

www.keywordpictures.com

ENSO **No ENSO**

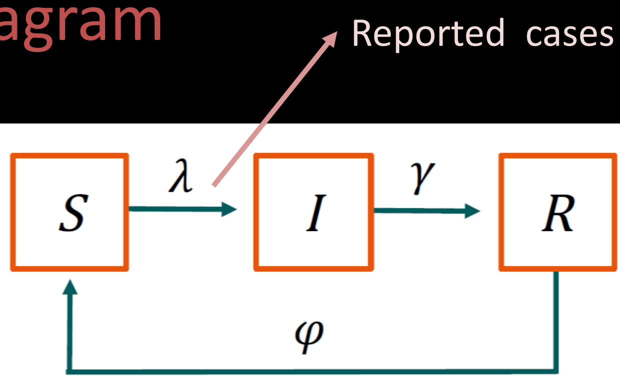
PARAMETER ESTIMATION
Sequential Monte Carlo method

MODEL COMPARISON
Based on likelihood

Parameters were estimated with a method that ***maximizes the likelihood*** *and allows for the inclusion of both* ***measurement and process noise*** *, as well as* ***hidden variables***

Ionides et al. PNAS 2006, King et al. Statistical inference for partially observed Markov processes (R package) http://pomp.r-forge.r-project.org

Model diagram

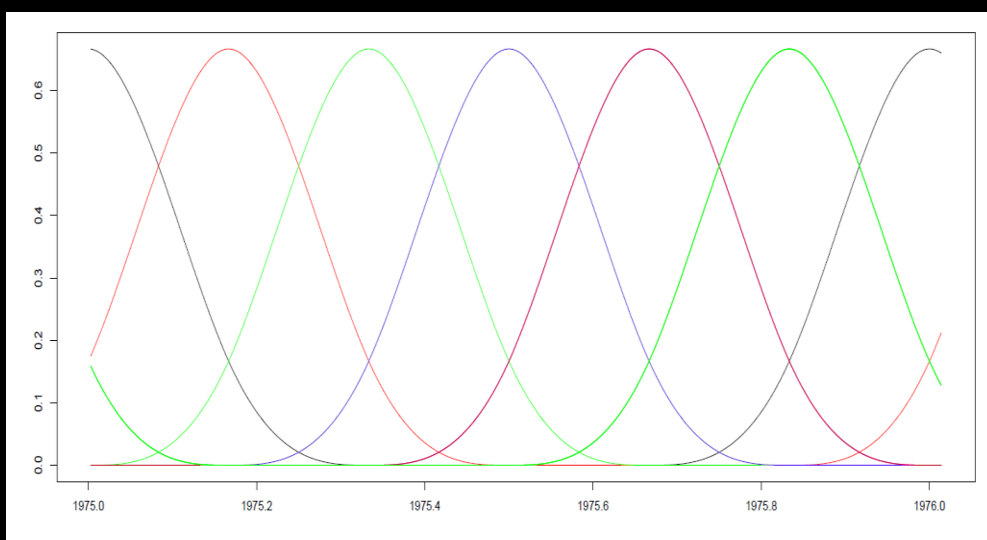


$$\lambda = \text{trend}\left(\begin{matrix}\text{secondary}\\ \text{transmission}\end{matrix} + \begin{matrix}\text{primary}\\ \text{transmission}\end{matrix}\right)$$

$$\text{secondary transmission} = \boldsymbol{\beta}\frac{I}{N}$$

$$\boldsymbol{\beta} = \text{seasonality} \cdot f(ENSO) \cdot \text{noise}$$

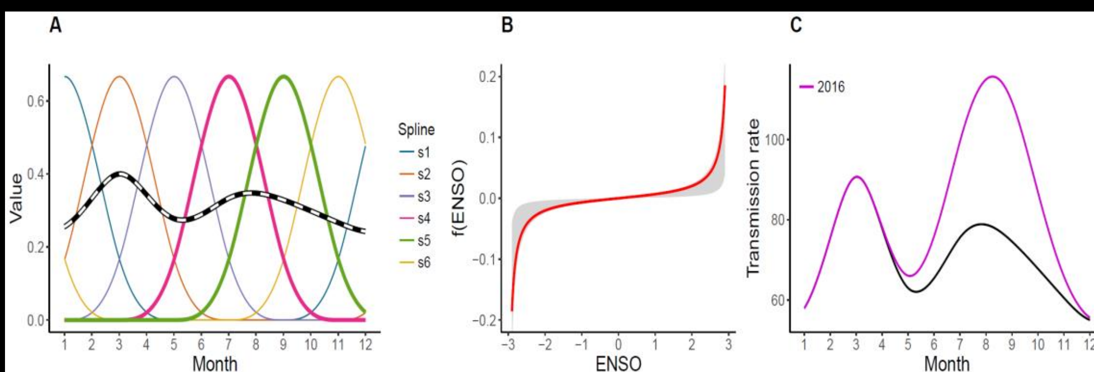
β : seasonality and ENSO



B-splines (1 to 6)

Time

$$\beta = \exp[\sum_{1}^{6} a_i season_i + b.season5.ENSO(January)]$$



Force of infection

$$\lambda_E(t) = \overbrace{e^{-\eta(t-t_0)}}^{\text{long-term trend}} \left[\beta(t)\left[\frac{I(t)}{N(t)}\right] + \omega\right]$$ noise

'secondary' transmission

'primary' transmission

Inference method:

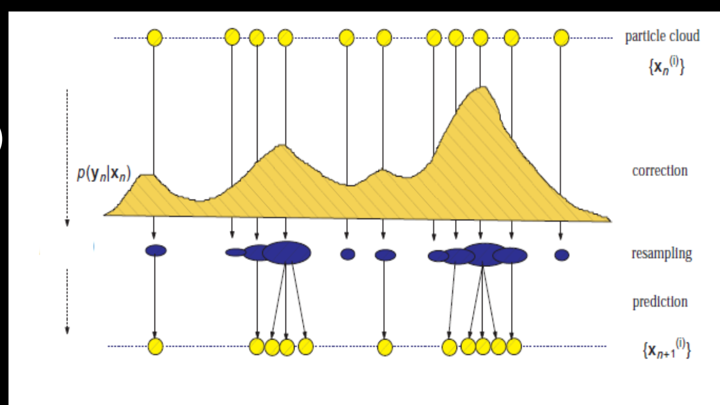
King AA, N D, Ionides EL. Statistical Inference for Partially Observed Markov Processes via the R Package pomp. J Stat Softw. 2016; 69(1): 1–43.

Likelihood maximization by iterated filtering (based on sequential Monte Carlo methods --- particle filters)

can accommodate:

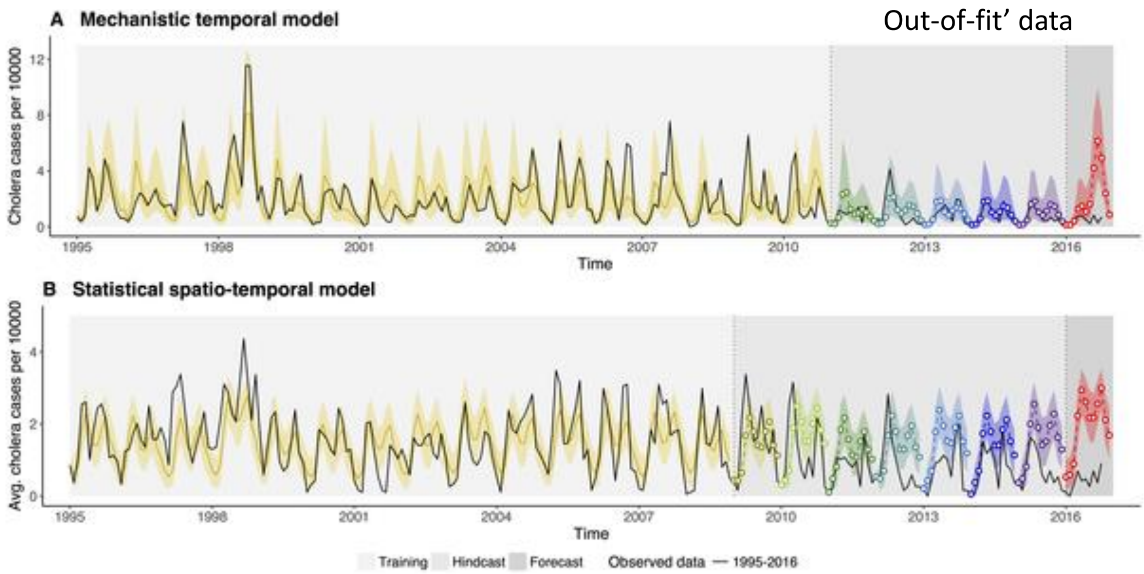
- flexible model formulations ; continuous time
- unobserved variables (e.g. susceptibles)
- stochasticity , trends
- measurement error (under-reporting)

See Laneri et al (PloS Comp. Biol. 2010) for inclusion of covariates and pseudo-code in a malaria example



From Z. Chen 2009

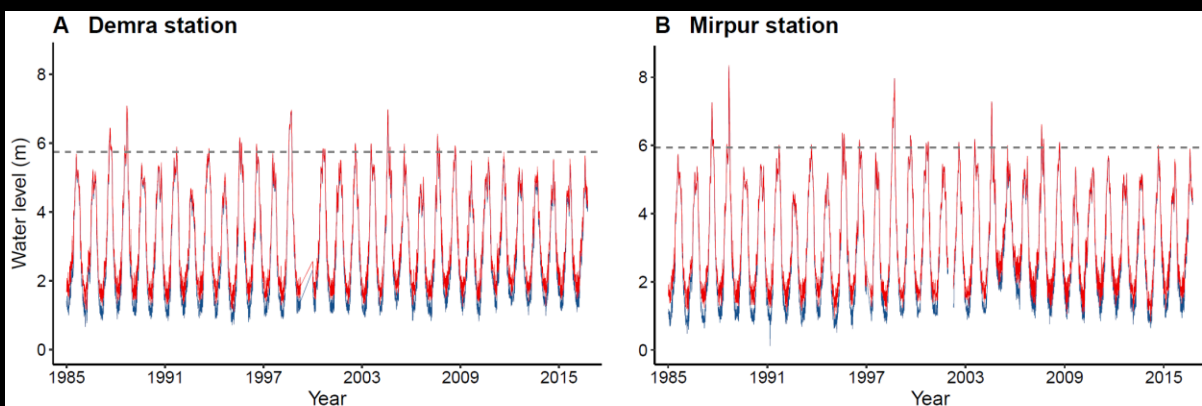
Fig 2. Comparison of simulated and predicted monthly cases with those reported for Dhaka, Bangladesh.

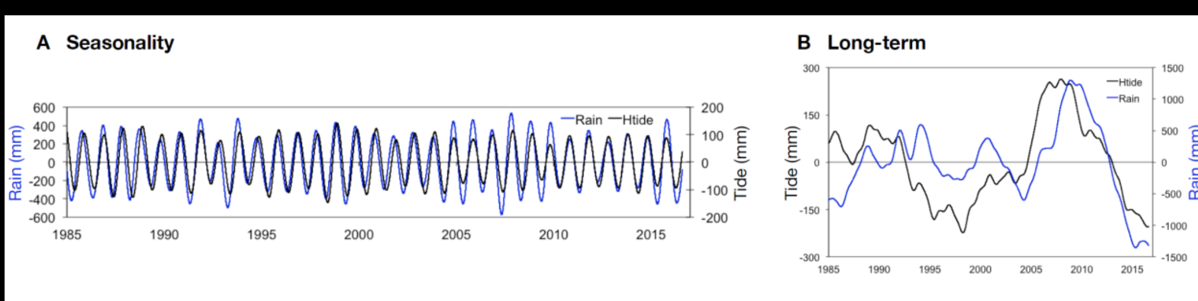


Martinez PP, Reiner RC Jr, Cash BA, Rodó X, Shahjahan Mondal M, et al. (2017) Cholera forecast for Dhaka, Bangladesh, with the 2015-2016 El Niño: Lessons learned. PLOS ONE 12(3): e0172355. https://doi.org/10.1371/journal.pone.0172355
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0172355

PLOS | ONE
TENTH ANNIVERSARY

Water level and rainfall in Dhaka

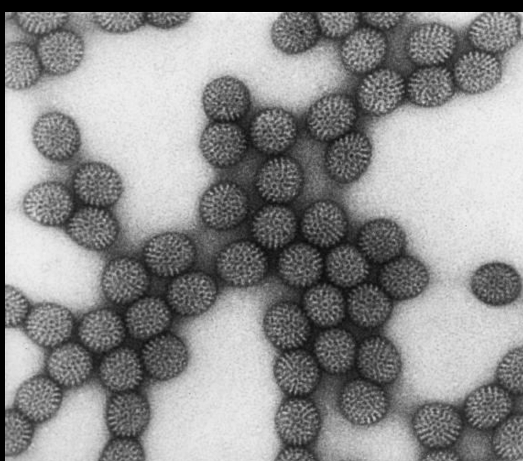




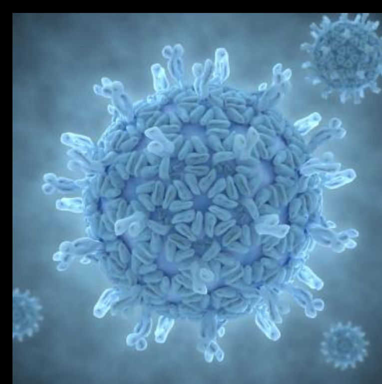
Some conclusions

- Model with ENSO better explains the retrospective data including the large epidemic of 1998
- It also predicts the low incidence of ‘out-of-fit’ data during non-EL Nino years
- It overpredicts the response to the 2015-16 event.
- This appears to reflect a decrease susceptibility to flooding in the city, and perhaps a decadal change in rainfall conditions

Rotavirus: segmented RNA virus

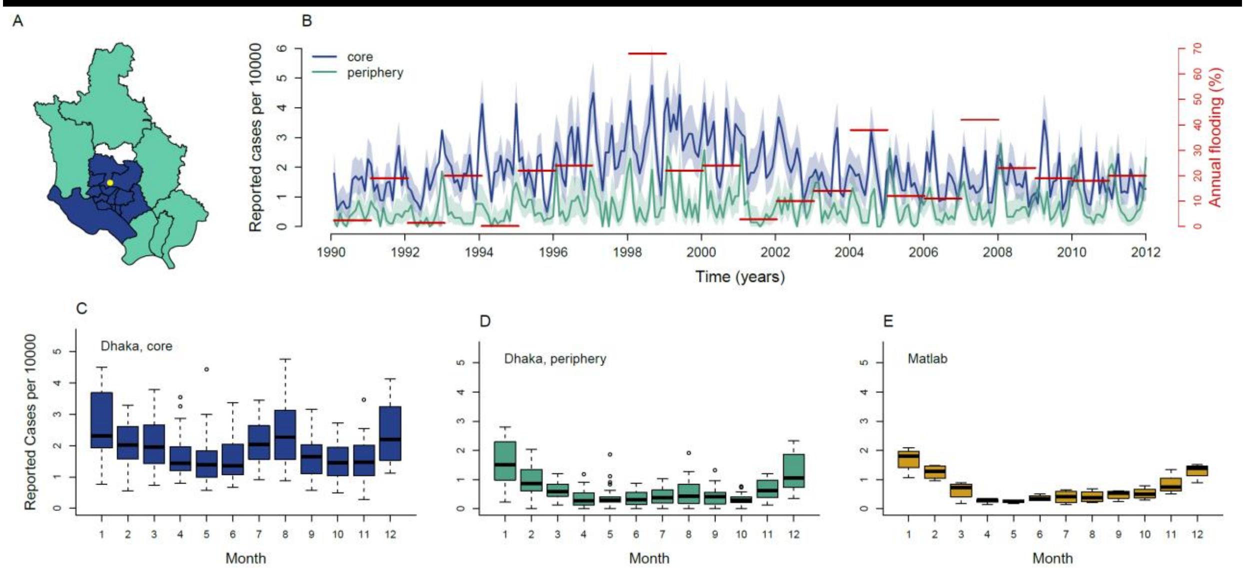


Transmission electron micrograph of rotavirus particles
http://pathmicro.med.sc.edu/virol/rotaviruses.htm

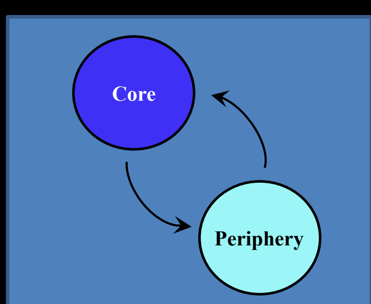


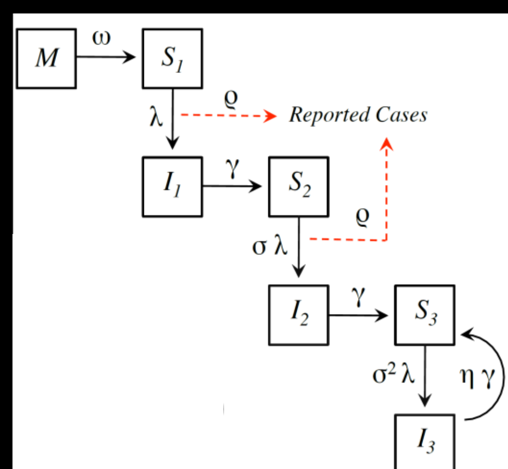
http://www.babymed.com/infections/rotavirus

Rotavirus: empirical patterns



Transmission model





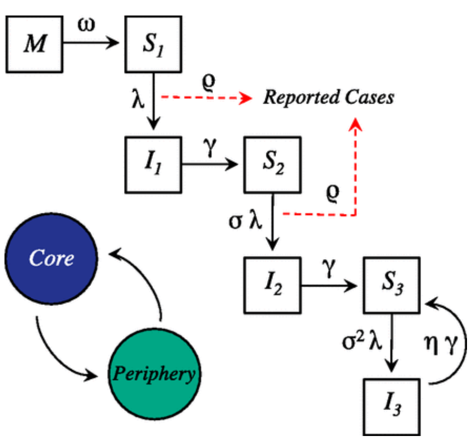
Martinez *et al., PNAS 2016*

Transmission model

Force of Infection

α = coupling ($0 \leq \alpha \leq 1$)

$$\lambda_i = \beta_i \left[\alpha_i \frac{(I_{1i} + I_{2i} + I_{3i})}{P_i} + (1 - \alpha_j) \frac{(I_{1j} + I_{2j} + I_{3j})}{P_i} \right]$$



Transmission rate

$$\beta_i = \exp\left[\sum_{k=1}^{6} b_{ki} s_k \; + \; b_{fi} s_4 F \right] \left[\frac{d\Gamma}{dt} \right]$$

seasonality ***flooding*** (interannual variation) ***process noise***

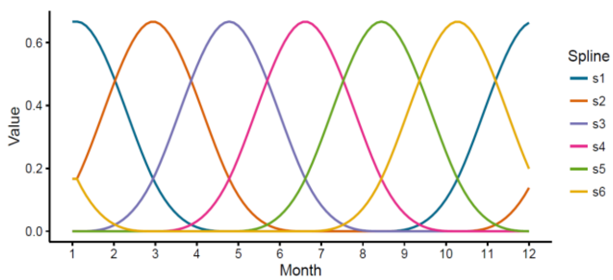
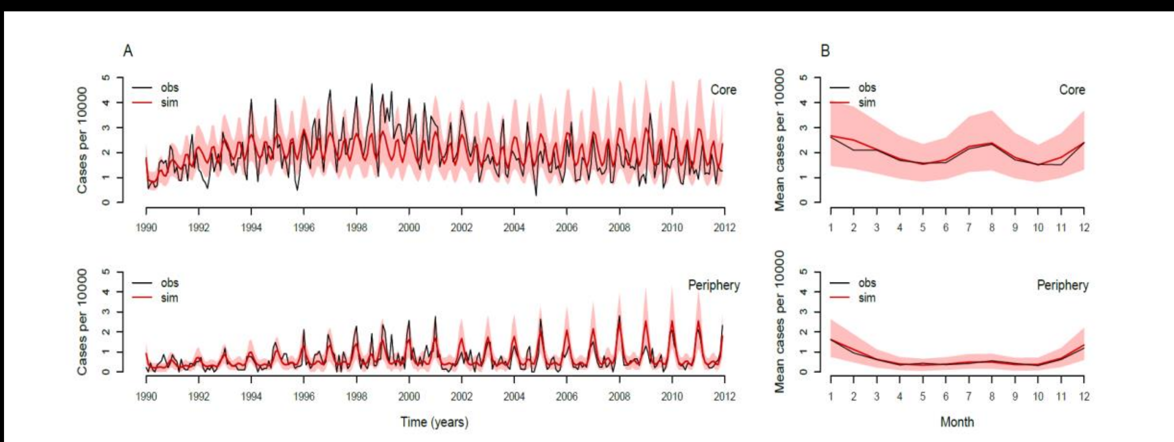
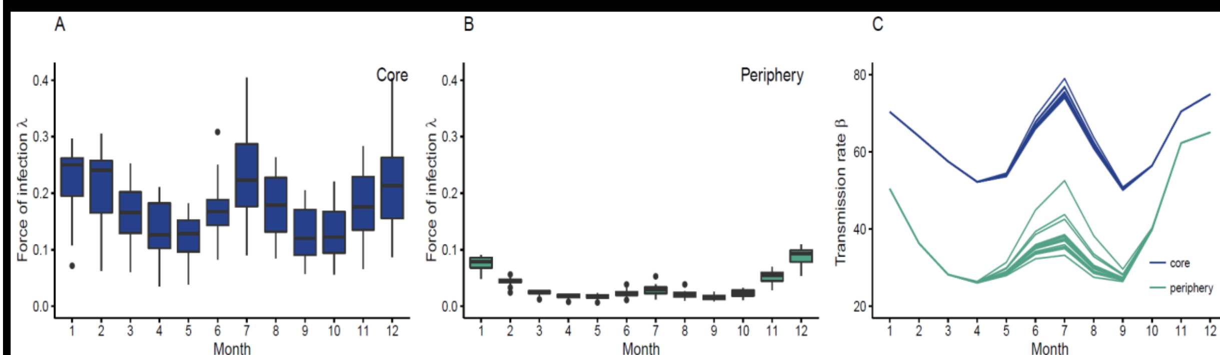


Table 1. A likelihood-based comparison of the different models

Model	log-likelihood	SE	no. param	AIC	LR Test
With flooding effect	-1577.6	0.33	25	3205.2	
Without flooding effect	-1582.2	0.35	23	3210.4	p-value $= 0.01$



Martinez *et al., PNAS 2016.*



>> Higher force of infection in the core

>> Especially, during the monsoons

>> Transmission in the core continues outside the two main seasons (no deep troughs)

Some general implications

- Dense urban areas can enhance transmission and facilitate more endemic dynamics
- In these areas, enhanced responses to climate forcing may be seen even in infections that are not considered climate sensitive to begin with
- These responses are reflected primarily in changes to the seasonality
- More epidemic behavior, in areas where disease persistence throughout the year is more marginal, will exhibit responses to climate forcing at multiannual rather than seasonal scales

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Seasonality in cholera dynamics: A rainfall-driven model explains the wide range of patterns in endemic areas

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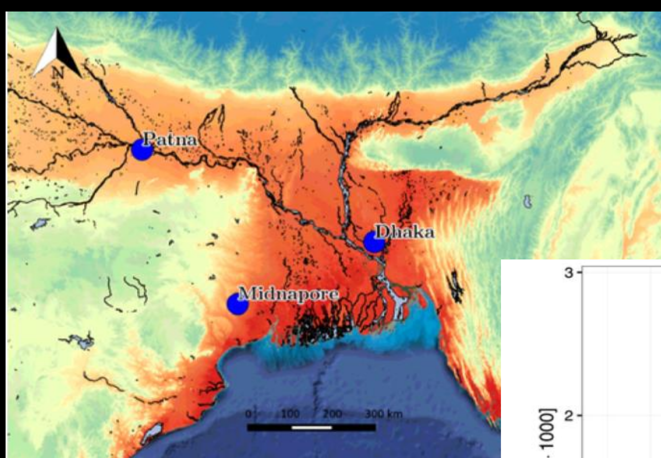
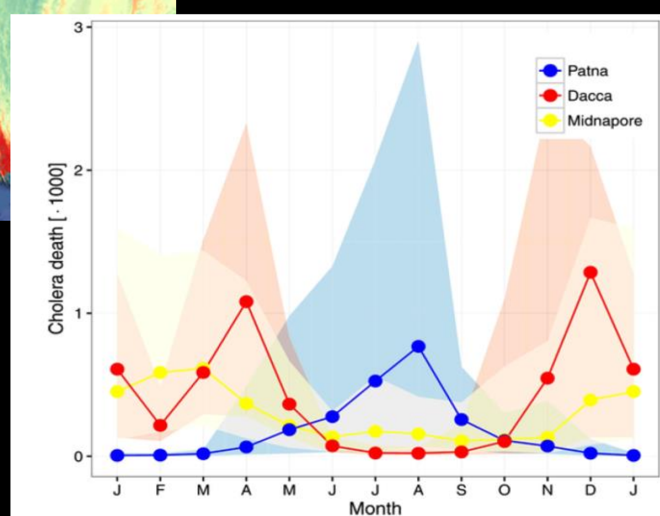
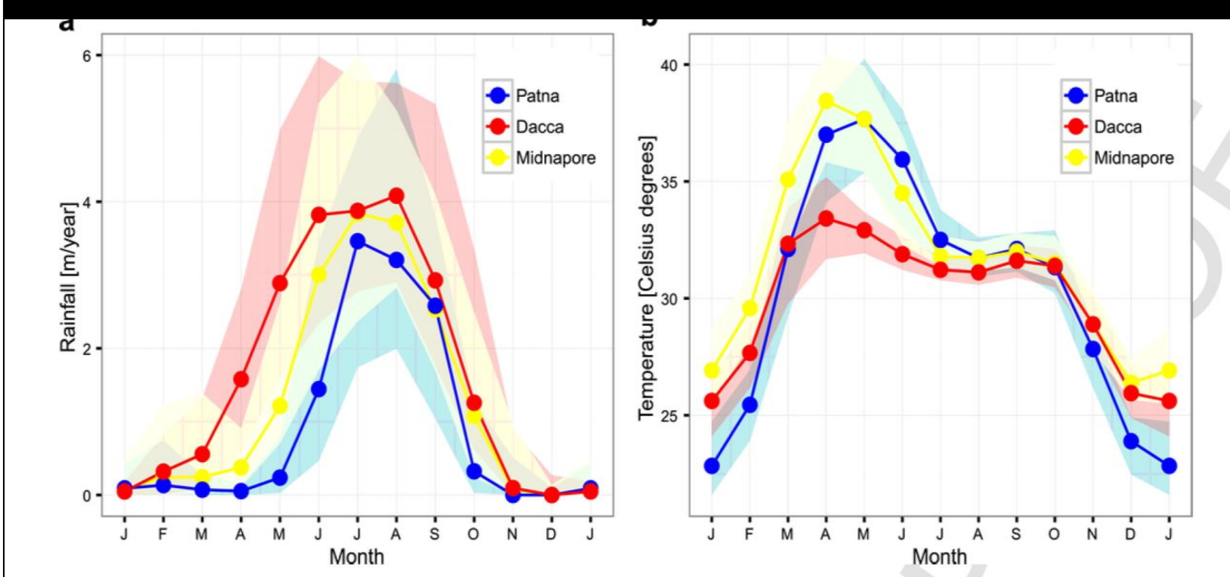
Climate variables and seasonality





Seasonality of rainfall and temp

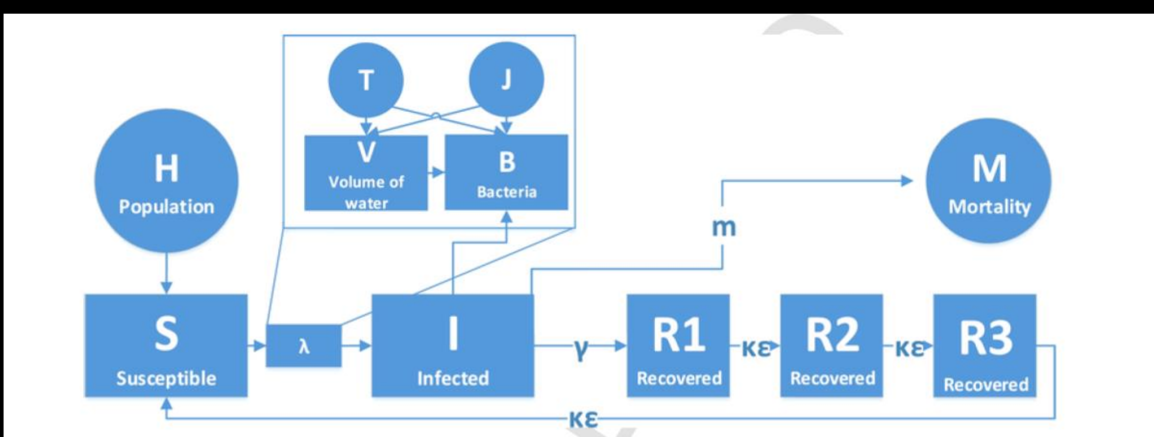


The model

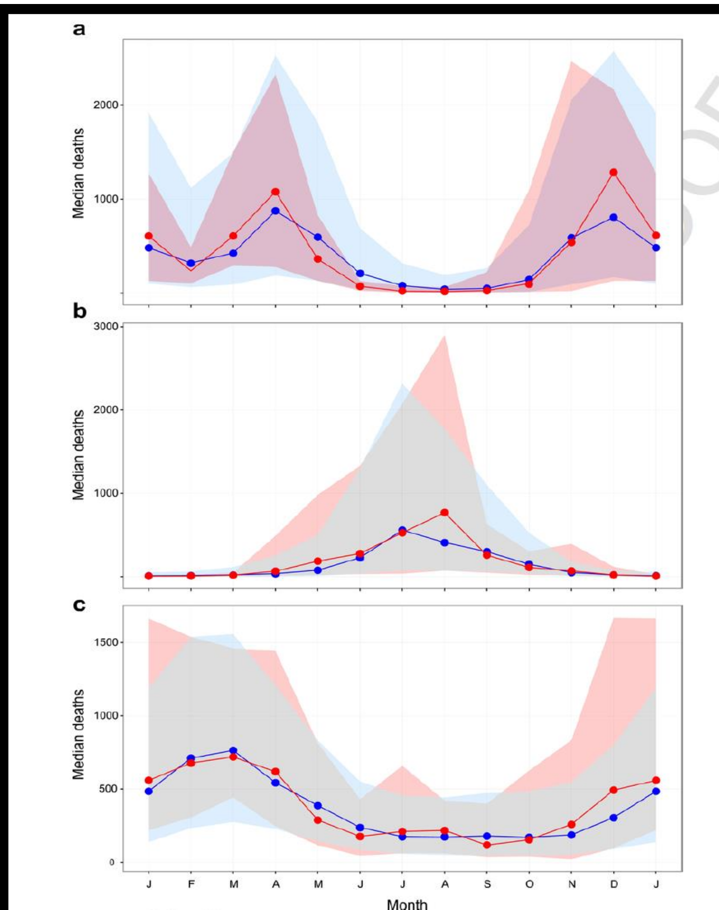
$$\frac{dV}{dt} = J(t) - ET(T,V) - f(V)\cdot V$$

$$\lambda(t) = \beta \frac{\frac{B(t)}{V(t)A}}{\frac{B(t)}{V(t)A} + K},$$

$$\frac{dB}{dt} = -\mu_B(T)\,B + p(t)\left[1 + \phi \cdot J(t)\right] I \cdot \xi(t) - f(V)\,B$$



Seasonality: Model and data

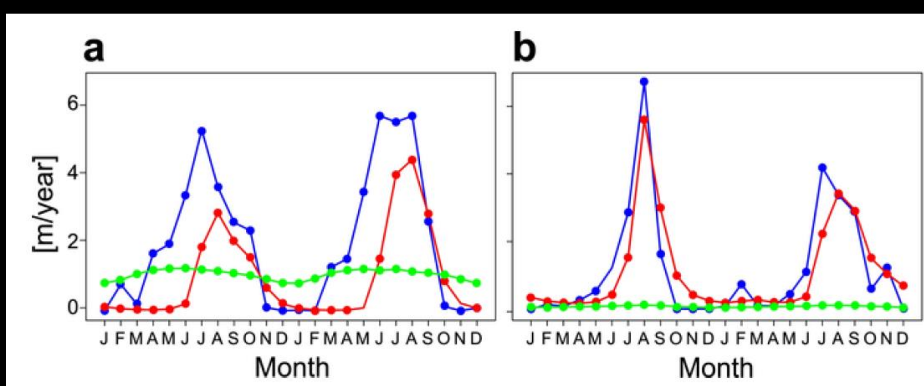


The historical Bengal region encompasses all the seasonal patterns observed worldwide

Monthly data: 1891-1941

Rainfall and 'hydrology'

Dhaka Patna

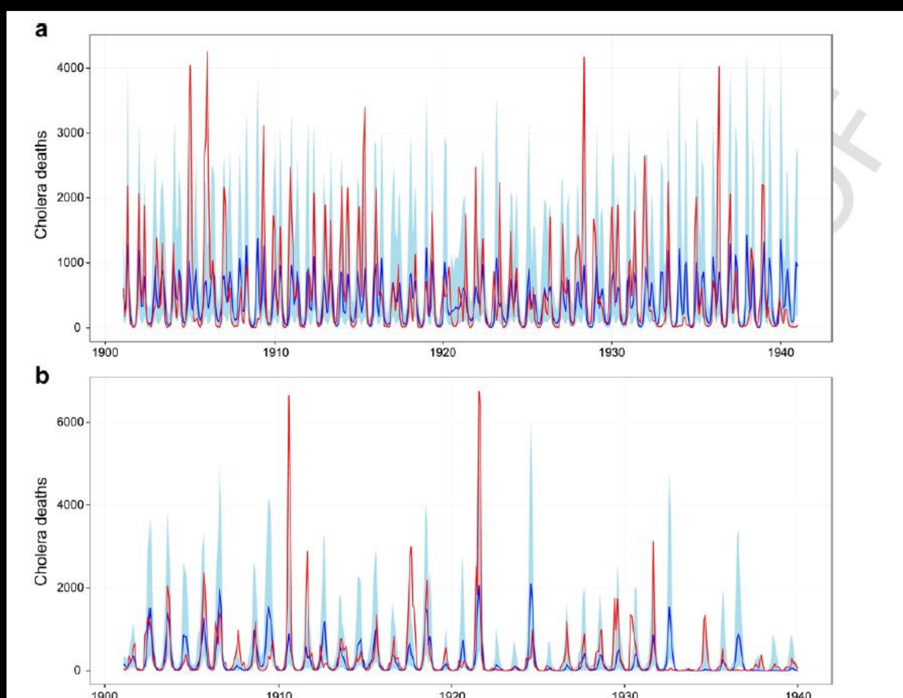


drainage rainfall

Interannual variability

Dhaka

Patna



Gracias

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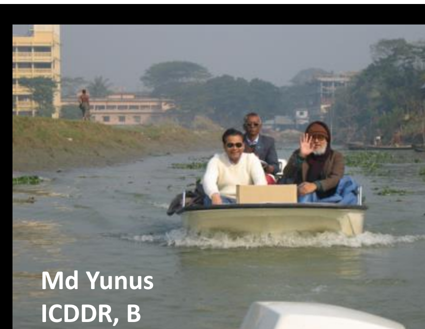

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Conclusions and Implications

- Cholera epidemics appear primarily limited by the local depletion of susceptibles
- Explicit 'space' matters (the dynamics are distributed in space or in a network)
- **Stochasticity (demographic noise) might be essential to the epidemic dynamics of infectious diseases, beyond the recognized effect of small population size on extinction.**


NOAA, Oceans and Health
Howard Hughes Medical Institute
Graham Environmental Sustainability Institute (GESI, UM)