Using serology to measure incidence of recent *Vibrio cholerae* O1 infection

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with

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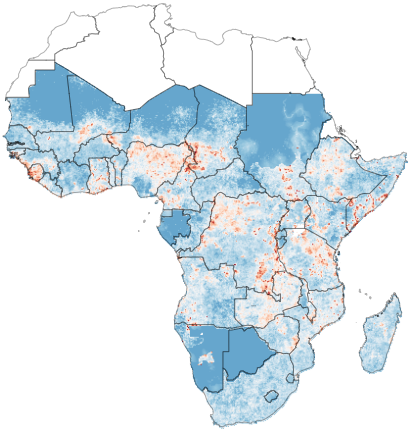
GTFCC Surveillance and Epi WG Meeting :: 15 April 2018

Outline

Cholera Risk and Burden

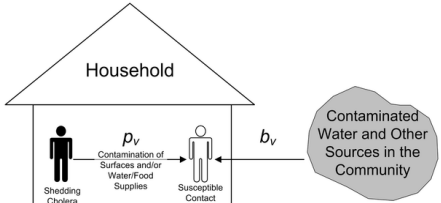


Lessler et al, 2018, The Lancet

OCV Effectiveness and Impact

WASH Effectiveness and Impact

Transmission Dynamics



Sugimoto et al, 2015, PLoS NTD

Dreams of a perfect serologic marker

- Numeric threshold of a single serologic biomarker to identify those 'recently' infected
- Low variability in antibody response to infection between people (e.g., age, infection inoculum, severity, co-morbidities)
- Cheap, simple and rapid assay

A Serological Survey for Cholera Antibodies in Rural East Pakistan

1. The Distribution of Antibody in the Control Population of a Cholera-vaccine Field-trial Area and the Relation of Antibody Titre to the Pattern of Endemic Cholera *

W. H. MOSLEY,[1] A. S. BENENSON [2] & R. BARUI

Incomplete Correlation of Serum Vibriocidal Antibody Titer with Protection from *Vibrio cholerae* Infection in Urban Bangladesh

Debasish Saha,[1,*] Regina C. LaRocque,[2,3,*] Ashraful I. Khan,[1] Jason B. Harris,[2,3] Yasmin Ara Begum,[1] Syed M. Akramuzzaman,[1,†] Abu S. G. Faruque,[1] Edward T. Ryan,[2,3,5] Firdausi Qadri,[1] and Stephen B. Calderwood[2,3,4]

Seroepidemiological Studies of El Tor Cholera in Bangladesh: Association of Serum Antibody Levels with Protection

Roger I. Glass,* Ann-Mari Svennerholm, M. R. Khan, Shamsul Huda, M. Imdadul Huq, and Jan Holmgren

From the International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh; and the Department of Medical Microbiology, University of Göteborg, Göteborg, Sweden

Frequency of Reexposure to *Vibrio cholerae* O1 Evaluated by Subsequent Vibriocidal Titer Rise after an Episode of Severe Cholera in a Highly Endemic Area in Bangladesh

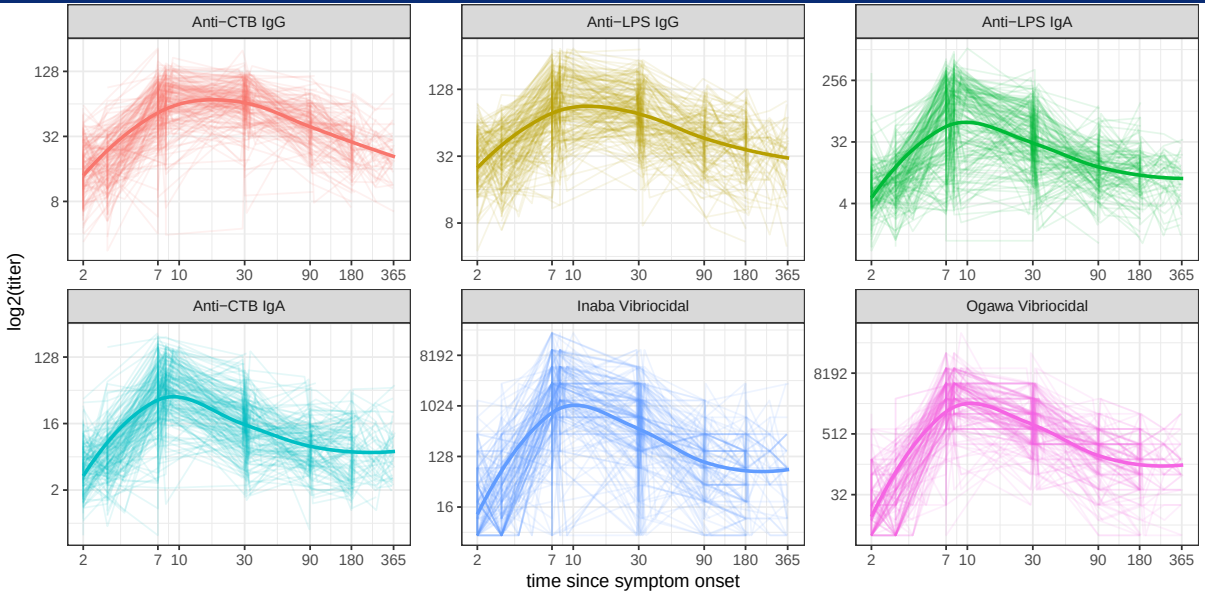
Ana A. Weil,† Fahima Chowdhury,† Ashraful I. Khan, Daniel T. Leung, Taher Uddin, Yasmin Ara Begum, Nirod Chandra Saha, Richelle C. Charles, Regina C. LaRocque, Jason B. Harris, Edward T. Ryan, Firdausi Qadri,‡ and Stephen B. Calderwood*‡

Seroepidemiologic Survey of Epidemic Cholera in Haiti to Assess Spectrum of Illness and Risk Factors for Severe Disease

Brendan R. Jackson,* Deborah F. Talkington, James M. Pruckler, M. D. Bernadette Fouché, Elsie Lafosse, Benjamin Nygren, Gerardo A. Gómez, Georges A. Dahourou, W. Roodly Archer, Amanda B. Payne, W. Craig Hooper, Jordan W. Tappero, Gordana Derado, Roc Magloire, Peter Gerner-Smidt, Nicole Freeman, Jacques Boncy, Eric D. Mintz, and the Cholera Serosurvey Working Group†

- Vibriocidal antibodies are useful
  - Marker for recent infection (no agreed upon threshold)
  - Indirect [non-mechanistic] correlate of protection (at least in adults) with no numeric threshold (only fold-rise)
- Other important markers of infection
  - Antibody responses to lipopolysaccharide (LPS) of *V. cholerae* (no threshold)
  - Antibody responses to O-specific polysaccharide of LPS (no threshold)
  - Antibody responses to the cholera toxin (typically the B-subunit) (no threshold)

Antibody kinetics after infection with *V. cholerae*



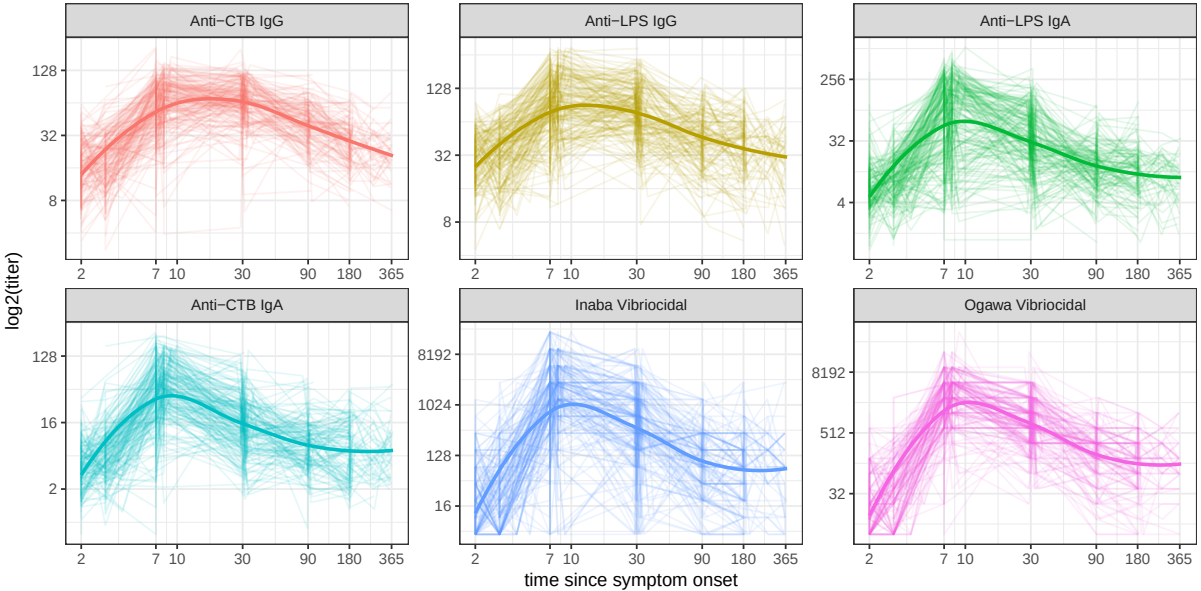
Guiding questions

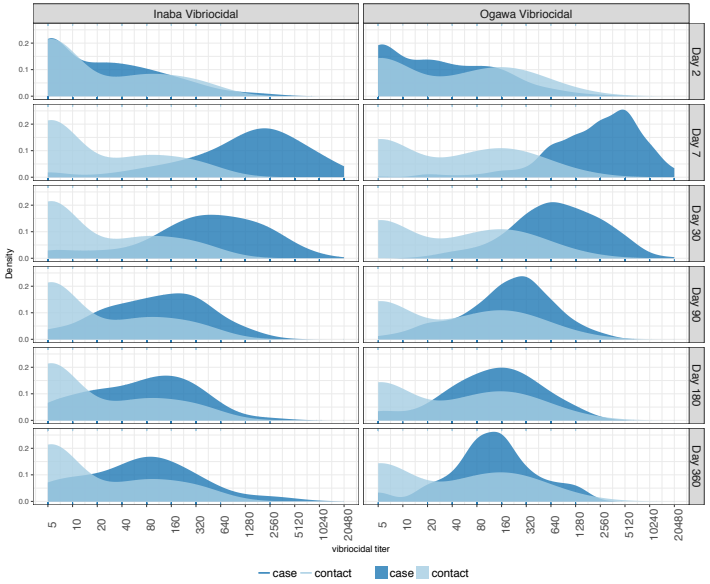
- Can cross-sectional serological measures identify individuals recently infected with *V. cholerae* O1?
- Which serological measures are most important markers of infection over different time frames?
- Can serological models of recent infection be useful in epidemiologic practice?

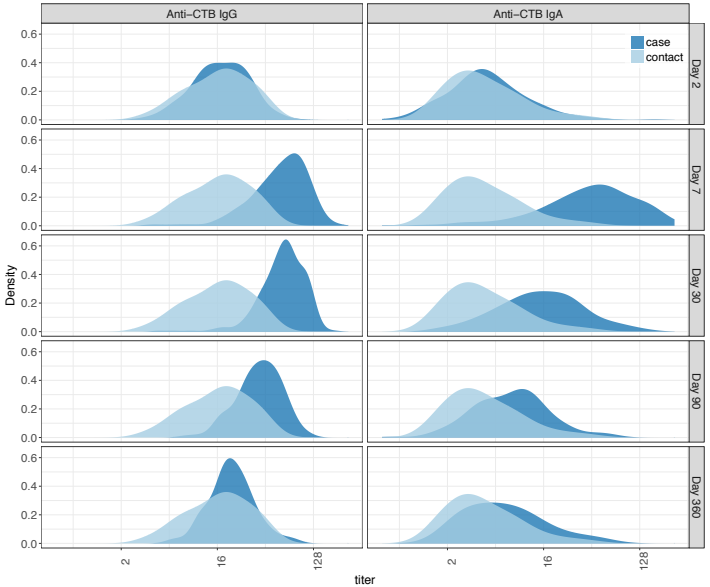
Outline

The Data

- Cohort of confirmed cholera cases and uninfected household contacts (used as 'controls')
- Serological followup from day of presentation through 1 year (cases) or 30-days (contacts)
- Vibriocidal antibodies, anti-CTB IgG and IgA, anti-LPS IgG, IgA and IgMs (subset only)


Anti−CTB IgG
Anti−LPS IgG
Anti−LPS IgA
Anti−CTB IgA
Inaba Vibriocidal
Ogawa Vibriocidal
log2(titer)
time since symptom onset
2
7
10
30
90
180
365
128
32
8
256
4
16
2
8192
1024
512

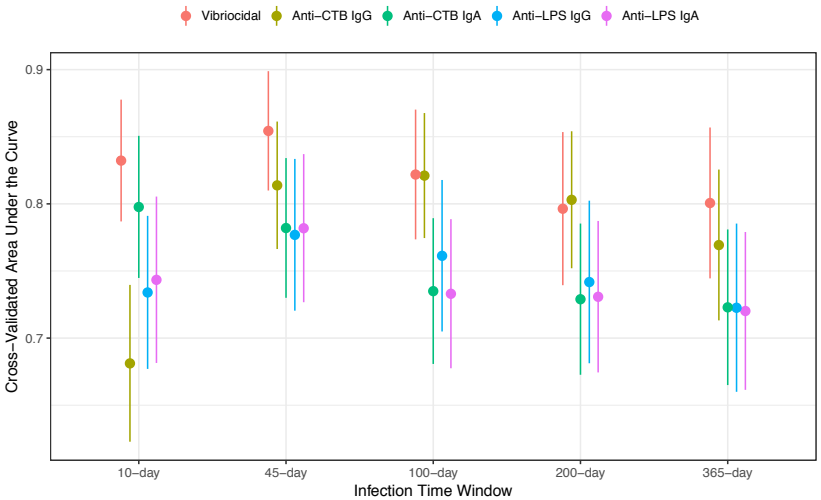

Inaba Vibriocidal
Ogawa Vibriocidal
Day 2
Day 7
Day 30
Day 90
Day 180
Day 360
Density
0.0
0.1
0.2
5
10
20
40
80
160
320
640
1280
2560
5120
10240
20480
vibriocidal titer
case
contact
case
contact

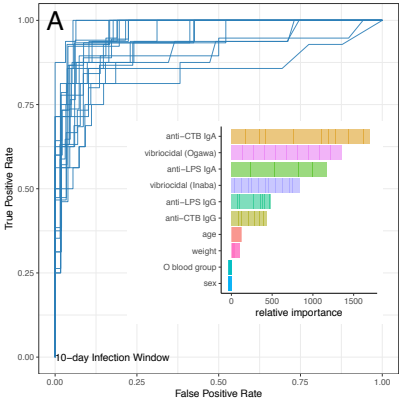

Anti−CTB IgG
Anti−CTB IgA
case
contact
Day 2
Day 7
Day 30
Day 90
Day 360
Density
0.0
0.2
0.4
0.6
2
16
128
titer

How well can a single antibody identify infections in the last year?

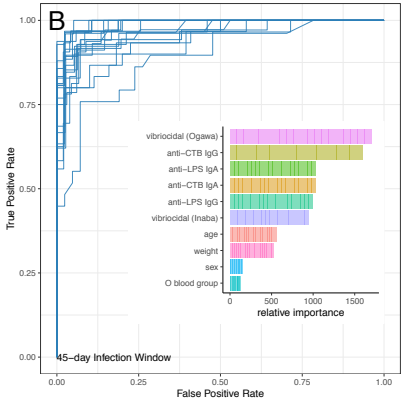
antibody	sensitivity mean (95% UI)	specificity mean (95% UI)	modal titer
vibriocidal	79.3 (70.4-88.1)	92.9 (85.0-100.0)	320
CTB-IgG	77.0 (67.6-85.7)	84.5 (74.3-93.3)	32
CTB-IgA	69.1 (59.4-80.0)	81.1 (68.0-91.5)	9
LPS-IgG	57.0 (46.8-67.6)	91.9 (84.1-97.9)	61
LPS-IgA	70.4 (60.3-80.0)	78.5 (66.0-89.2)	13

How well can a single antibody identify infections in the last year?

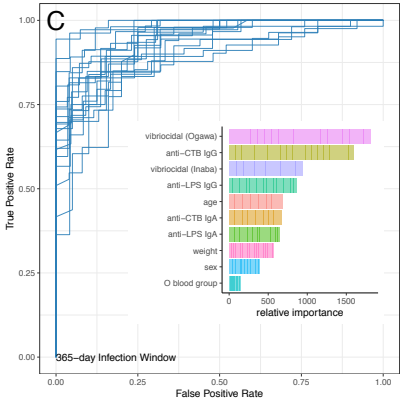




Area Under the Curve (AUC) = 95%



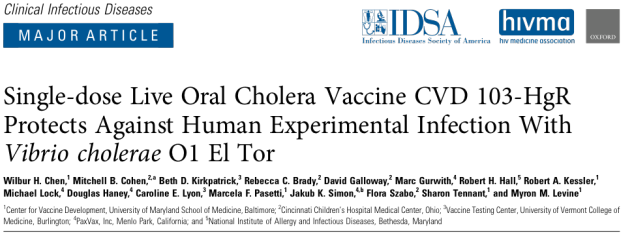
Area Under the Curve (AUC) = 97%



Area Under the Curve (AUC) = 95%

Are we overfitting? Is this generalizable?

- External validation of model with data from (cholera-naive) 38 North American volunteers challenged with O1 El Tor **Inaba** and followed for 6-months
- Focused on CTB, vibriocidal and demographics only



Clinical Infectious Diseases

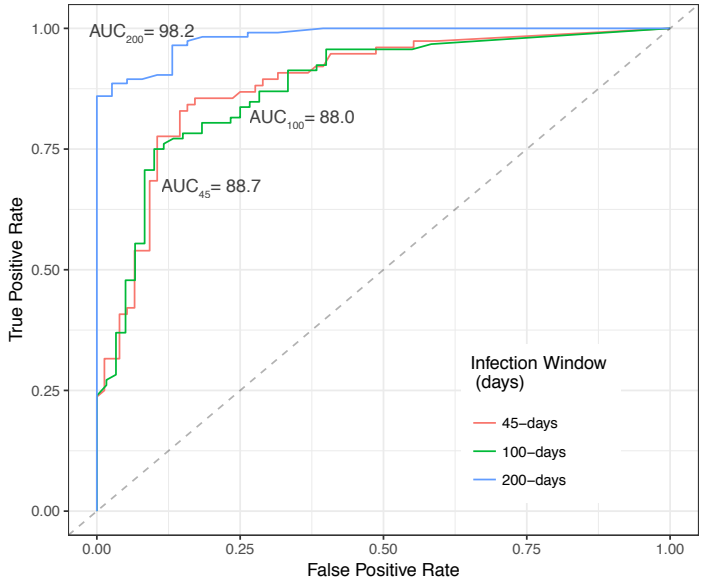
MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Single-dose Live Oral Cholera Vaccine CVD 103-HgR Protects Against Human Experimental Infection With *Vibrio cholerae* O1 El Tor

Wilbur H. Chen,[1] Mitchell B. Cohen,[2,a] Beth D. Kirkpatrick,[3] Rebecca C. Brady,[2] David Galloway,[2] Marc Gurwith,[4] Robert H. Hall,[5] Robert A. Kessler,[1] Michael Lock,[4] Douglas Haney,[4] Caroline E. Lyon,[3] Marcela F. Pasetti,[1] Jakub K. Simon,[4,b] Flora Szabo,[2] Sharon Tennant,[1] and Myron M. Levine[1]

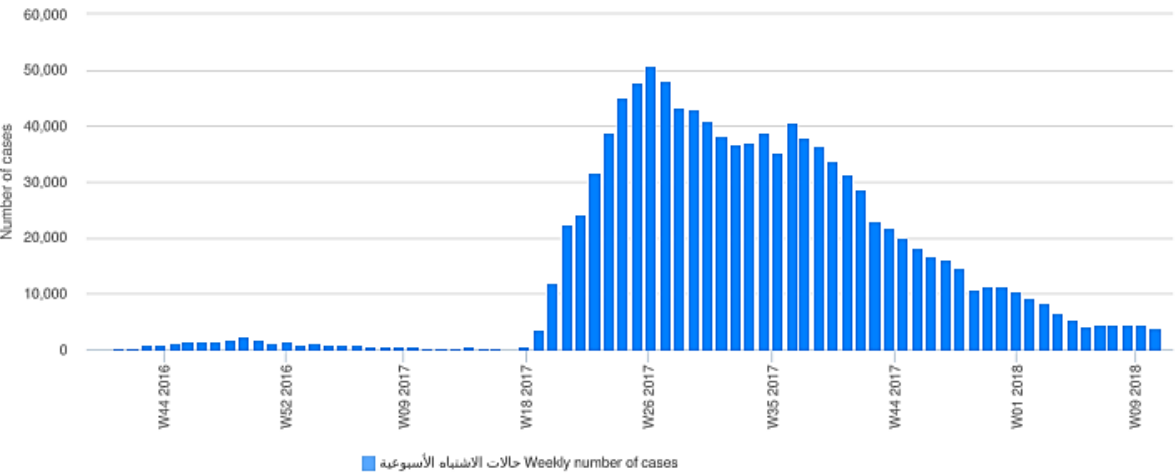
[1]Center for Vaccine Development, University of Maryland School of Medicine, Baltimore; [2]Cincinnati Children's Hospital Medical Center, Ohio; [3]Vaccine Testing Center, University of Vermont College of Medicine, Burlington; [4]PaxVax, Inc, Menlo Park, California; and [5]National Institute of Allergy and Infectious Diseases, Bethesda, Maryland

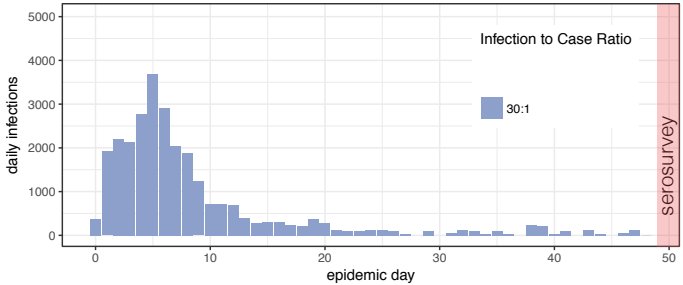

AUC200= 98.2
AUC100= 88.0
AUC45= 88.7
True Positive Rate
False Positive Rate
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
Infection Window
(days)
45–days
100–days
200–days

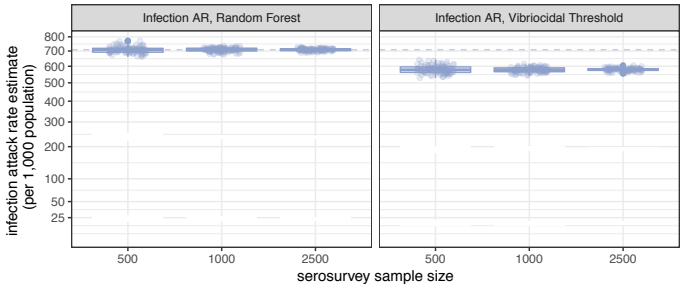
Outline

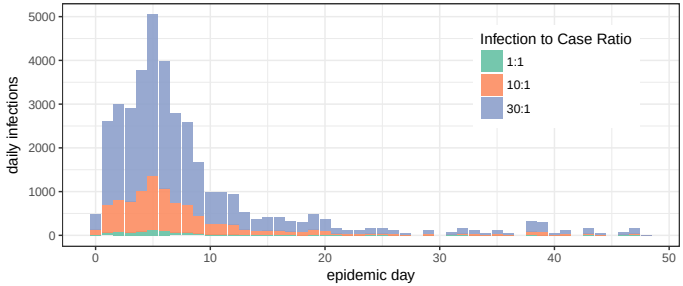
How big was that outbreak? Can serosurveys help?

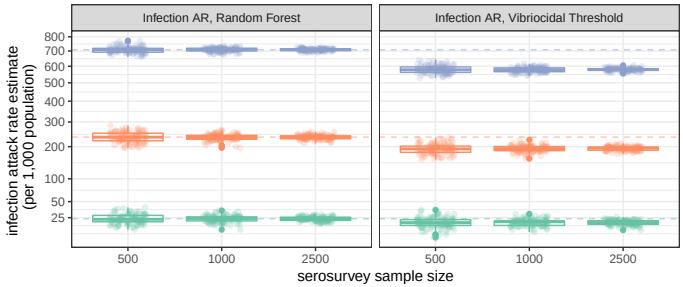
Figure 1. Epi curve of suspected cholera cases (n=1,080,422), April 2017 to 17 March 2018.




Infection to Case Ratio
30:1
serosurvey
daily infections
epidemic day
5000
4000
3000
2000
1000
0
0
10
20
30
40
50


Infection AR, Random Forest
Infection AR, Vibriocidal Threshold
infection attack rate estimate
(per 1,000 population)
800
700
600
500
400
300
200
100
50
25
500
1000
2500
serosurvey sample size


Infection to Case Ratio
1:1
10:1
30:1
daily infections
epidemic day
0
1000
2000
3000
4000
5000
0
10
20
30
40
50


Infection AR, Random Forest
Infection AR, Vibriocidal Threshold
infection attack rate estimate
(per 1,000 population)
serosurvey sample size
800
700
600
500
400
300
200
100
50
25
500
1000
2500

Summary

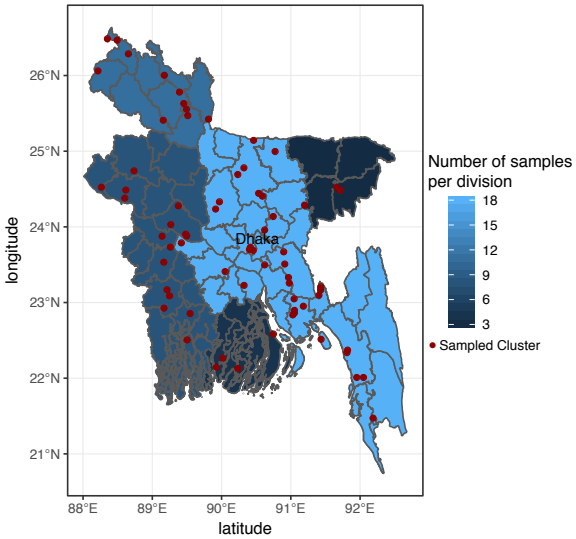
- We can do a pretty good job identifying recent infections (within past year)
- We can classify with only 1-2 antibodies (vibriocidals and anti-CTB IgG or IgA, depending on exposure window)
- Demographic factors, like age, add little to the models
- ‘one-size-fits-all’ models may work to estimate recent infection incidence in endemic and epidemic settings

Outline

Future challenges and questions

- What other immune responses might help classify incidence at different time frames?
- How do we adapt to partially vaccinated populations?
- Do those exposed but asymptomatic/mildly symptomatic have similar antibody trajectories?
- Can we adapt field-appropriate methods (like DBS) to collect these data in key areas of cholera transmission?
- How large will serosurveys have to be in low incidence settings?
- Serosurvey design recommendations for different uses

Estimating Annual Incidence in Bangladesh



Field-adapted Methods for Serum Collection