Mathematical modeling of cholera

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Who is CSQUID?



- Biostatistics
- Vaccine trial design and analysis
- Mathematical modeling of infectious disease
- Cholera, dengue, influenza, tuberculosis, malaria, HIV, varicella











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Modeling cholera in Haiti and Bangladesh

Haiti



Bangladesh



Cholera in Haiti



Barzilay et al. Cholera surveillance during the Haiti epidemic-the first 2 years. N Engl J Med 368:599-609. 2013.

- · Cholera had not been seen in Hispaniola for over a century.
- First cholera cases appeared in October 2010.
- 418,000 cases, 228,000 hospitalizations, and 6,000 deaths reported in the first year of the epidemic.

First questions from public health officials

- How fast will cholera spread in Haiti?
- When will the epidemic peak?
- How many people will the epidemic affect?
- Would mass vaccination have any effect?



Abrams, Copeland, Tauxe, Date, Belay, Mody, Mintz. Real-time modelling used for outbreak management during a cholera epidemic, Haiti, 2010–2011. Epidemiol Infect 141(6):1276–85. 2013.

First published modeling efforts



Bertuzzo et al. Prediction of the spatial evolution and effects of control measures for the unfolding Haiti cholera outbreak. Geophys Res Lett 38:L06403. 2011.



Andrews and Basu. Transmission dynamics and control of cholera in Haiti: an epidemic model. Lancet 377(9773):1248-55. 2011.



Tuite et al. Cholera epidemic in Haiti, 2010: Using a transmission model to explain spatial spread of disease and identify optimal control interventions. Ann Intern Med 154(9):593–601. 2011.



Chao et al. Vaccination strategies for epidemic cholera in Haiti with implications for the developing world. Proc Natl Acad Sci 108(17):7081–5. 2011.

Basic model of cholera dynamics



SIR model with an "Environmental" compartment

- 4 kinds of people: Susceptible, exposed, infectious, and recovered.
- Susceptible people are exposed to *Vibrio cholerae* from infected contacts or the environment.
- After a few days, Exposed people become Infectious.
- Infectious people contaminate the environment.
- Infectious people Recover, then become Susceptible again.

Why include a water compartment?



- Water compartment can maintain the infectious agent.
 - · People are not the only reservoir for the pathogen.
 - Water compartment allows the epidemic to continue when there are no infected people.
- The epidemic can travel with people or water.
 - People can bring cholera to new population centers.
 - Water can carry cholera downstream.

Modeling the initial spread of cholera in Haiti



Chao, Halloran, Longini. Vaccination strategies for epidemic cholera in Haiti with implications for the developing world. *Proc Natl Acad Sci.* 108(17):7081-5. 2011.

- Cholera started from a single point on the Artibonite River.
- Cholera spread along rivers and highways.
- We modeled interventions that could be implemented during the first wave of the epidemic.

Africa

Modeling interventions



- Vaccination can prevent infection or reduce severity of illness.
- Improved sanitation and hygiene can reduce exposure to *Vibrio cholerae*.

Modeling interventions in Haiti



- Vaccinating before the epidemic.
- Vaccinating during the epidemic.
- Targeted vaccination during the epidemic.
- Targeted vaccination + hygiene campaigns during the epidemic.

Agent-based model of cholera transmission

• About 3000 lines of C++ code.

Haiti

- Synthetic population of about 9,500,000 people.
 - Census data used for age distribution and household sizes.
 - LandScan gridded population density estimates to place households on a map.
- River and highway location data from public sources.
- The 2-dose vaccine took 3 weeks to reach full efficacy in the model.
- Why agent-based modeling?
 - Heterogeneity of the population
 - · Geographical targeting was important
 - Timing of interventions was important

Africa

Cholera in Bangladesh



- Cholera affected the Bay of Bengal region for thousands of years.
- Most of Bangladesh is near sea level.
- The Ganges River Delta floods frequently.
- Bangladesh is one of the most densely populated countries.
- Bangladesh is ranked 155/187 by per capita GDP.

Monsoon-driven cholera outbreaks in Bangladesh



Akanda et al. Population vulnerability to biannual cholera outbreaks and associated macroscale drivers in the Bengal Delta. Am J Trop Med Hyg 89(5):950–9. 2013.

- Cholera activity peaks once or twice per year in Bangladesh.
- Peaks can occur in the spring or fall, before and after monsoon season.

Bangladesh

Large cholera vaccination trial in Matlab, Bangladesh



Ali et al. Herd immunity conferred by killed oral cholera vaccines in Bangladesh: a reanalysis. Lancet 366:44–9. 2005.

- Individually randomized mass cholera vaccination trial in 1985–1989. (Clemens et al. Field trial of oral cholera vaccines in Bangladesh: results from three-year follow-up. Lancet 335(8684):270–3. 1990.)
- 49,336 cholera vaccinees, 24,667 placebo recipients.
- Three years of follow-up.

- Vaccine coverage varied in different areas, from over 50% to less than 28%.
- Areas with higher coverage had lower incidence among non-vaccinees.

Modeling the vaccine trial



Longini, Nizam, Ali, Yunus, Shenvi, Clemens. Controlling endemic cholera with oral vaccines. *PLoS Med* 4(11):e336. 2007.

- An agent-based model was based on this trial.
- Synthetic population of 183,826 people in a 384 km² area.
- Individuals organized in families and baris (household clusters).
- Women and children infected within their own subregion.
- Men commute and may also be infected at their workplaces.
- Cholera transmission was simulated for one year.
- A fraction of the population could be vaccinated before the epidemic season.

Modeling mass vaccination





- Using the model, we can **extrapolate** the observations from the trial to any coverage level.
- Simulated vaccination of 0%, 14%, 38%, and 58% of the population.
- Mass vaccination protects both vaccinated *and* unvaccinated people.
- Vaccinating 50–70% of the population controls transmission in rural Bangladesh in the model.

Africa

How effective was mass vaccination in Bangladesh?



- If a vaccine is 65% effective, then one should avert at least 65% of cases.
- The observed reduction in cases was greater.
- The model was used to understand the relationship between coverage and incidence.

"Indirect protection" or "Herd immunity"



Vaccinated people are less likely to become infected *and* less likely to infect others. Therefore, vaccines can protect *more* than those who are vaccinated.

How often should you vaccinate in Bangladesh?



- Vaccinate only once: incidence will go down for the first year then return to pre-vaccination levels in a few years.
- Vaccinate every three years: incidence will be reduced but may cycle every three years.
- Vaccinate every year: incidence will be lower but the program may be more expensive.

Cholera vaccine is becoming cheaper and more available



Guinea. David Di Lorenzo/MSF. 2012.

- WHO pre-qualification of Shanchol in 2011.
- WHO decided to establish a stockpile of 2 million doses in 2012.
- GAVI supported expansion of stockpile in November 2013.
- How do we best use the limited supply?

Cost effectiveness of mass vaccination



- We are developing an Excel-based tool to estimate the cost effectiveness of mass vaccination (available at http://www.stopcholera.org).
- This tool can be used to help evaluate the cost effectiveness of vaccinating different sub-populations in a country.
- Calculations assume **direct protection only**. (conservative estimates, more generally applicable)

Targeted vaccination



Vaccination can be more cost-effective when high-risk sub-populations are prioritized.

- Targeting toddlers if they have higher incidence than adults.
- Targeting geographic regions with higher incidence.
- Targeting groups with less access to care and who would have higher mortality when infected.

Cholera in Haiti and Bangladesh



- "Epidemic" cholera.
- Known time and place of introduction of cholera.
- Consistent surveillance since the introduction of cholera.

Modelers go where the data is.





- "Endemic" cholera.
- Cholera studied for decades.
- Very good surveillance in Matlab.
- Study of large mass vaccination trial.

Haiti

Africa

Reported cholera in Africa



Cholera, 2012. Weekly Epidemiological Report. No. 31, 2013, 88, 321-336.

(Some) countries report the number of cholera cases and deaths to the World Health Organization.

Cholera activity can be focal



Bompangue Nkoko et al. Dynamics of cholera outbreaks in Great Lakes region of Africa, 1978–2008. Emerg Infect Dis 17:2026–34. 2011.

For example, cholera outbreaks in the Democratic Republic of the Congo is concentrated along the Great Lakes.

Frequency of cholera outbreaks





Cholera can be sporadic, periodic (multi-year cyles), or annual.

Different settings for cholera in Africa



Freetown, Sierra Leone. BBC News



Goma, DRC. Phil Moore / AFP - Getty Images



Port Bouet, Abidjan, Côte d'Ivoire



Uganda/DRC border

Cholera is introduced to vulnerable populations in complex ways.

Future research directions

- Studying the epidemiology of cholera in Africa.
 - Geographic hotspots.
 - Temporal patterns of cholera activity.
 - Vulnerable populations.
 - The role of mobile populations (e.g., fishermen, farmworkers, refugees) in cholera transmission.
- Modeling strategies to use a limited supply of vaccine wisely.
- Modeling WASH interventions.
- Studying the evolution of cholera in Haiti.
- Working with Bangladeshi officials to prepare a cholera investment case.

Africa

Thank you!



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