

BIOST/STAT 578 A  
Statistical Methods in Infectious Diseases  
Lecture 16  
February 26, 2009

Cholera: ecological determinants and vaccination



# Latest big epidemic in Zimbabwe



# Support

- International Vaccine Institute
- National Institute of Allergy and Infectious Diseases 'Epidemiology and Ecology of *Vibrio cholerae* in Bangladesh' grant 5R01AI039129-08
- National Institute of General Medical Sciences MIDAS grant 5U01GM070749-02
  - “Containing Bioterrorist and Emerging Infectious Diseases”

# Ecological & Epidemiological Publications

- Longini, I.M., Yunus, M., Zaman, K., Siddique, A.K., Sack, R.B. and Nizam, A.: Epidemic and endemic cholera trends over thirty-three years in Bangladesh. *Journal of Infectious Diseases* **186**, 246-251 (2002).
- Sack, R.B., Siddique, K., Longini, I.M., *et al.*: A four year study of the epidemiology of *Vibrio cholerae* in four rural areas in Bangladesh. *Journal of Infectious Diseases* **187**, 96-101 (2003).
- Huq, A., Sack, R.B., Nizam, A., Longini, I.M., *et al.*: Critical factors influencing the occurrence of *Vibrio cholerae* in the environment of Bangladesh. *Applied and Environmental Microbiology* **17**, 4645-4654 (2005).
- Longini, I.M., Nizam, A., Ali, M., Yunus, M., Shenvi, N. and Clemens, J.D.: Controlling endemic cholera with oral vaccines. *Public Library of Science (PloS), Medicine* **4** (11) 2007: e336  
[doi:10.1371/journal.pmed.0040336](https://doi.org/10.1371/journal.pmed.0040336)



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# Ecology of Cholera

# Cholera Vibrios



*Vibrio cholerae*, bakteria wywołująca cholere, wciąż jest przyczyną śmierci w krajach słabo rozwiniętych.

(c) Dartmouth Electron Microscope Facility

# Copepods



# Humans



# Ecology of Cholera in Rural Bangladesh

# Support

- National Institute of Allergy and Infectious Diseases grant R01AI039129
  - “Epidemiology and Ecology of *Vibrio cholerae* in Bangladesh”
- National Institute of General Medical Sciences MIDAS grant 5U01GM070749
  - “Containing Bioterrorist and Emerging Infectious Diseases”
- International Vaccine Institute, Seoul Korea



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# Ecology of Cholera in Rural Bangladesh

- 1997 – 2001: Four sites
- 2004 – 2008: Two sites



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# Surveillance Sites In Bangladesh



⊕ NIH Surveillance Sites  
 ☆ Cities



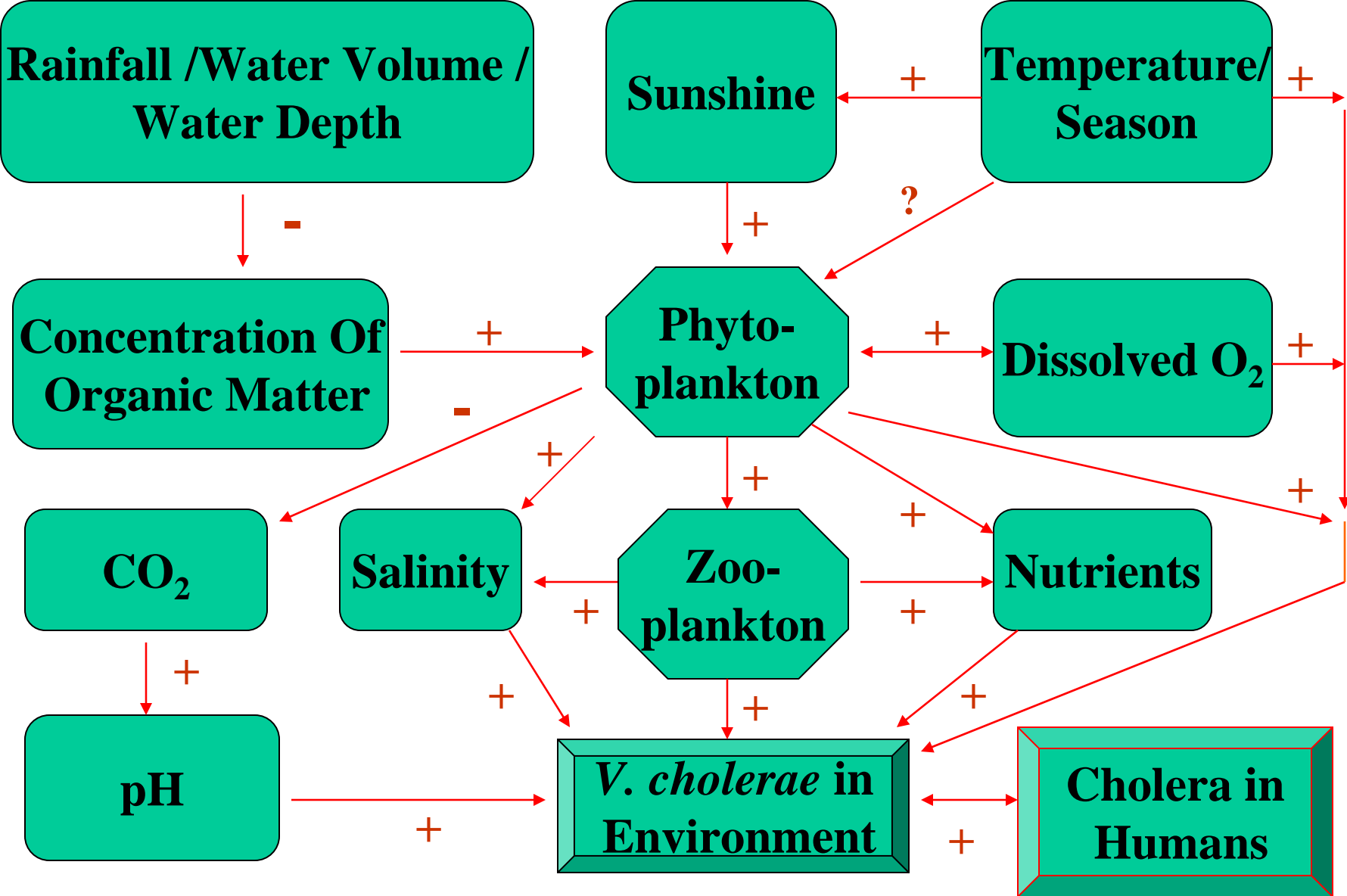
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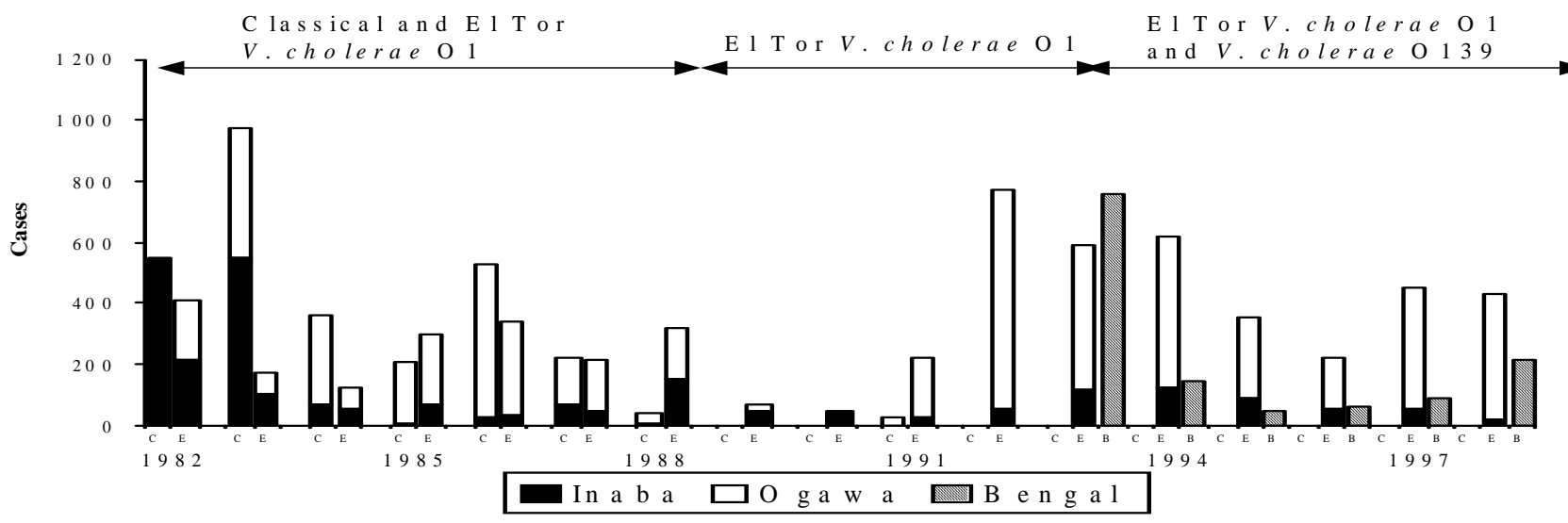
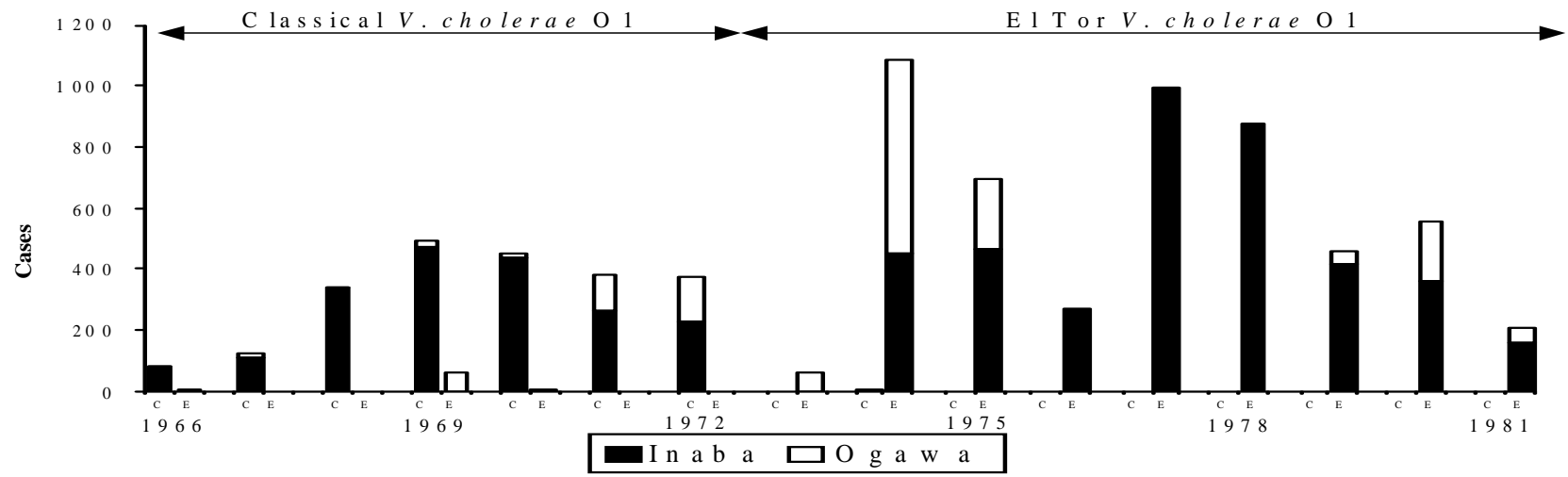


# Surveillance Sites In Bangladesh



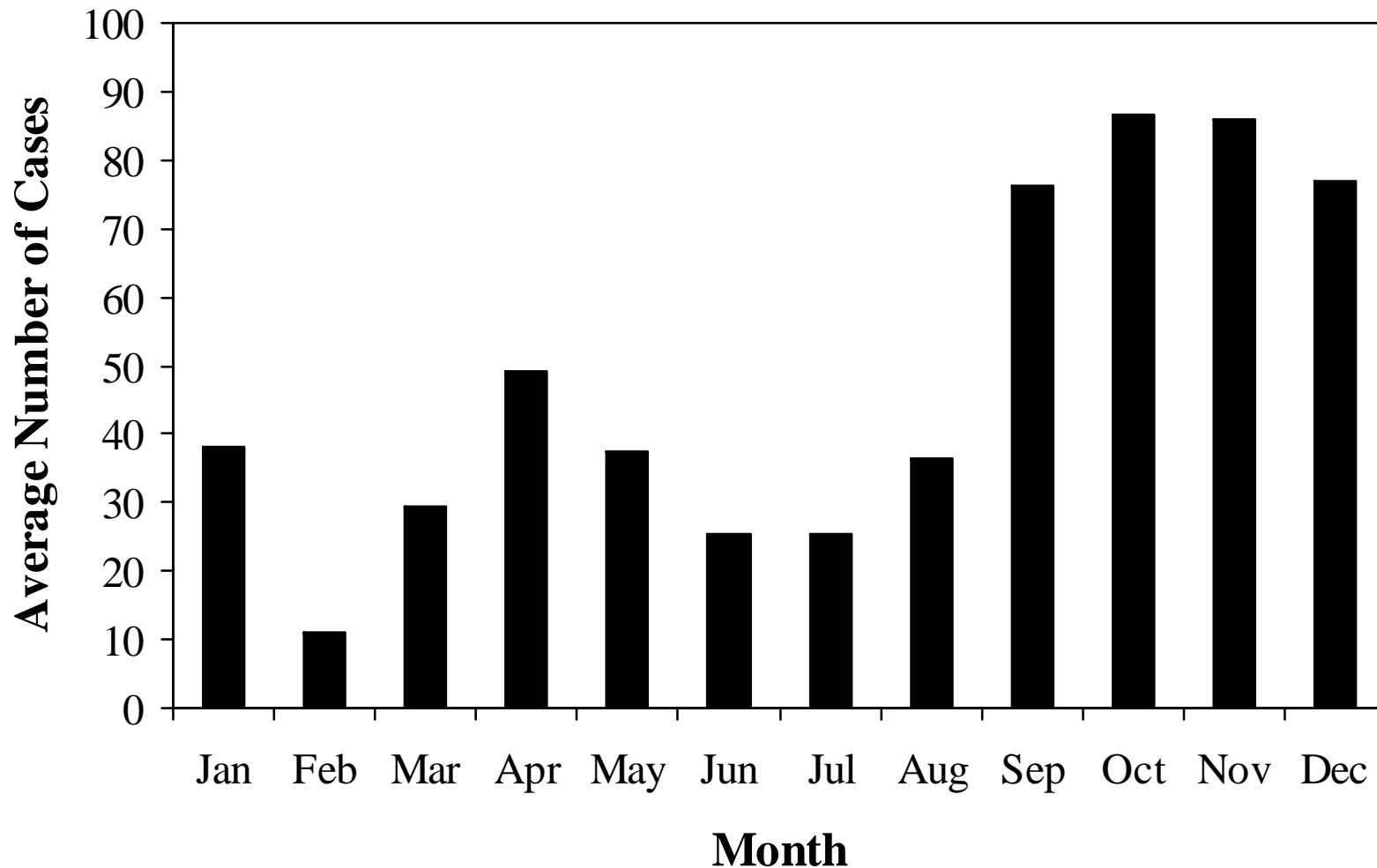
# Hypothesized Associations





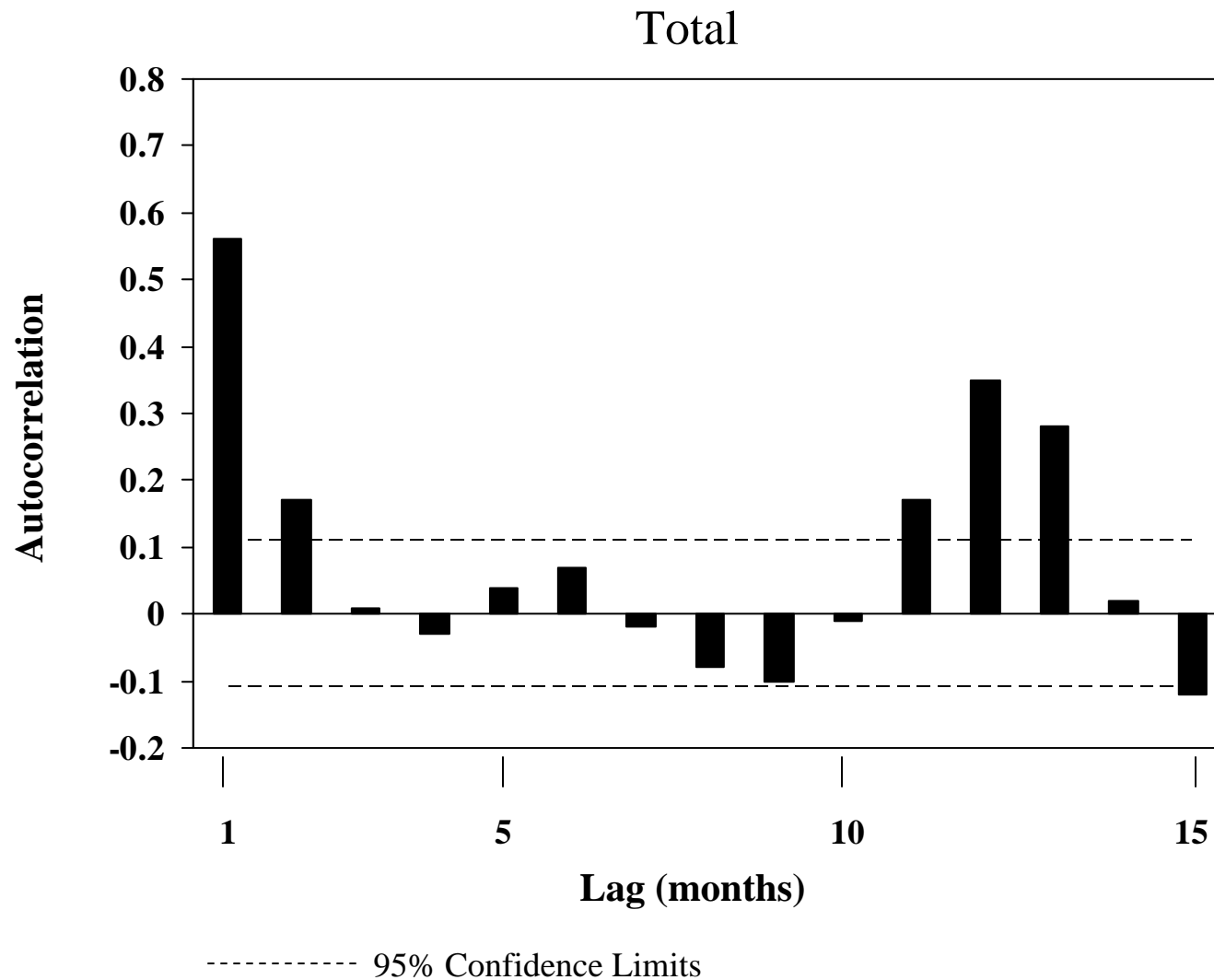
Source: Longini, I.M., et al., *J Infect Dis* **186**, 246-251 (2002).

Average monthly number cholera cases over the 33 year period 1966-1998, Matlab, Bangladesh.



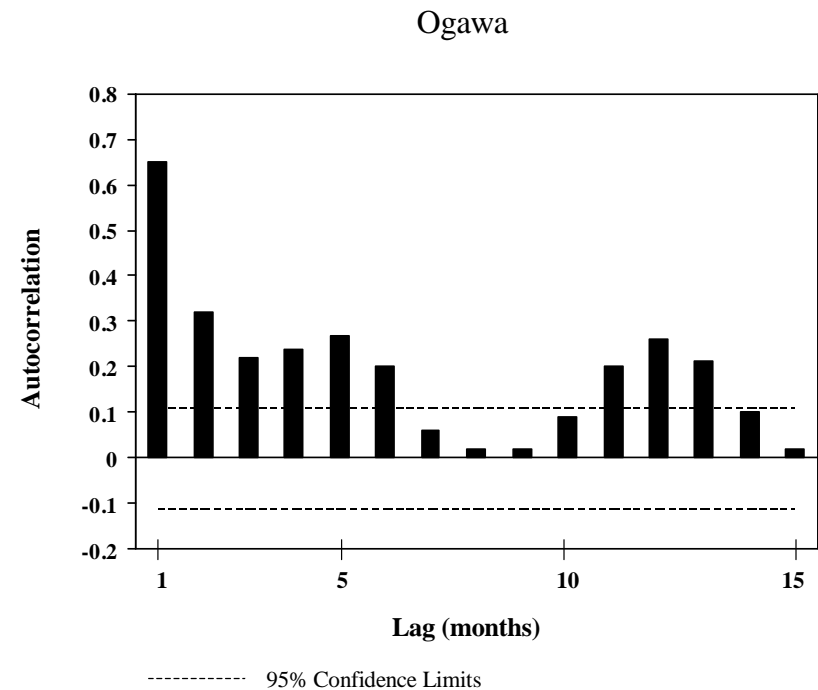
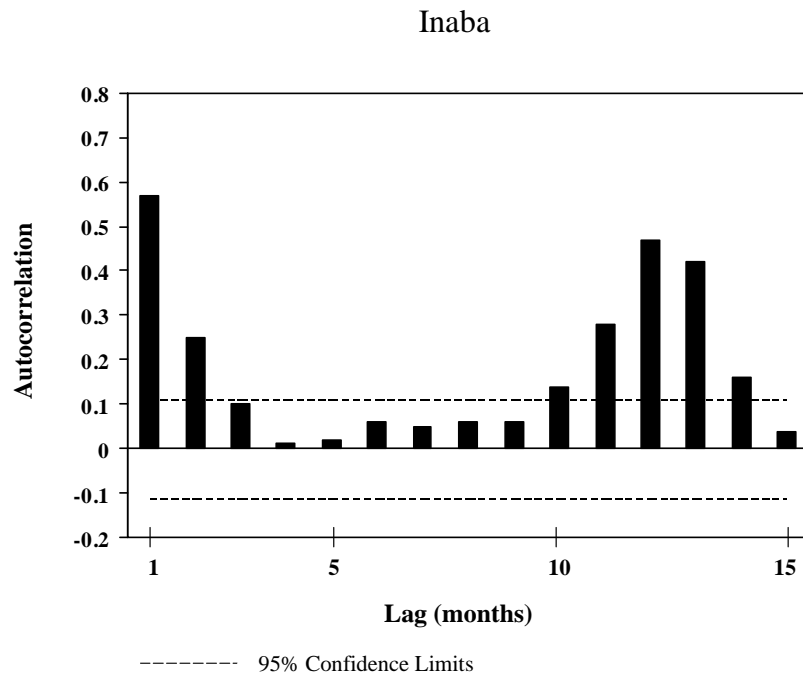
Source: Longini, I.M., et al., *J Infect Dis* **186**, 246-251 (2002).

# Correlogram for total cholera cases over the 33 year period 1966-1998, Matlab, Bangladesh



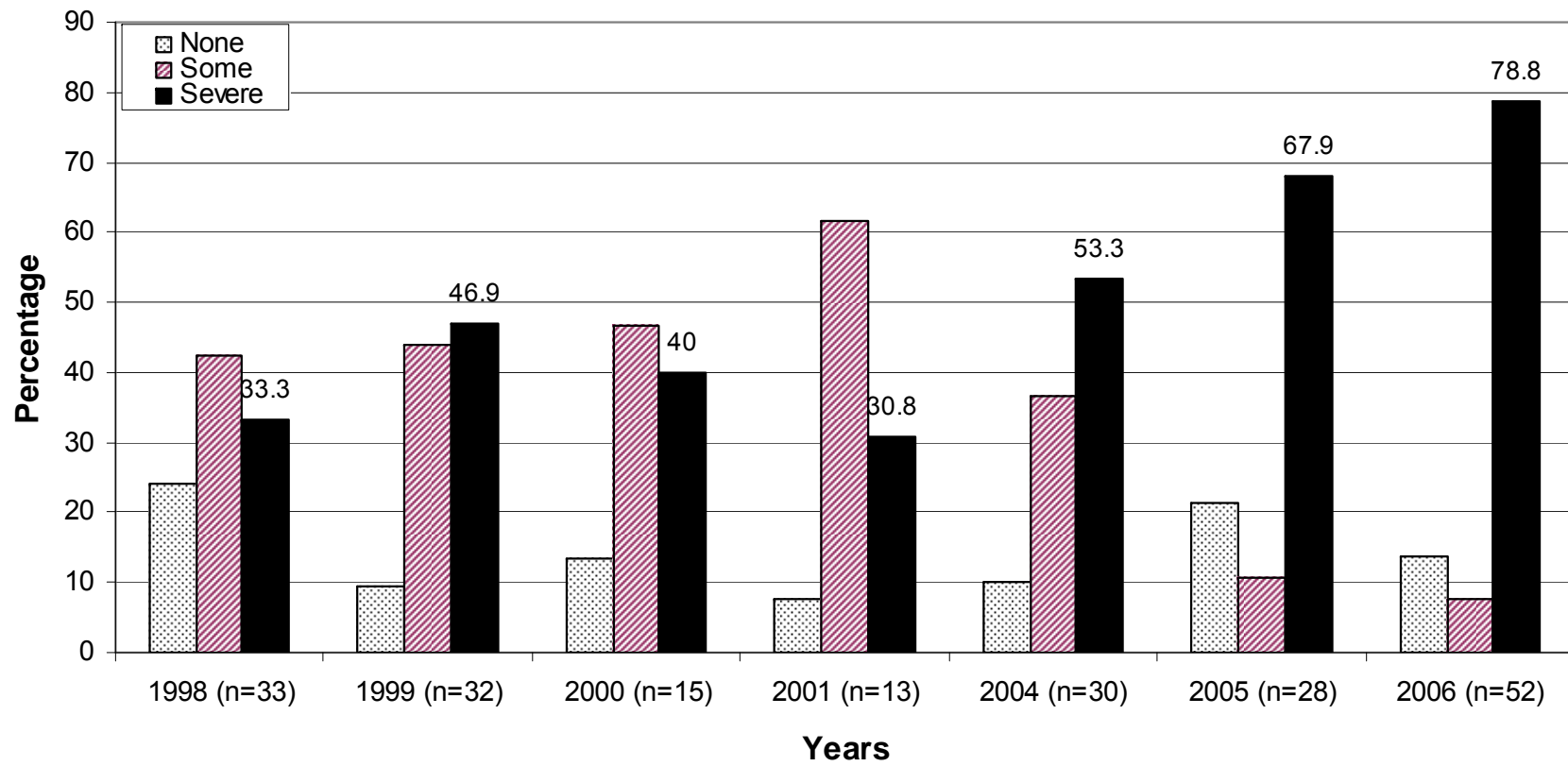
Source: Longini, I.M., et al., *J Infect Dis* **186**, 246-251 (2002).

# Correlogram for Inaba and Ogawa serotypes over the 33 year period 1966-1998, Matlab, Bangladesh



Source: Longini, I.M., et al., *J Infect Dis* **186**, 246-251 (2002).

**Dehydration status of *V. cholerae* O1 biotype El Tor infected patients in Bakerganj:  
1998 - 2001 and 2004 - 06**



# 8<sup>th</sup> Cholera Pandemic

- El Tor vibrio with Classical toxin



2004 – 2008



FEB 28 2005



FEB 28 2005











# Study Design

- Simultaneous clinical and environmental surveillance every 15 days, at four sites:
  - began in March, 1997 at Matlab and Chhatak
  - began in June, 1997 at Bakerganj and Chaugaucha

# Methods: Clinical Surveillance

- Each site visited for three days by two physicians
- All patients seen with watery diarrhea admitted into study
- Stool culture for *V. cholerae*

# Environmental Surveillance

Four surface waters (ponds, lakes, rivers)  
sampled at each clinical site

- *V. cholerae* identification

Culture

DNA probes to identify cholera toxin-producing organisms

- Zooplankton and phytoplankton, identification & enumeration
- Environmental parameters (physical, coliforms)

# Methods: Statistical Analyses

## Quantifying Associations Between Environmental Variables and Cholera Outbreaks

Goal: Build a regression model to

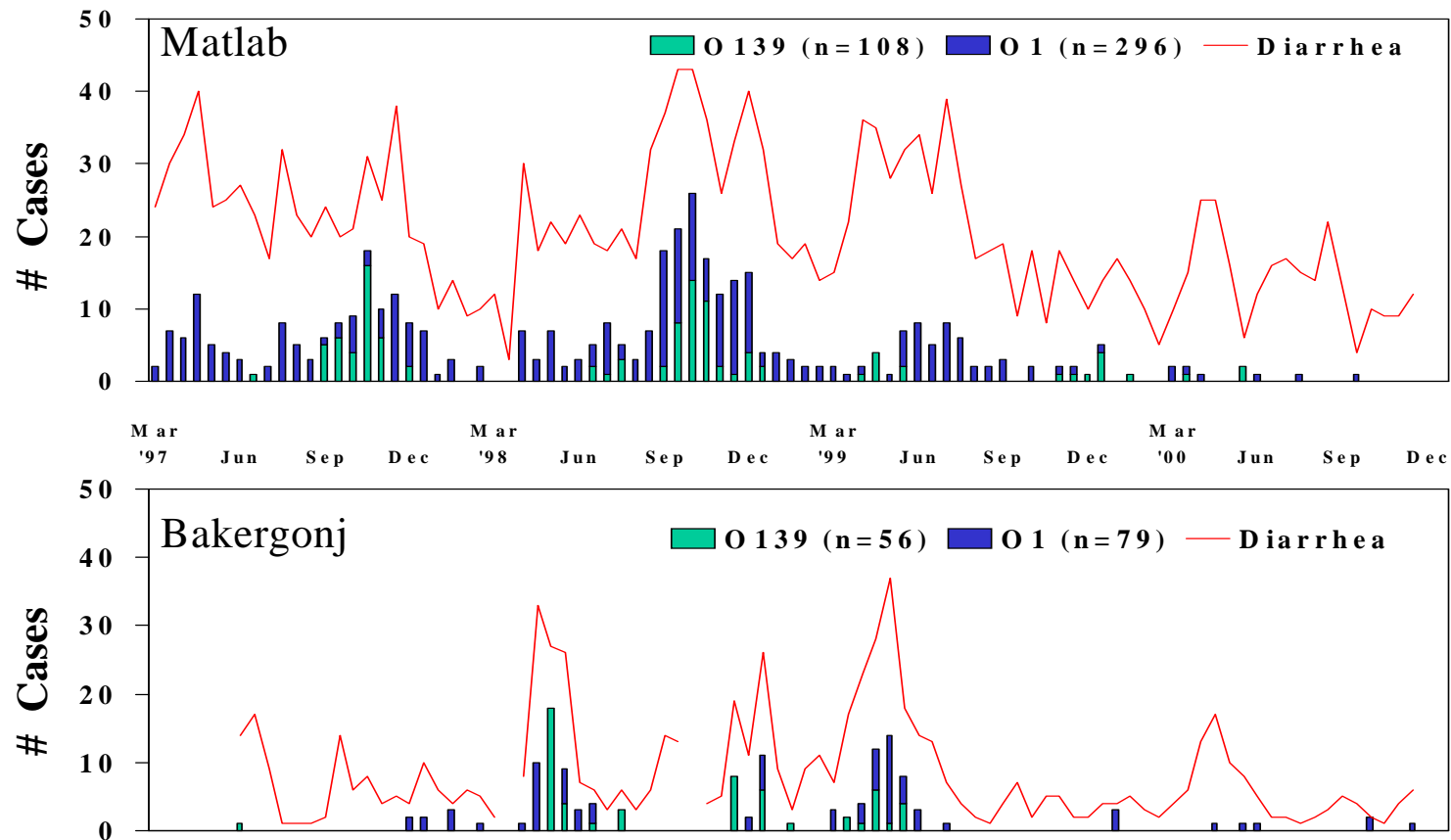
- identify environmental variables that are associated with occurrence of cholera cases in humans, quantify associated risk
- identify time lag between changes in environmental variables and associated changes in # of cholera cases

# Methods: Statistical Analyses

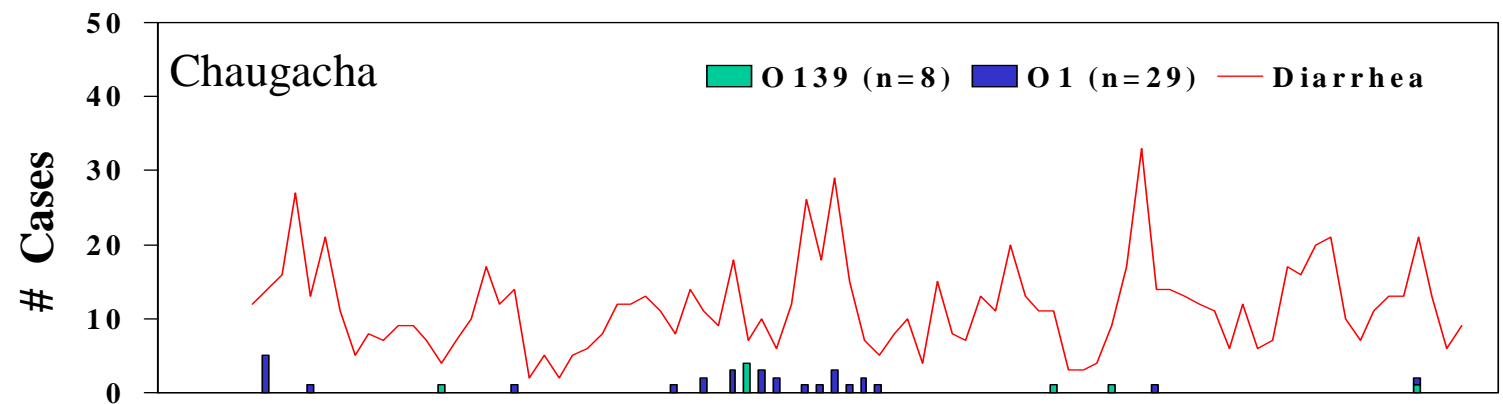
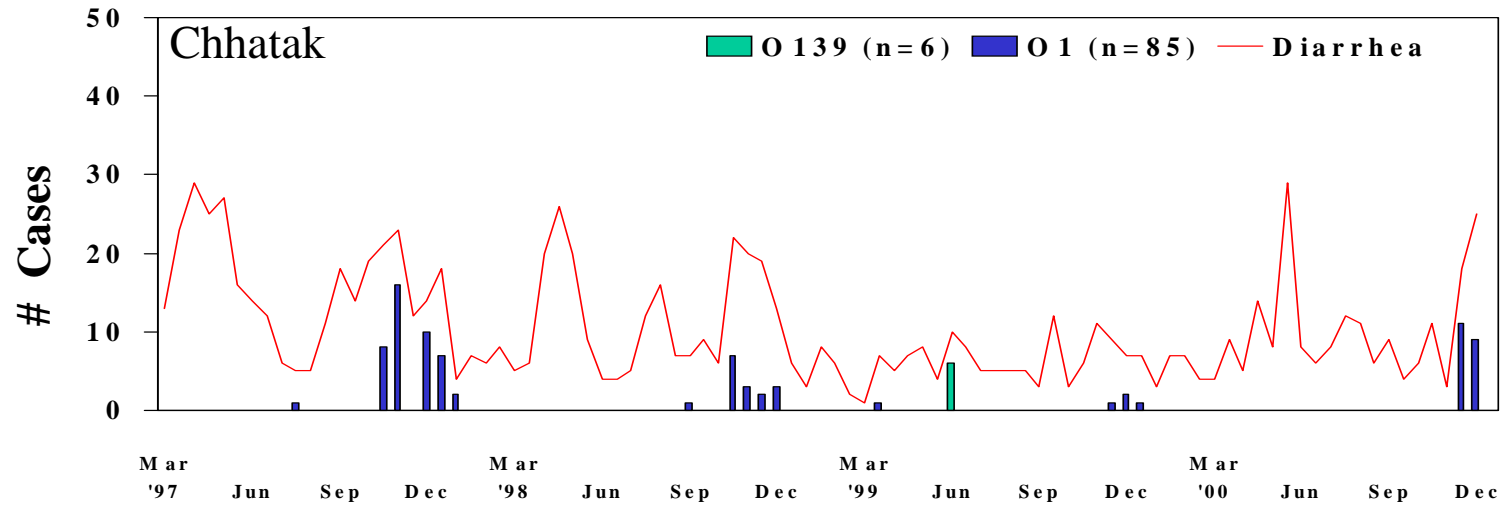
## Quantifying Associations Between Environmental Variables and Cholera Outbreaks

- Initial screening: lagged correlations between # of cholera cases & environmental variables
- Further screening: Stepwise regression of # of cases on lagged environmental variables
- Poisson regression of # of cholera cases on selected environmental variables; risk ratios quantifying change in risk of cholera associated with changes in environment.

# Cholera and Diarrhea Cases Over Time



# Cholera and Diarrhea Cases Over Time



# Results: Environmental Surveillance

<u>Variable</u>	<u>n</u>	<u>mean</u> <sup>1</sup>	<u>max</u> <sup>1</sup>	<u>% +</u>
Copepod Count	1022	1.7	4.4	54
Cyanobact. Ct.	1042	4.3	8.1	72
Probe Count	1013	1.0	4.5	26
Fecal Colif. Ct.	991	1.4	4.5	96

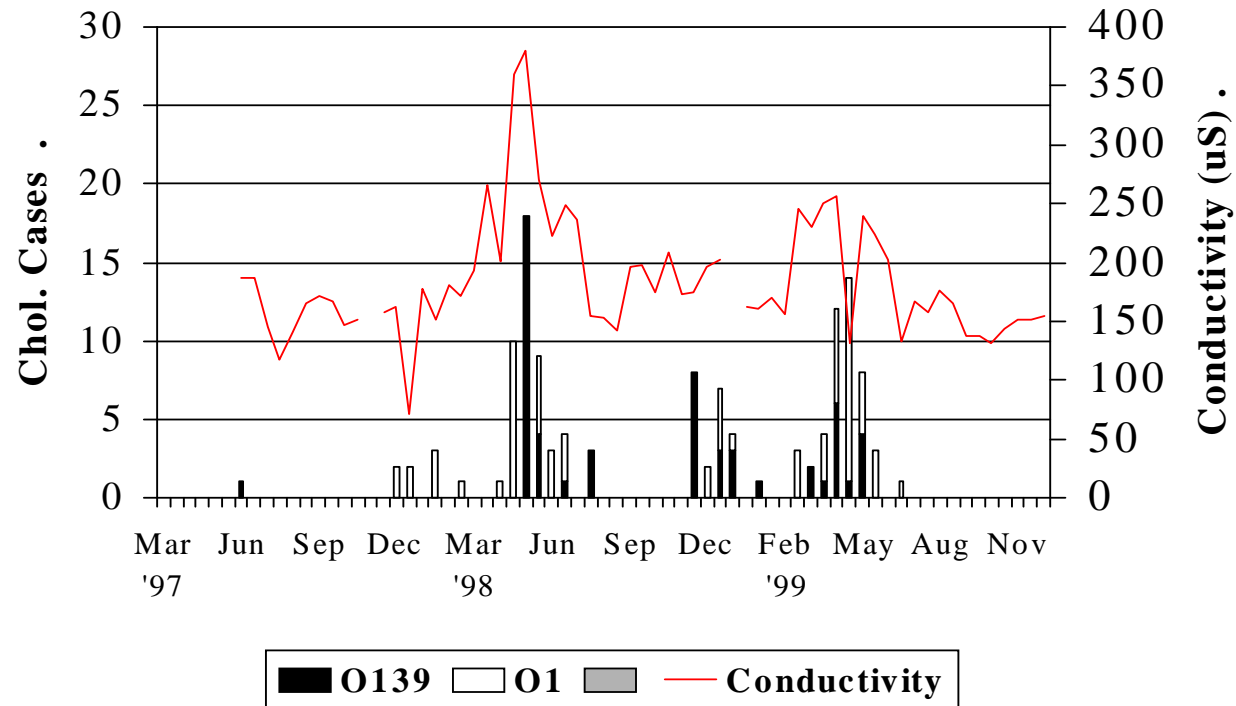
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1. Log scale

# Results: Environmental Surveillance

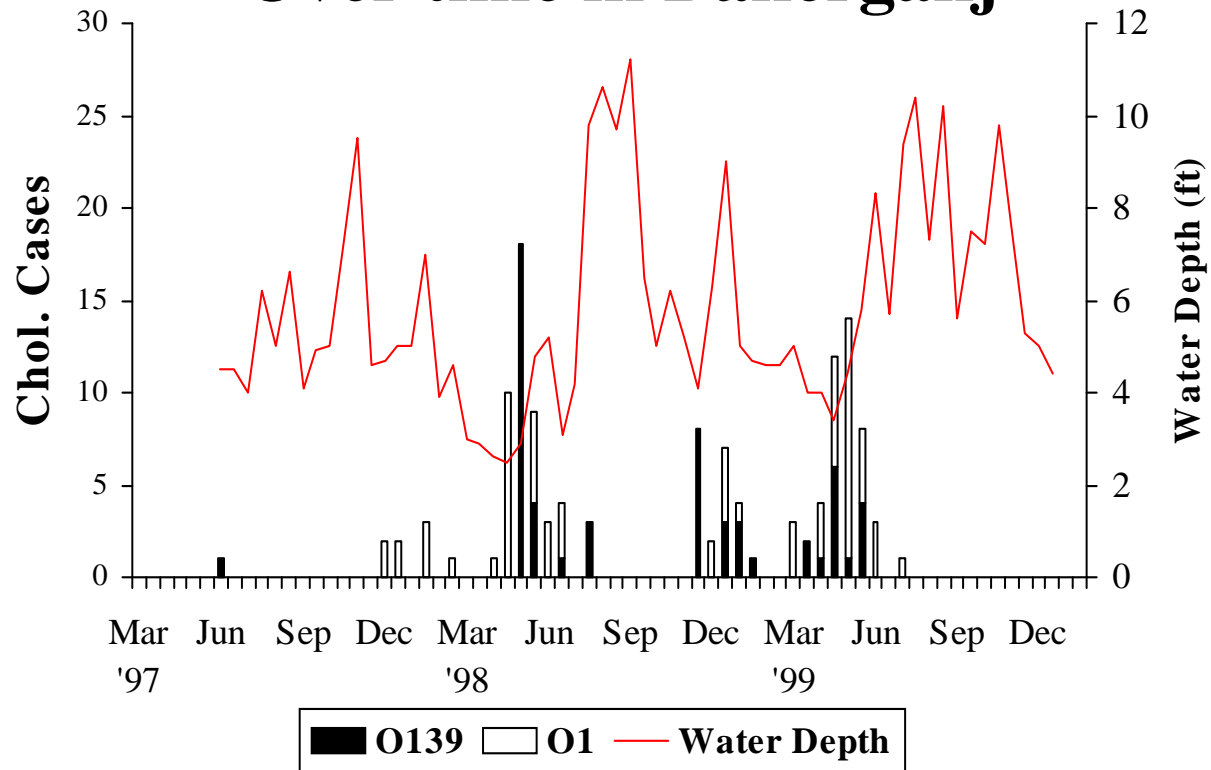
<u>Variable</u>	<u>n</u>	<u>mean (std)</u>	<u>min.</u>	<u>max.</u>
Conductivity( $\mu$ S)	1038	243 (220)	15	1568
Water Temp ( $^{\circ}$ C )	1038	28 (4)	16	38
Water Depth (ft)	1035	8 (6)	1	60
Air Temp. ( $^{\circ}$ C )	1038	28 (5)	15	39
pH	1029	7 (1)	5	9
Diss.O <sub>2</sub> (mg/l)	658	4 (4)	0	53
Salinity(ppt)	1008	.1 (.1)	0	1

# Cholera Cases and Lake Water Conductivity Over time in Bakerganj



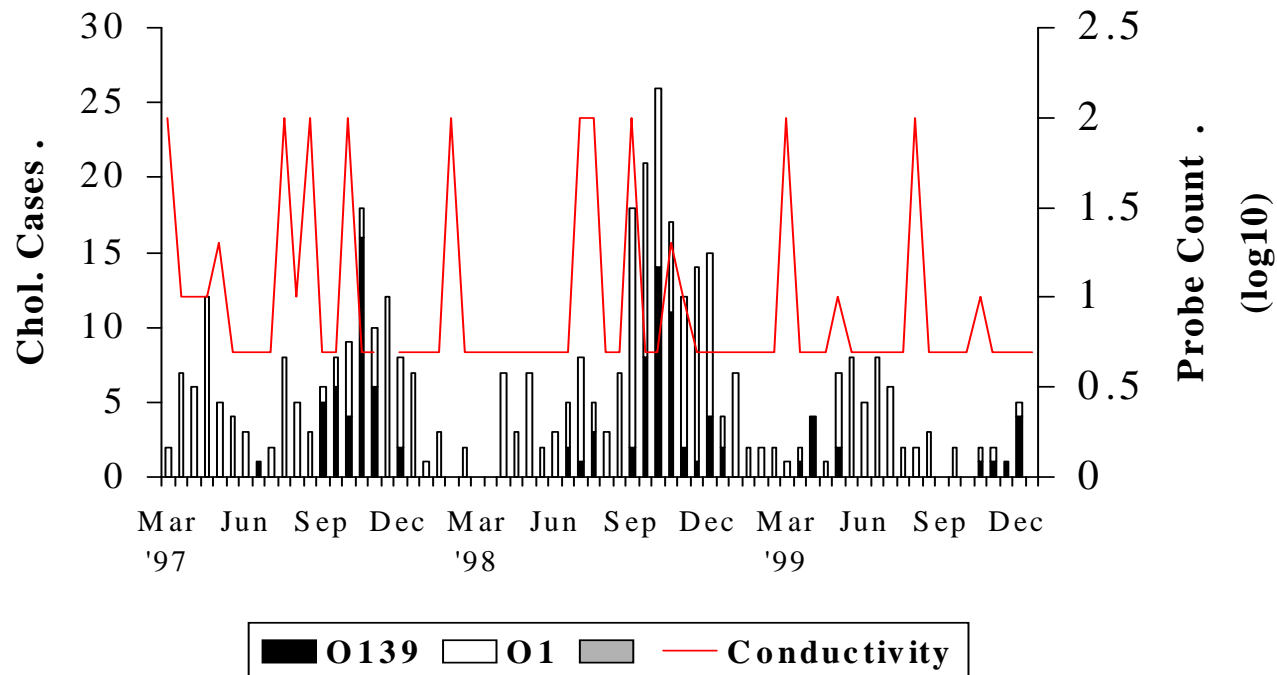
<u>Lag</u>	<u>Correlation</u>	<u>Lag</u>	<u>Correlation</u>
No lag	0.54	6 Weeks	0.43
2 Weeks	0.58	8 Weeks	0.15
4 Weeks	0.47		

# Cholera Cases and Pond Water Depth Over time in Bakerganj



<u>Lag</u>	<u>Correlation</u>	<u>Lag</u>	<u>Correlation</u>
No lag	-0.28	6 Weeks	-0.43
2 Weeks	-0.49	8 Weeks	-0.38
4 Weeks	-0.43		

# Cholera Cases and Lake Water Probe Results Over time in Matlab



<u>Lag</u>	<u>Correlation</u>	<u>Lag</u>	<u>Correlation</u>
No lag	0.02	6 Weeks	0.07
2 Weeks	0.15	8 Weeks	0.27
4 Weeks	0.10		

# Lagged Poisson Regression

Let  $Y_{it}$  be the number of reported cholera cases at time  $t$ , in area  $i$ . We assume that  $Y_{it}$  follows a Poisson distribution with mean  $\mu_{it}$ .

$X_{ijt}$  is the  $j^{\text{th}}$  predictor at time  $t$ , in area  $i$ .

$$\ln(\mu_{it} | X_{ijt}) = \beta_{0ij} + \beta_{1ij} X_{1ijt-\tau_{1ij}} + \beta_{2ij} X_{2ijt-\tau_{2ij}} + \dots + \beta_{kij} X_{kijt-\tau_{kij}},$$

$$t \geq \max\{\tau_{1ij}, \tau_{2ij}, \dots, \tau_{kij}\}.$$

# Regression results

- $RR_{ij}(\text{☺}) = \exp(\text{☹} \text{Ⓜ})$ 
  - ☹ goes with a lagged  $X_{ij}$
  - Ⓜ change in  $X_{ij}$
- Predictions and credibility intervals constructed using MCMC methods for Poisson regression

# Results: Poisson Regression

## Bakergonj River Predictors

<u>Variable (lag<sup>1</sup>)</u>	<u><math>\Delta</math></u>	<u>Risk Ratio for change of <math>\Delta</math> (95% CI)</u>
Conduct. (8)	+150 $\mu$ S	1.3 (1.2, 1.3)
Copepods (0)	+10	1.4 (1.2, 1.7)

- 
1. Lag, in weeks, between a change of  $\Delta$  units in the environmental variable and a subsequent change in the number of cholera cases.

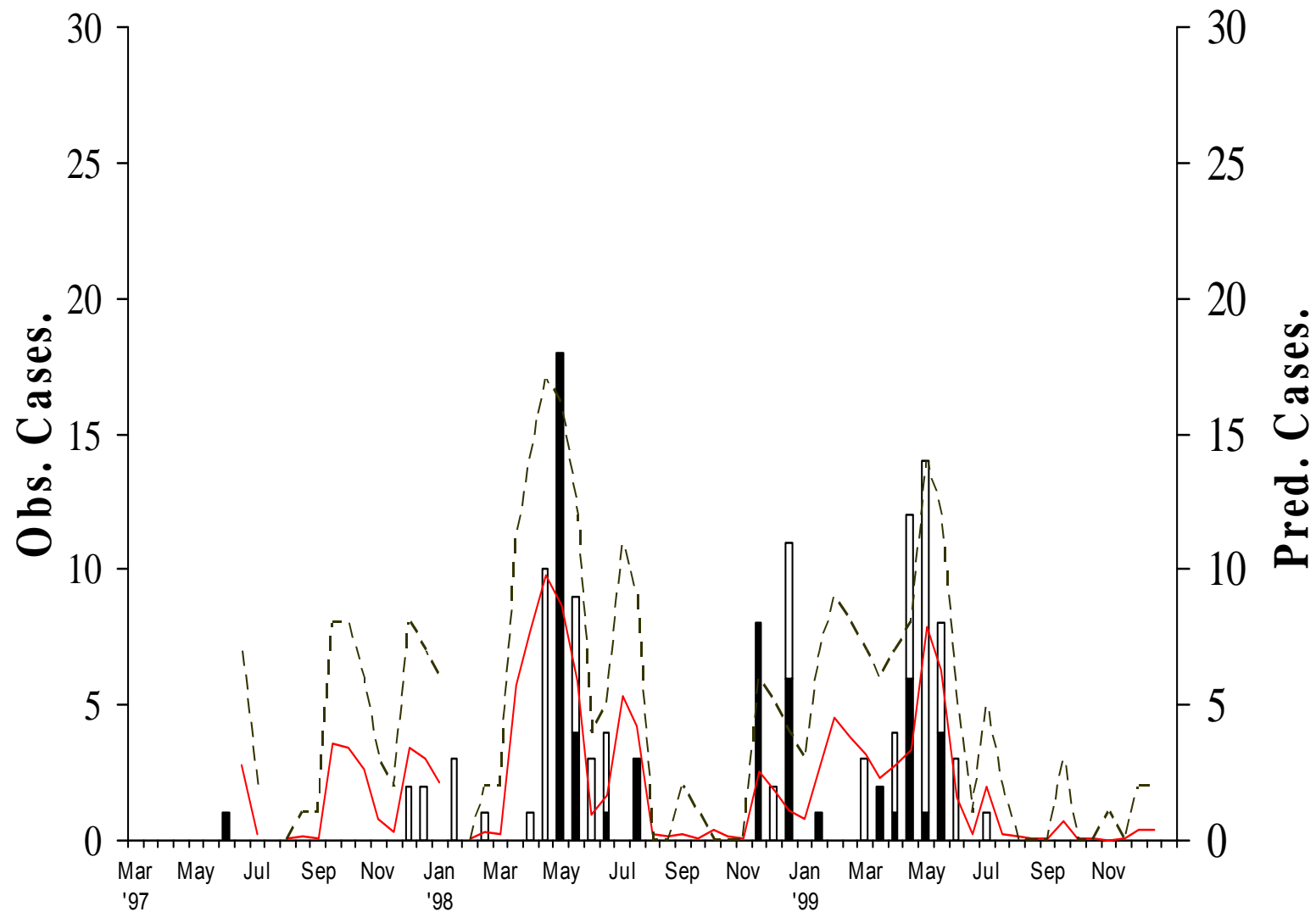
# Poisson Regression Results: Bakergonj Lake 2 Predictors

<u>Variable (lag)</u>	<u><math>\Delta</math></u>	<u>Risk Ratio for change of <math>\Delta</math> (95% CI)</u>
Conduct. (4)	+150 $\mu$ S	4.1 (2.6, 6.6)
PH (8)	+1	1.7 (1.3, 2.2)
Cyanobact. (2)	+10	1.9 (1.6, 2.3)

# Poisson Regression Results: Bakergonj Pond Predictors

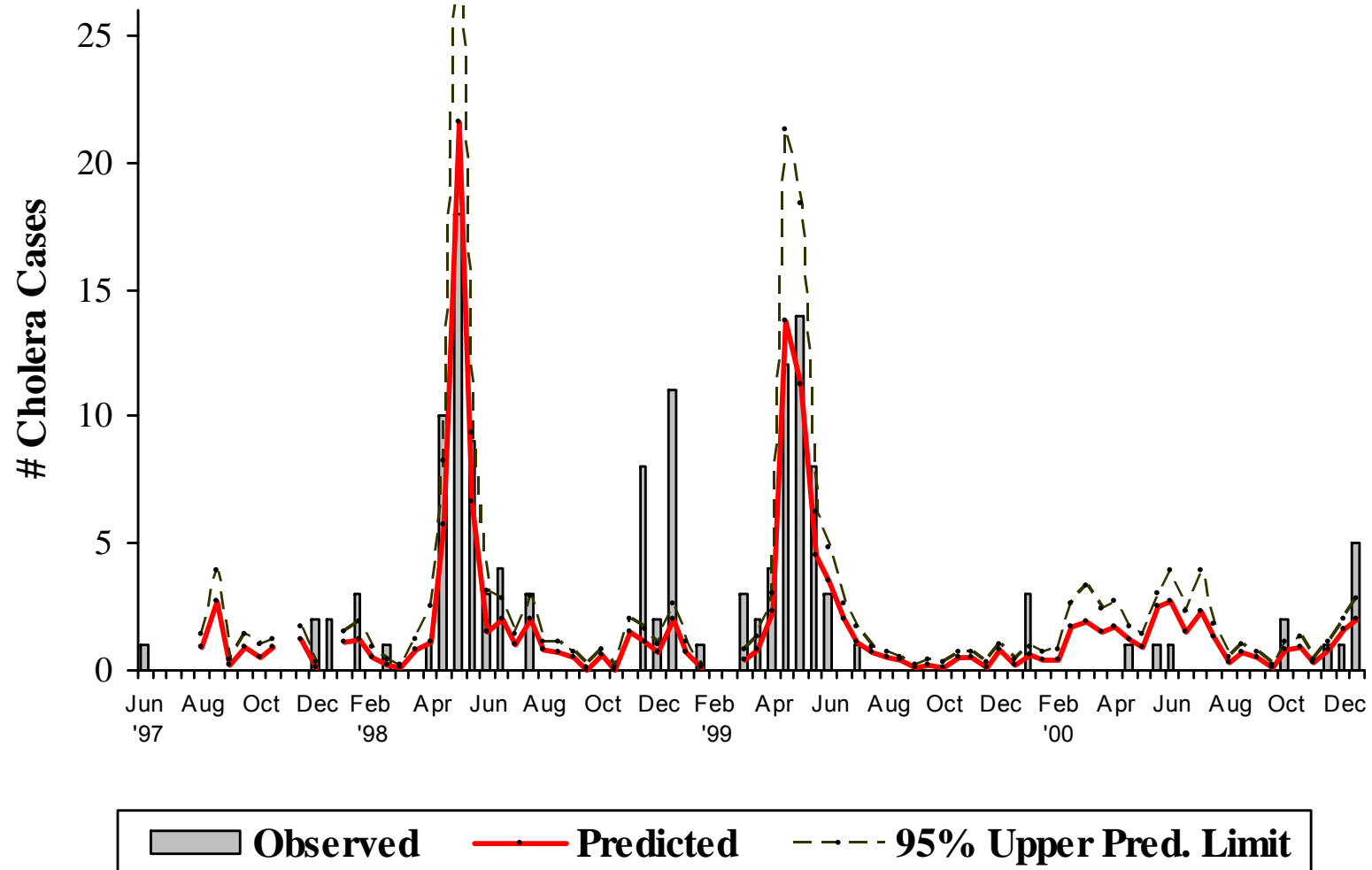
<u>Variable (lag)</u>	<u><math>\Delta</math></u>	<u>Risk Ratio for change of <math>\Delta</math> (95% CI)</u>
Water Depth (2)	-2 ft.	2.5 (1.9, 3.3)
Copepods (2)	+10	2.2 (1.7, 3.0)

# Bakergonj Pond Predictors Water Depth (2) and Copepods (2)



**■ O139** **□ O1** **— Predicted** **- - - 95% Upper CI**

# One month prediction in Bakerganj lake using water temperature, ctx gene probe count, conductivity, and rainfall



...of Cholera Cases in Bakerganj.

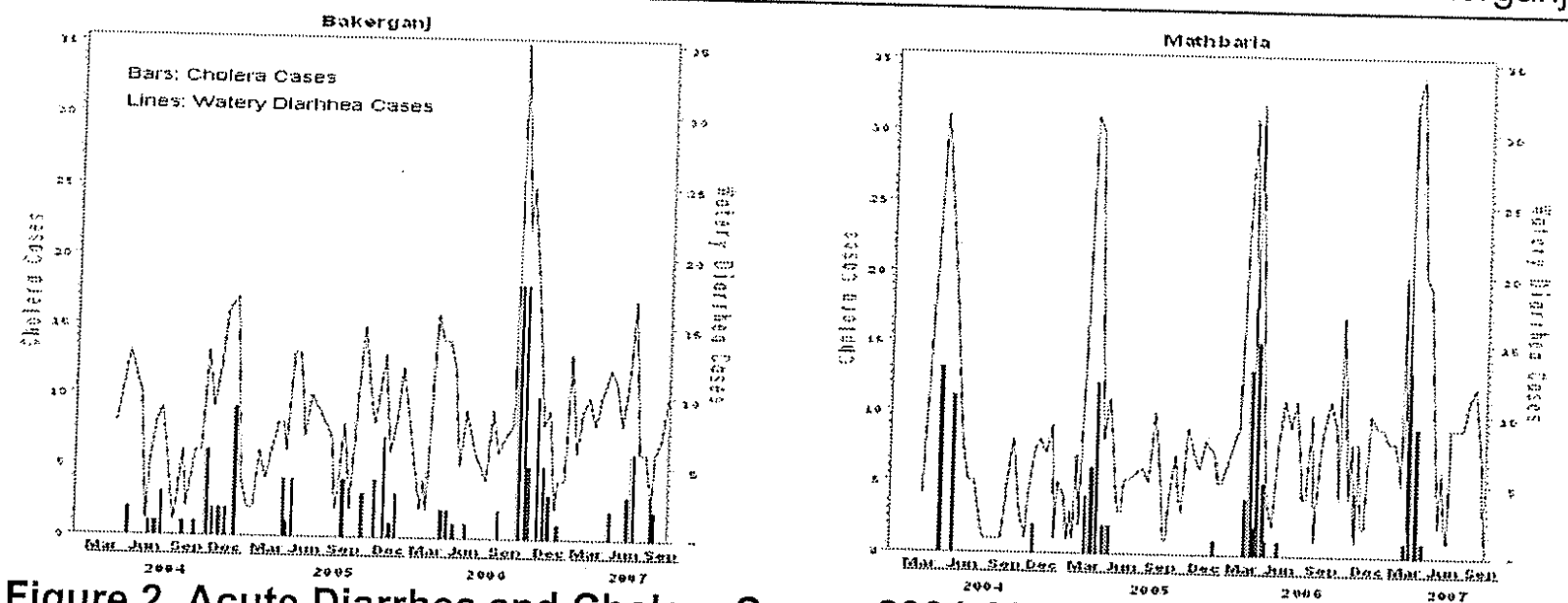


Figure 2. Acute Diarrhea and Cholera Cases, 2004-2007

**Table 1: Cholera Risk Ratios and 95% Confidence Intervals at Selected Sites**

Area	Site	Variable (lag, in weeks)	Risk Ratio Estimate for a change of $\Delta$	95% CI for Risk Ratio
Bakerganj	River	Water Depth (4)	1.3 ( $\Delta=-1$ ft)	(1.2, 1.4)
		Conductivity (4)	2.2 ( $\Delta=+150$ $\mu$ S)	(2.0, 2.5)
Mathbaria	Pond 2	Conductivity (1)	1.1 ( $\Delta=+150$ $\mu$ S)	(1.08, 1.14)
		Nauplii (1)	1.7 ( $\Delta=+100$ )	(1.5, 1.9)
		Water Depth (1)	2.2 ( $\Delta=-1$ ft)	(1.8, 2.6)
Mathbaria	Pond 3	Water Depth (1)	3.9 ( $\Delta=-1$ ft)	(2.9, 5.4)
		Water Temp. (1)	1.4 ( $\Delta=+5$ °C )	(1.0, 1.9)

# Summary: I

- Both *V. cholerae* O1 and O139 are widespread in Bangladesh
- Seasonal patterns of cholera are observed, but are not always identical in different locations
- Cholera outbreaks in different geographic areas may be synchronous
- Not all diarrhea outbreaks are cholera

# Summary: II

- The main environmental predictors of cholera outbreaks were:

Conductivity

Water depth

Concentrations of copepods

# Controlling Endemic Cholera With Killed Oral Vaccines

# RATIONALE

- Advances in dehydration therapy make case fatality rate low
- Still, estimated 150,000 deaths per year in most impoverished countries
- Licensed, oral killed whole-cell cholera vaccines (OCV) have been available for over a decade
  - 70% efficacy against disease
  - 2 years protection

# Weekly epidemiological record Relevé épidémiologique hebdomadaire

5 AUGUST 2005, 80th YEAR / 5 AOÛT 2005, 80<sup>e</sup> ANNÉE

No. 31, 2005, 80, 261–268

<http://www.who.int/wer>



## Contents

261 Cholera, 2004

**Cholera, 2004**

**Choléra, 2004**

“The role of OCVs as an additional public health tool to improve cholera control activities seems to be a promising strategy that needs to be further defined, especially for endemic settings.”<sup>4</sup>

4. Weekly Epidemiological Record, 5 August, 2005. World Health Organization.

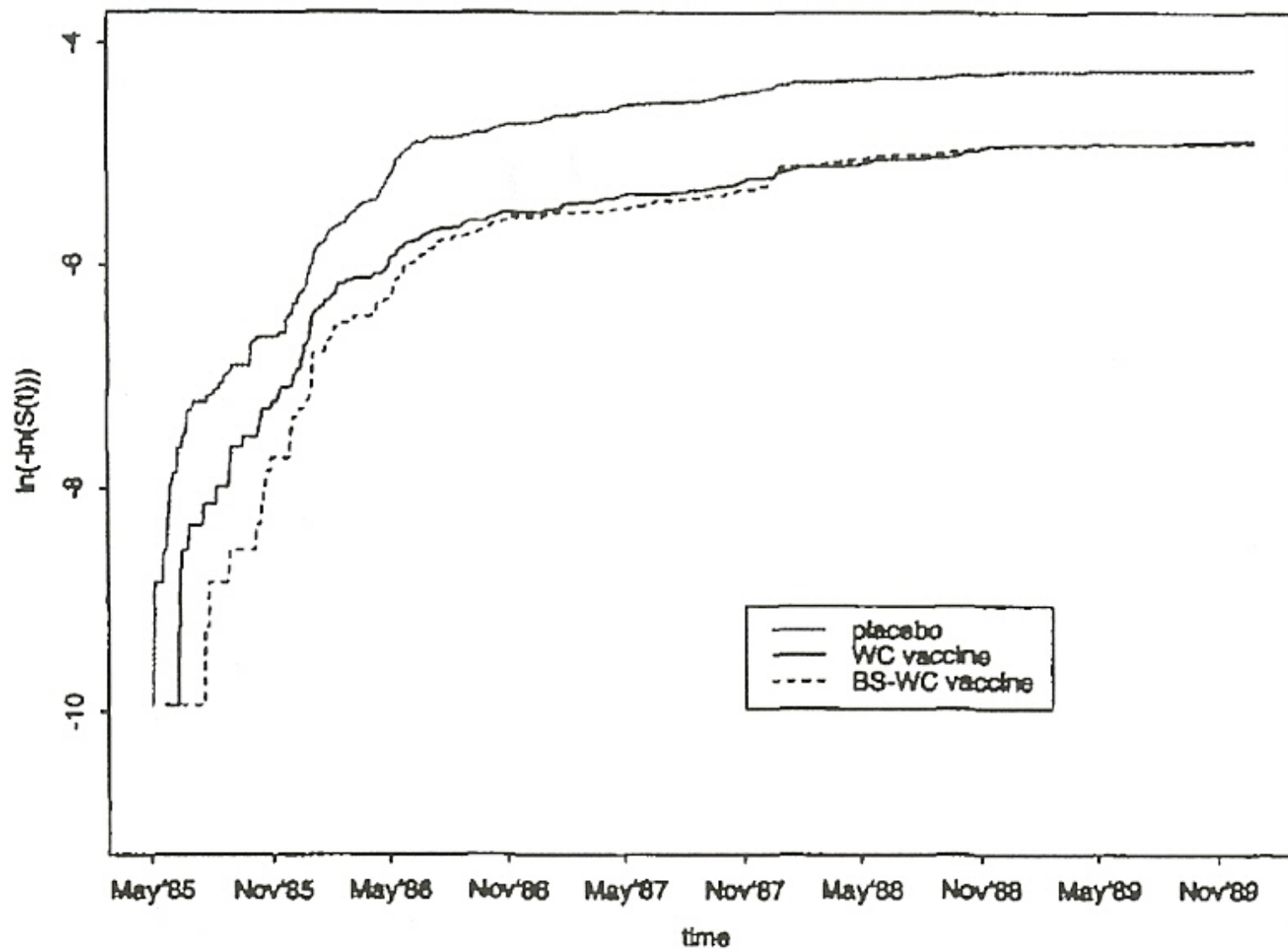
# Introduction



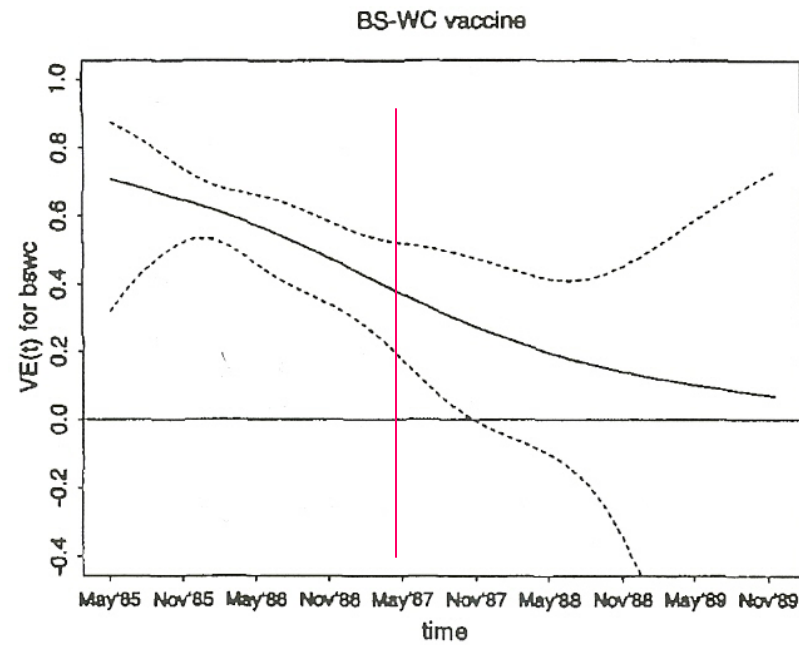
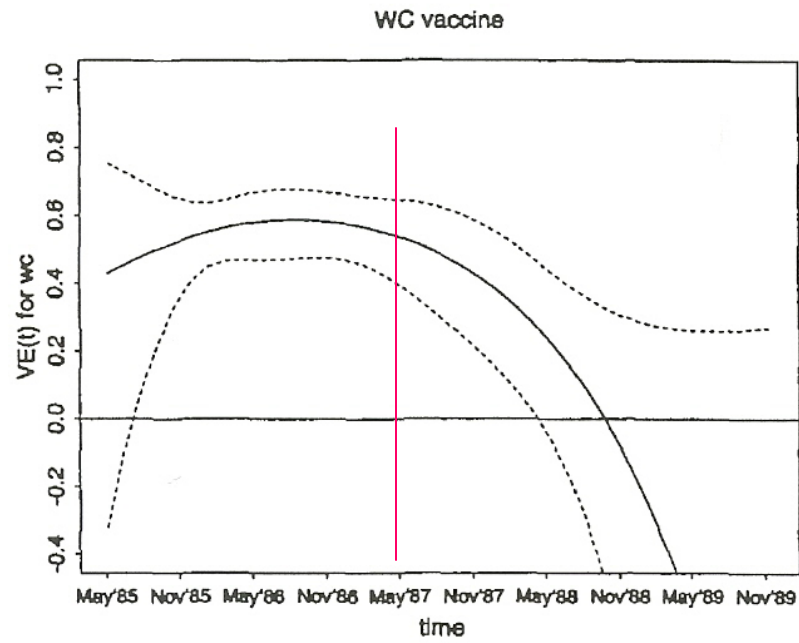
- Studies have shown that orally administered killed cholera vaccines are safe and protective
- Vaccines have not been adopted for use in most endemic regions due to cost and efficacy concerns

# Recent Analysis

- Mid 1980's randomized vaccine trial with OCV in Matlab, Bangladesh
  - 183,826 subjects
  - Current GIS mapping
  - Ali, M et al. Herd immunity conferred by killed oral cholera vaccines in Bangladesh: a reanalysis. *Lancet* **366**, 44 - 49 (2005).
  - Durham, L.K., Longini, I.M., Halloran, et al.: Estimation of vaccine efficacy in the presence of waning: Application to cholera vaccines. *American Journal of Epidemiology* **147**, 948-959 (1998).



Source: Durham, E.K., Longini, I.M., Halloran, M.E., Clemens, J.D., Nizam, A. and Rao, M.: *Am J Epidemiol* **147**, 948-959 (1998).



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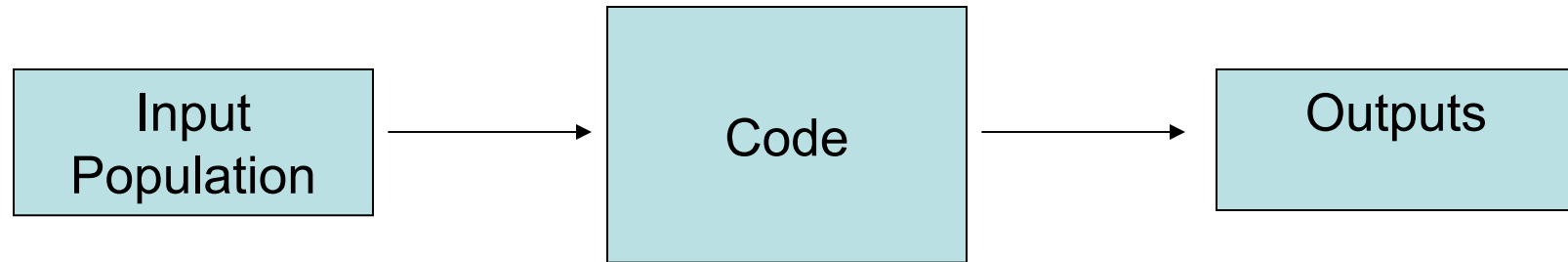
# Endemic Cholera

- Cholera always present
- Triggering events cause outbreaks
  - Sack RB et al. . A 4-Year Study of the Epidemiology of *Vibrio cholerae* in Four Rural Areas of Bangladesh. *J Infect Dis*, (2003).
  - Huq et al. Critical factors influencing the occurrence of *Vibrio cholerae* in the environment of Bangladesh. *Applied and Environmental Biology* (2005).

# Goals of Simulation Model

- Calibrate to historical attack rate and vaccine effectiveness data
- Simulate use of cholera vaccine at various coverage levels, study effectiveness measures
- Longini, I.M., Nizam, A., Ali, M., Yunus, M., Shenvi, N., Clemens, J.D.: Controlling endemic cholera with oral vaccines. (In preparation)

# Simulator Overview



- Population of Matlab in 1985

- ANSI c code models cholera natural history and community level transmission

- Developed on unix. Portable

- 1000 runs per simulation

- Illness attack rates

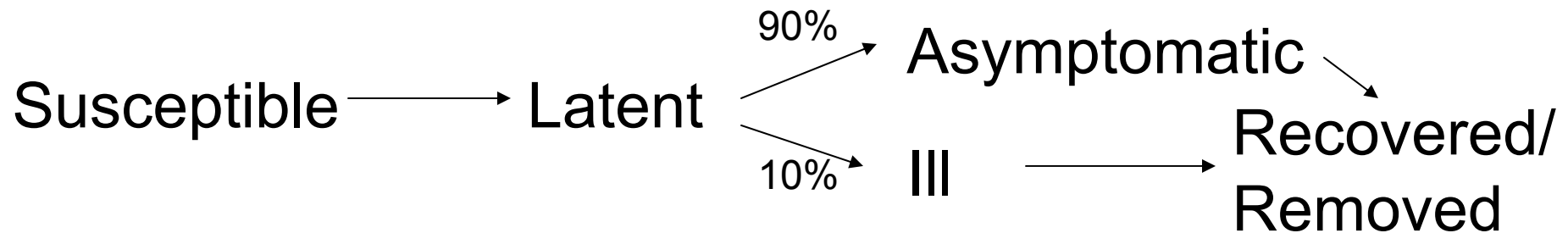
- Effectiveness measures

- Spatial distribution of cholera cases

# Simulator Elements

- Disease natural history model and parameters
- Community-level transmission of cholera infection
- Matlab population demographics (age, gender, location, travel within Matlab)
- Historical illness attack rate data for model calibration

# Cholera Natural History



In each subpopulation, on any given day of the epidemic, there is a probability of infection, determined by an infection function (next slide)

1 day: 40%  
2 days: 40%  
3-5 days: 20%

Uniform distribution  
7-14 days

## Additional assumptions:

- Ill shed at 10 times the rate of asymptomatics
- Working males:
  - circulate  $\geq 1$  day
  - Pr(withdrawal after ill) = 0.75

# Infection Function

The probability that a susceptible person will be infected in a particular location on day  $t$  is:

$$f = \left[ 1 - (1 - \theta^x bp)^{n_{uv}(t)} (1 - \theta^x \phi bp)^{n_v(t)} \right]$$

Where

$p$  = transmission probability

$\Theta$  =  $1 -$  vaccine efficacy against susceptibility ( $VE_s$ )

$x$  = 1 if susceptible is vaccinated, 0 if unvaccinated

$b$  = seasonal boost factor for first month

$n_{uv}(t)$  = # unvacc. infectious people

$n_v(t)$  = # vacc. infectious people

$\Phi$  =  $1 -$  vaccine efficacy against infectiousness ( $VE_i$ )

# Model Calibration

## Model input parameters

$p:$  0.000009

$b:$  10

$VE_s:$  0.7

$VE_i:$  0.5

Number of initial infectives: 5

Probability of withdrawal given ill: 0.75

Probability asymptomatic: 0.9

# Population Characteristics

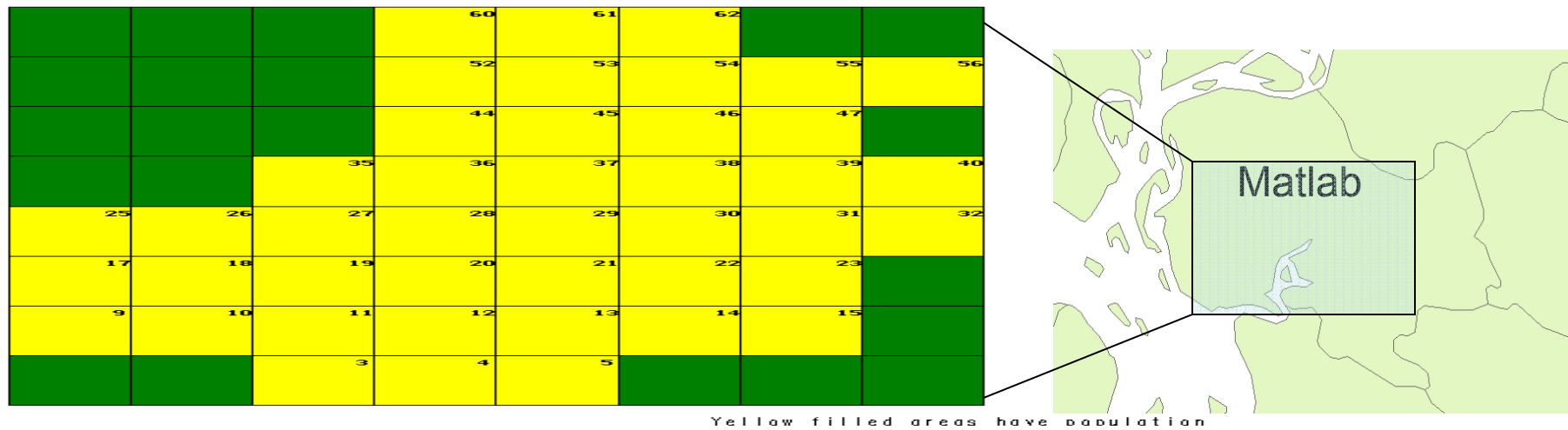
- 183,826 subjects from Matlab
- 50.5% Female 49.5% Males
- Geographic map
  - Bari code
  - X,Y coordinates
  - Age on 1/1/1985
- Vaccinated where children 2 – 15 years old and women > 15 years old.

# Population Characteristics

## Matlab “Grid”

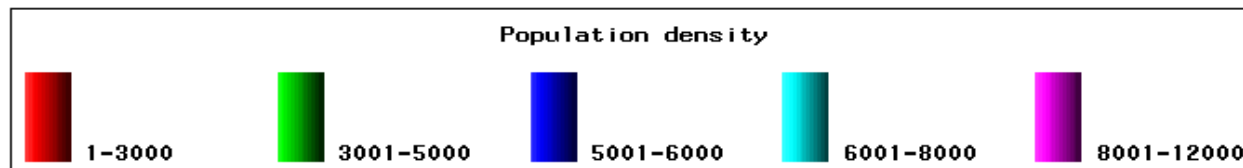
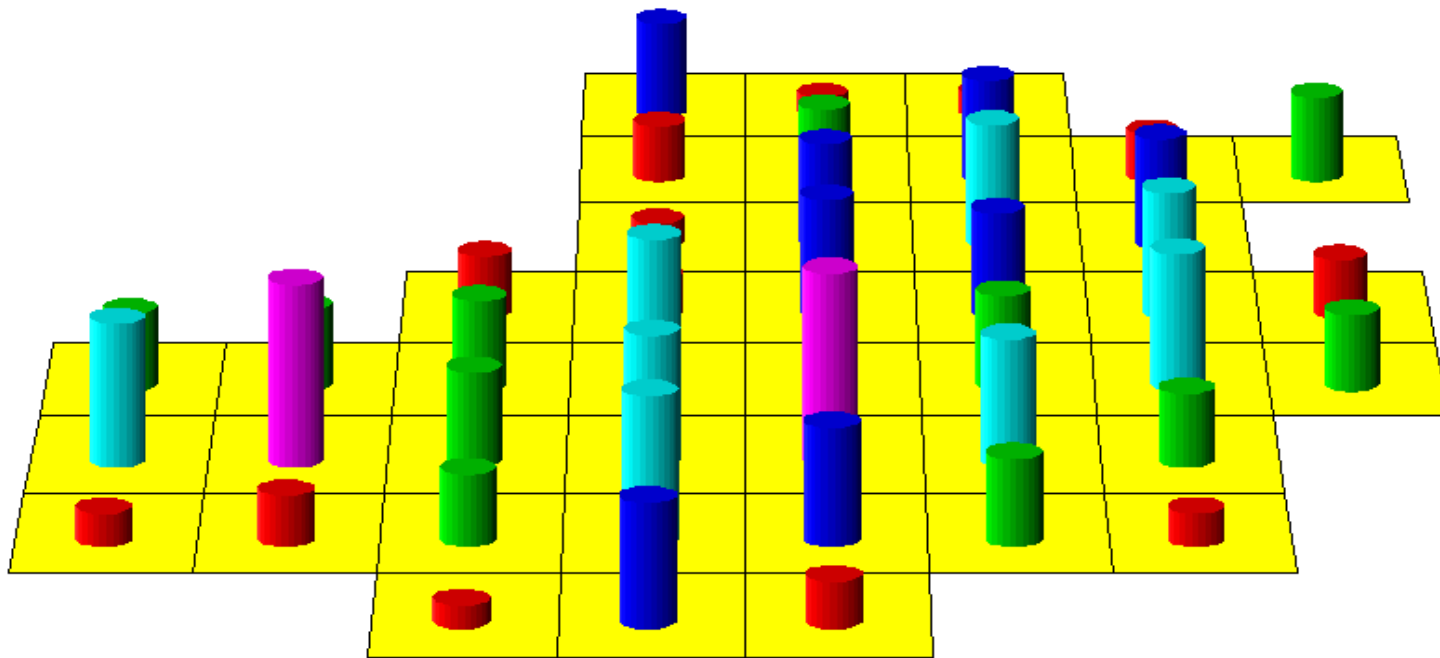
- Matlab area mapped to 64 ‘sub-regions’
- Each subject mapped to one of the sub-regions based on the GIS location

Matlab Location Map



# Population Characteristics

## Distribution of Population Across the Grid



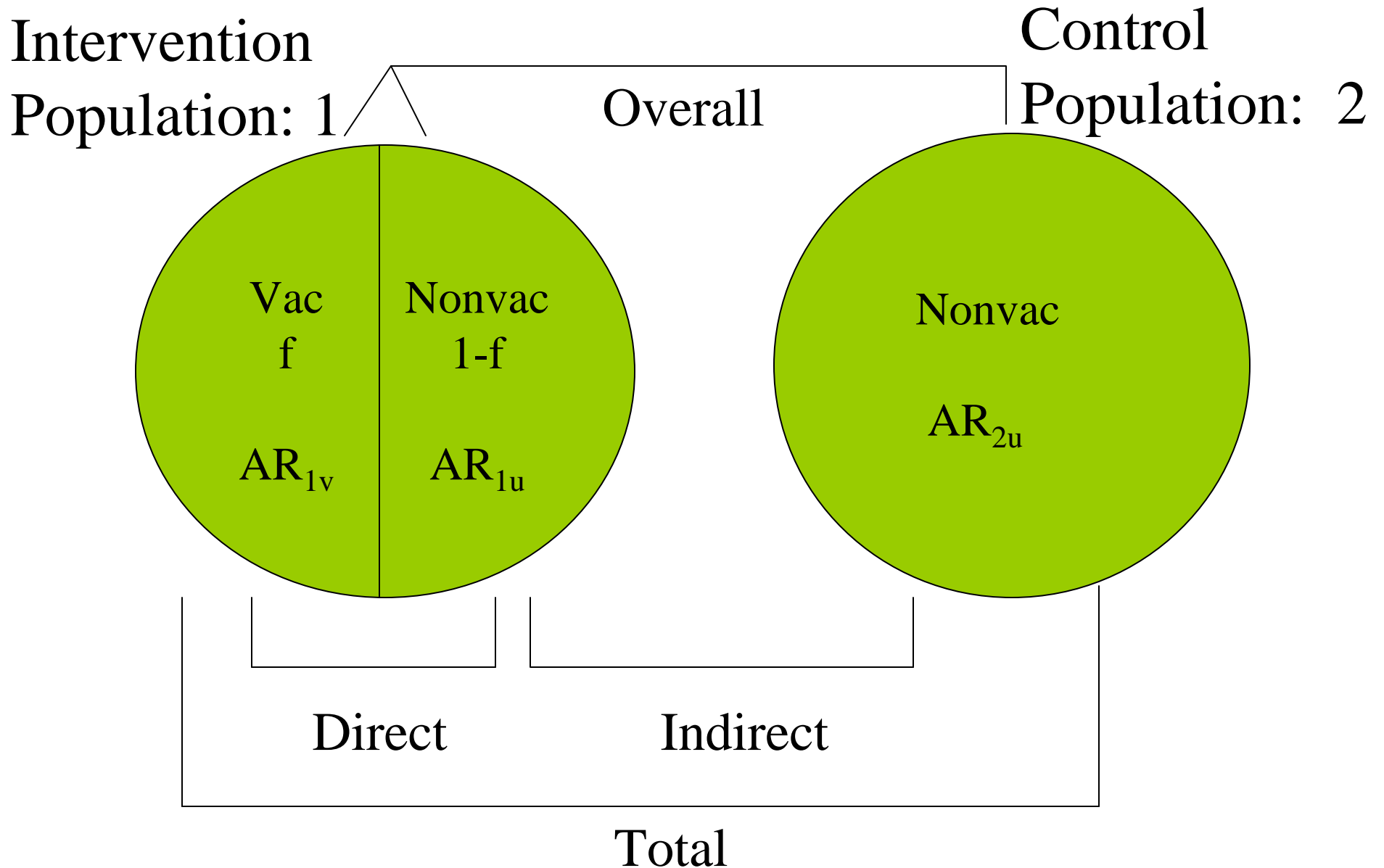
# Population Characteristics

## Connectivity Between Sub-regions

- Males over 16 years old, and 50% of males between 14 -16 years old were randomly assigned a work sub-region according to the following distance function:
  - 55% work and reside in same sub-region
  - 35% work 4-10km away from residence sub-region
  - 10% work >10km away<sup>4</sup>

4. Distance function derived from time traveled to school reported in Matlab Health and Socioeconomic Survey dataset, 1996. <http://www.icpsr.umich.edu/>

# Vaccine Effectiveness



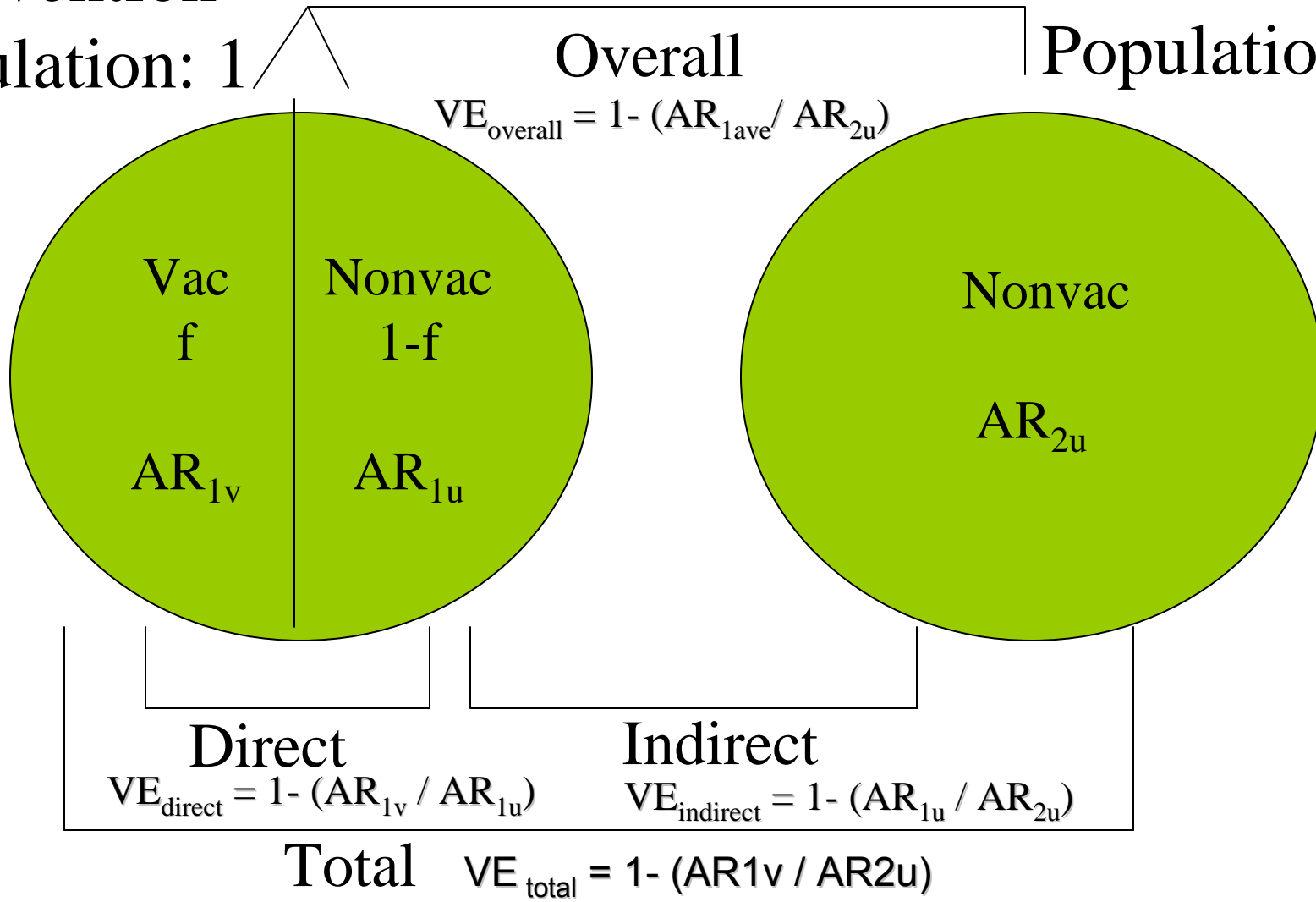
# Vaccine Effectiveness

Intervention

Control

Population: 1

Population: 2



# Vaccine Effectiveness

$$VE_{\text{direct}} = 1 - (AR_{1v} / AR_{1u})$$

$$VE_{\text{indirect}} = 1 - (AR_{1u} / AR_{2u})$$

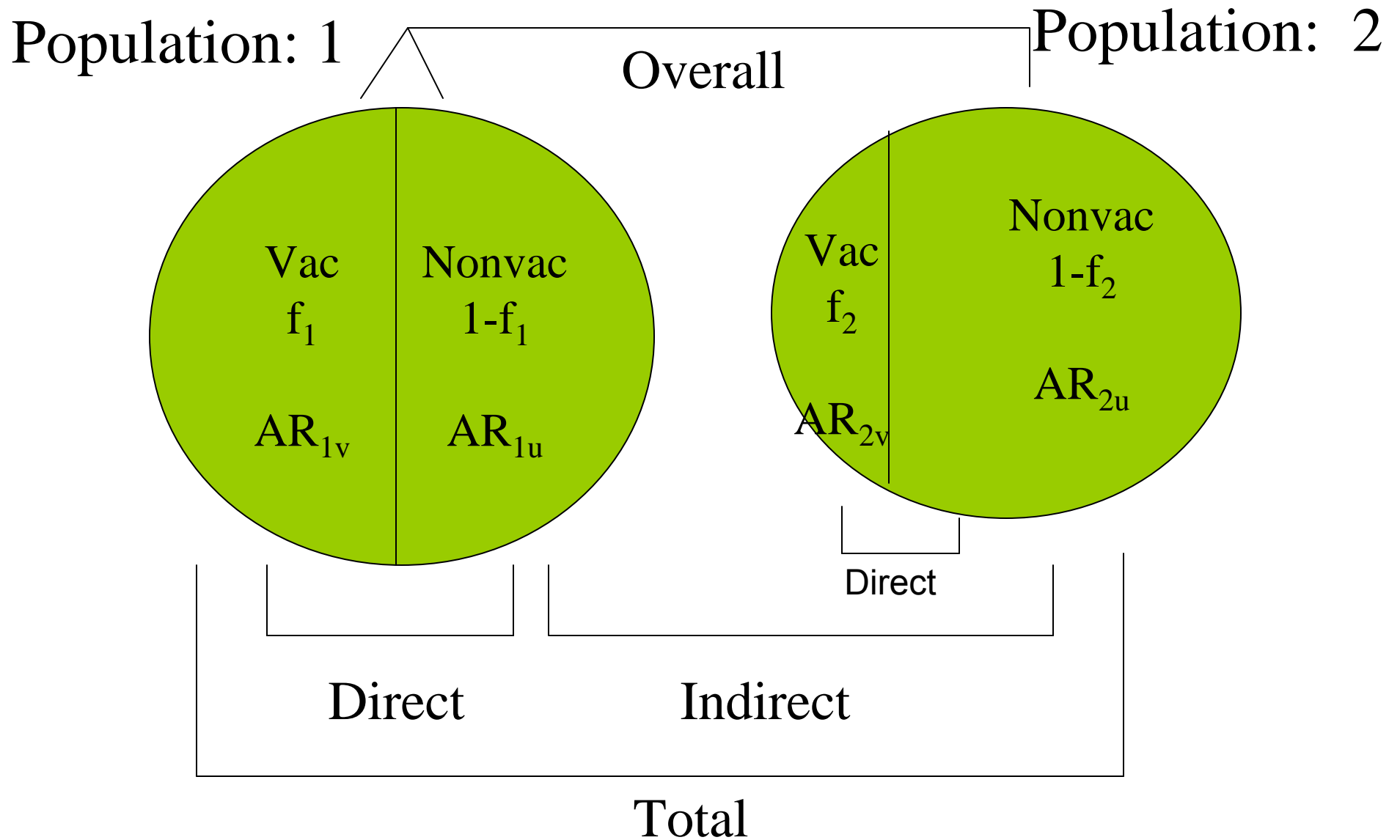
$$VE_{\text{total}} = 1 - (AR_{1v} / AR_{2u})$$

$$VE_{\text{overall}} = 1 - (AR_{1\text{ave}} / AR_{2u})$$

where  $AR_{1\text{ave}} = f AR_{1v} + (1 - f) AR_{1u}$

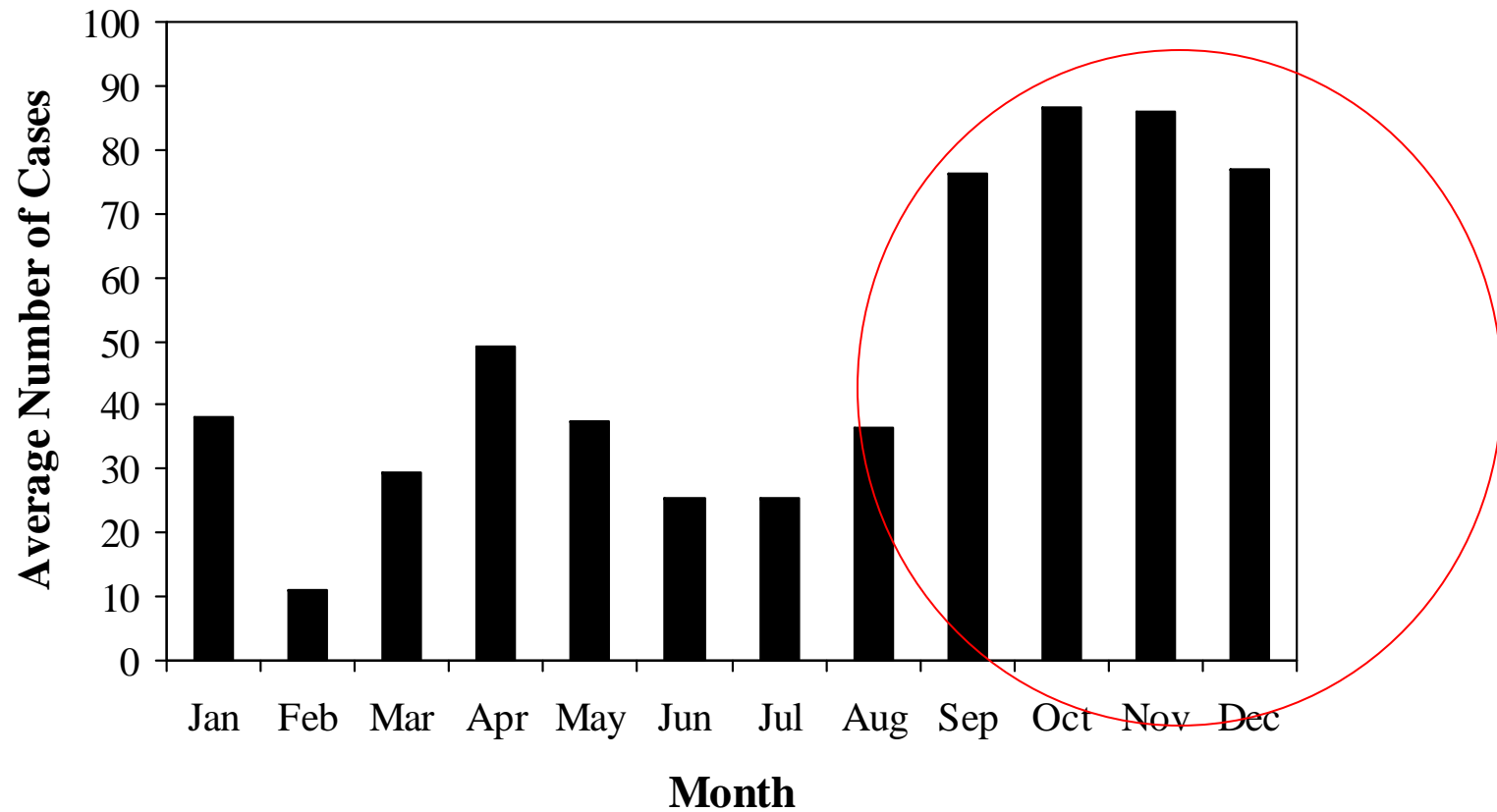
Halloran, *et al.*, *Am J Epidemiol* **146**, 789-803 (1997)

# Vaccine Effectiveness Gradient



# Model Calibration

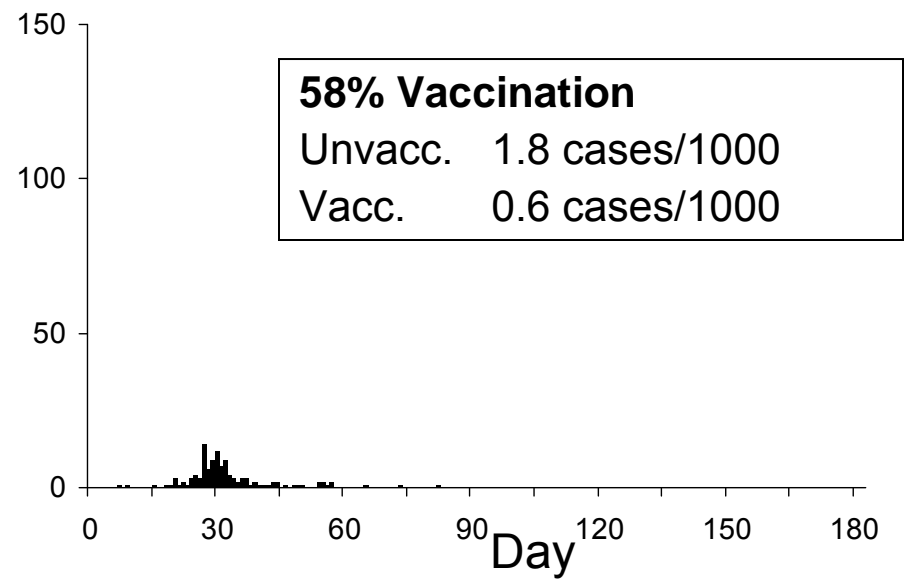
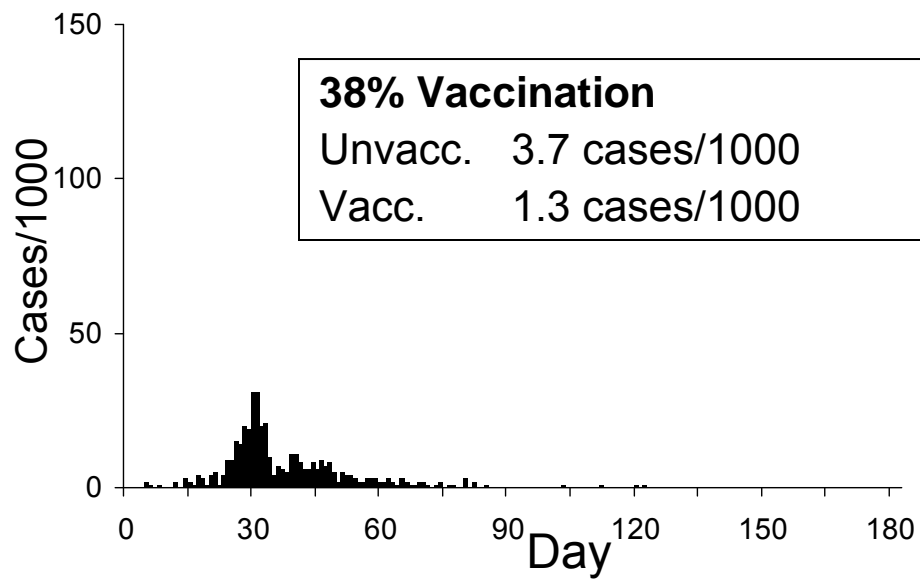
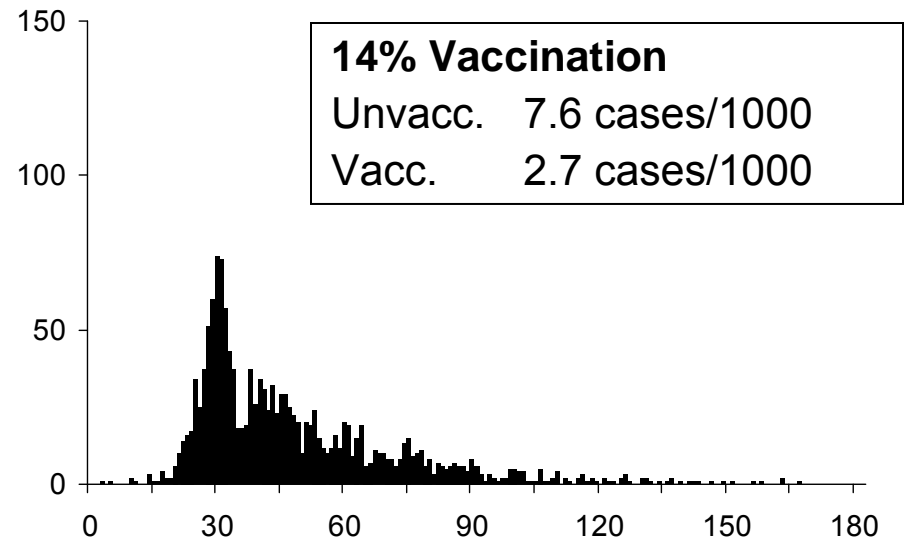
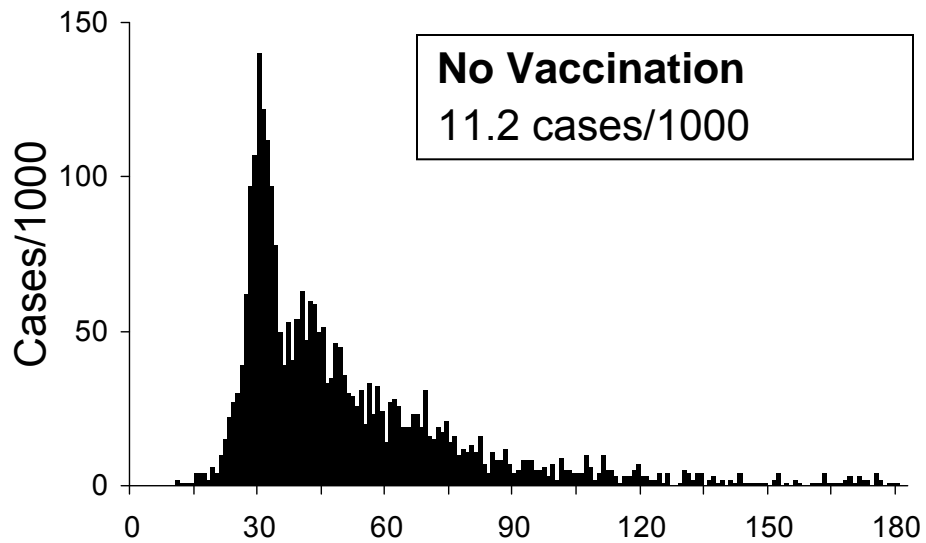
- Annual autumn/winter outbreaks in Matlab



## Vaccination Coverages, Average Incidence Rates and Direct Effectiveness (Calibration Runs)

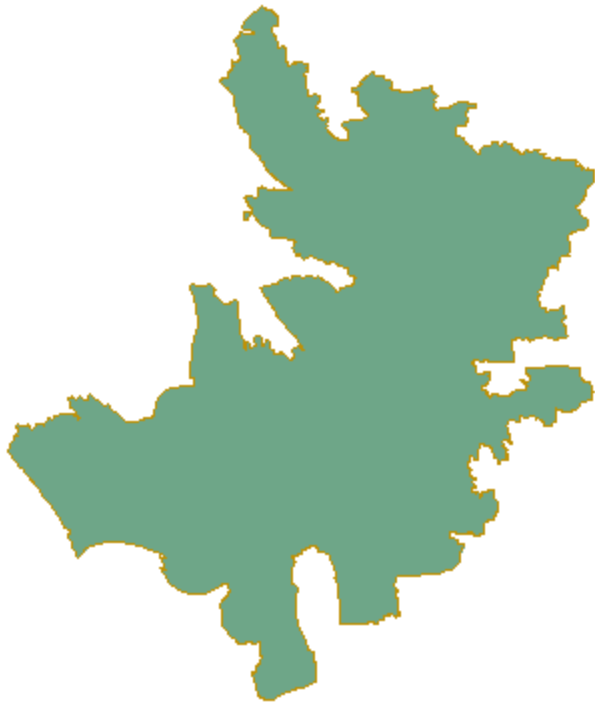
Vaccination Coverage (%)		Mean Cases/1000 (95% CI)				Mean Direct Effectiveness (%) (95% CI)	
		Placebo		Vaccinated		Observed	Simulated
Target Population	Overall Population	Observed	Simulated	Observed	Simulated		
14	9	7.0 (6.5, 7.5)	7.8 (1.9, 14.8)	2.7 (1.9, 3.5)	2.8 (0.5, 6.1)	62	65 (52, 77)
31	20	5.9 (5.4, 6.4)	4.7 (0.9, 10.2)	2.5 (2.0, 3.0)	1.7 (0.3, 3.8)	58	65 (55, 76)
38	25	4.7 (4.2, 5.2)	3.8 (0.8, 8.6)	1.6 (1.2, 2.0)	1.3 (0.2, 3.4)	67	65 (54, 77)
46	30	4.7 (4.2, 5.2)	2.8 (0.5, 6.8)	2.3 (1.9, 2.7)	1.0 (0.1, 2.5)	52	66 (54, 79)
58	38	1.5 (1.2, 1.8)	1.8 (0.3, 4.8)	1.3 (1.0, 1.6)	0.6 (0.1, 1.8)	14	66 (51, 80)

$\chi^2$  goodness-of-fit test for frequency data  $p = 0.84$



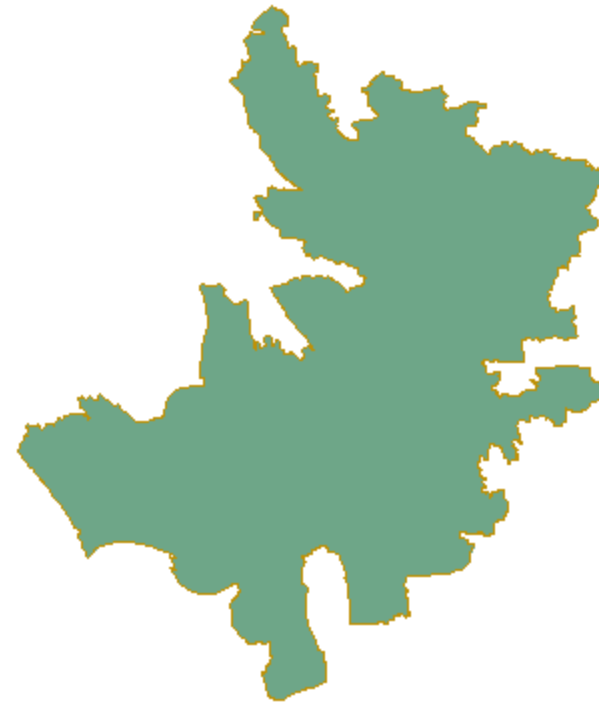
### Mass Vaccination: 0 % Day 1

Red: Ill Yellow:Recovered



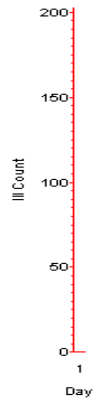
### Mass Vaccination: 58 % Day 1

Red: Ill Yellow:Recovered



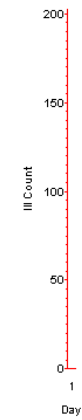
#### Epidemic curve: Day 1

Mass Vaccination:0 %



#### Epidemic curve: Day 1

Mass Vaccination:58 %

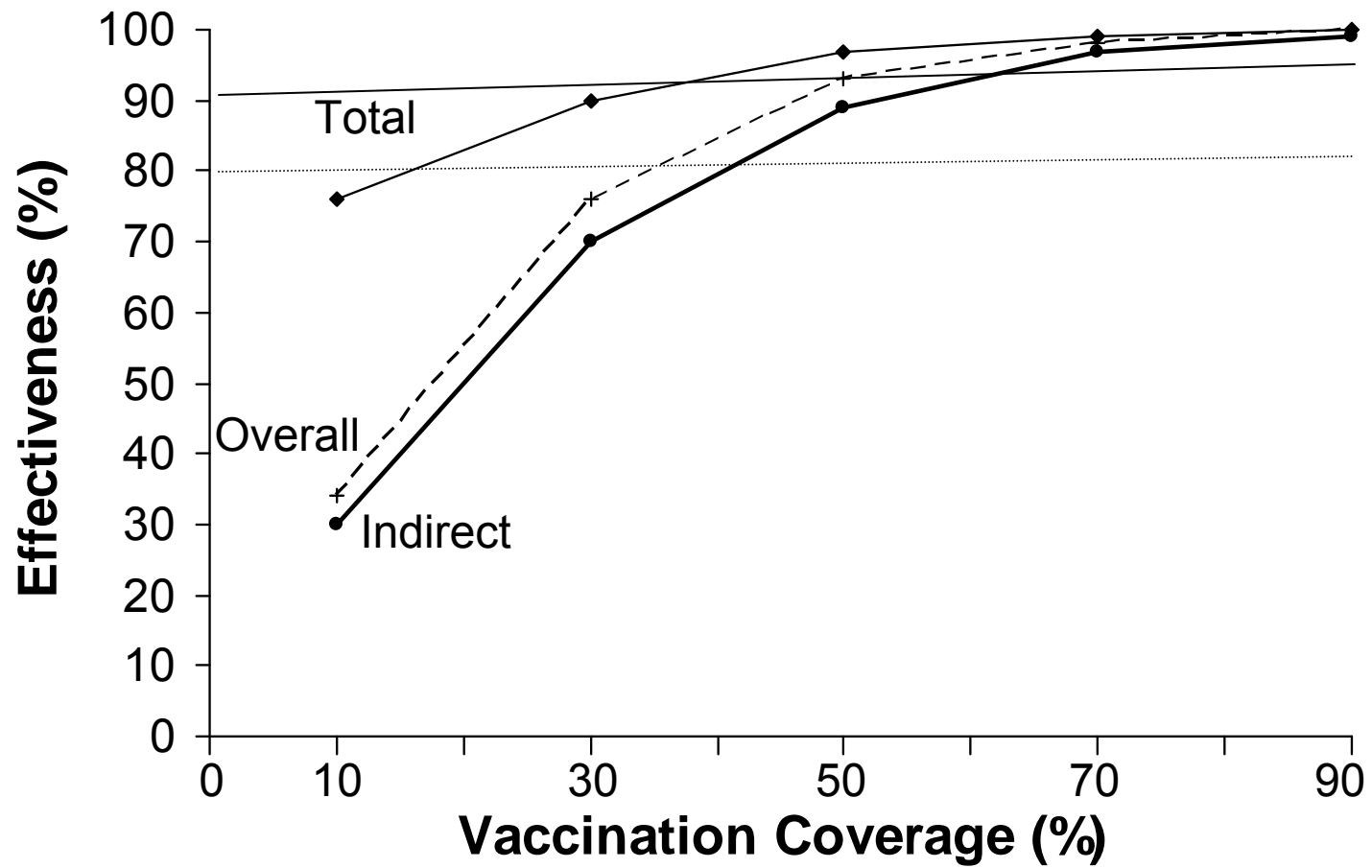


International Vaccine Institute  
Dedicated to preventing infectious diseases through science



Average Indirect, Total and Overall Effectiveness of Vaccination,  
and Cases Prevented 10,000 Per Doses

Vaccination Coverage (%)	Mean Effectiveness (%) (95%CI)			Mean # Cases Prevented per 10,000 Doses
	Indirect	Total	Overall	
10	30 (-39, 83)	76 (47, 95)	34 (-30, 84)	50
30	70 (31, 93)	90 (76, 98)	76 (44, 95)	40
50	89 (72, 98)	97 (91, 99)	93 (82, 99)	30
70	97 (91, 99)	99 (97, 100)	98 (95, 100)	20
90	99 (98, 100)	100 (99, 100)	100 (99, 100)	20



# Recommendations

- For endemic cholera
  - Should have at least 50% coverage
  - Vaccinate people every two years
  - If vaccine is limited, conduct environmental surveillance to target vaccination programs
  - Randomized community vaccine trial
- For epidemic cholera
  - Mobile stockpile of cholera vaccine
  - More work is needed to determine best vaccination strategy
    - Simulations

# Randomized Community Trial

- Paired control and vaccinated communities (at least 10 pairs).
- Or at least a gradient in coverage
- Could expand the WHO/IVI trial in Mozambique to do this
- Need study of environmental predictors of cholera in Africa



The End