Modeling the effectiveness of mass cholera vaccination in Bangladesh

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INSTITUTE FOR DISEASE MODELING
INTELLECTUAL VENTURES

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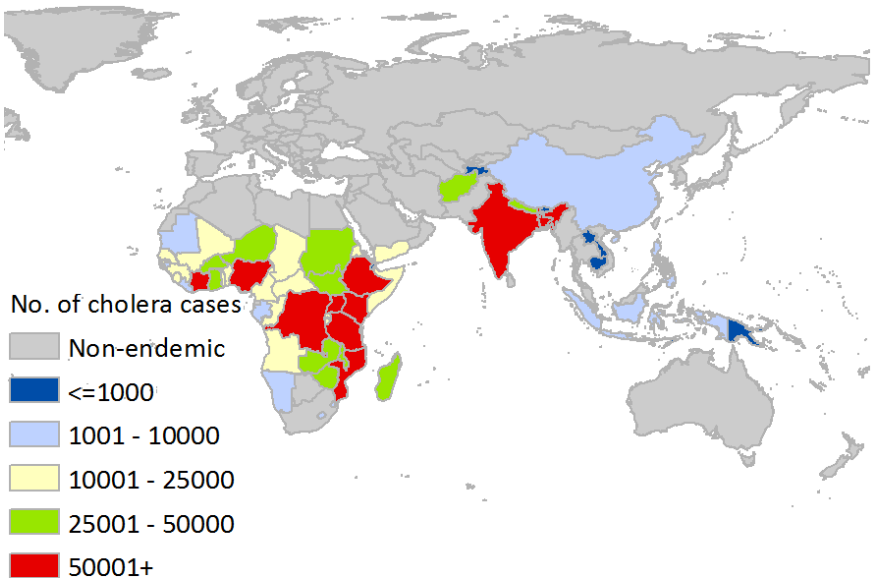
Vibrio cholerae in Bangladesh

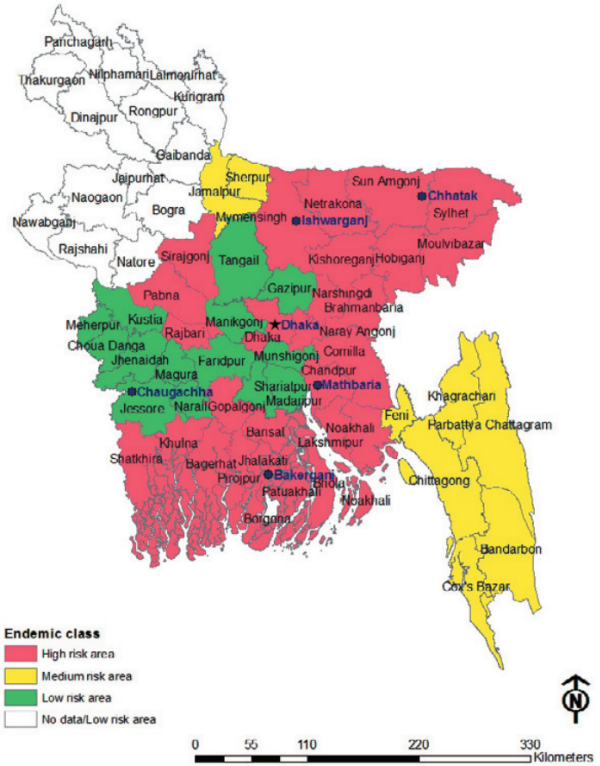


Ali et al. Updated Global Burden of Cholera in Endemic Countries. PLoS NTDs. 2015.

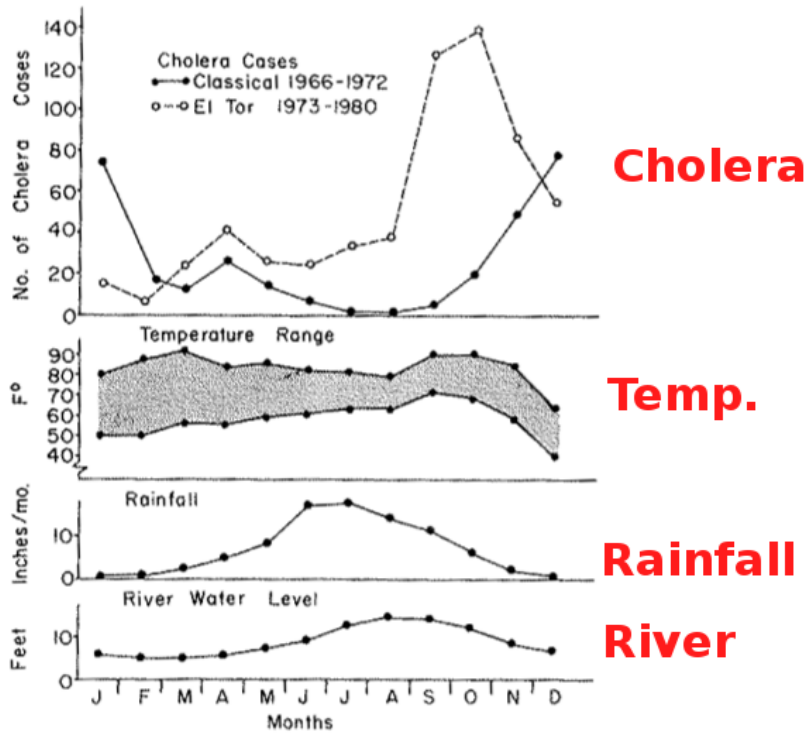
Dhaka, Bangladesh

- Cholera is *endemic* around the Bay of Bengal.
- *Vibrio cholerae* is part of the estuarine ecosystem.
- The toxin adopted by *V. cholerae* causes cholera.

Burden of cholera in Bangladesh



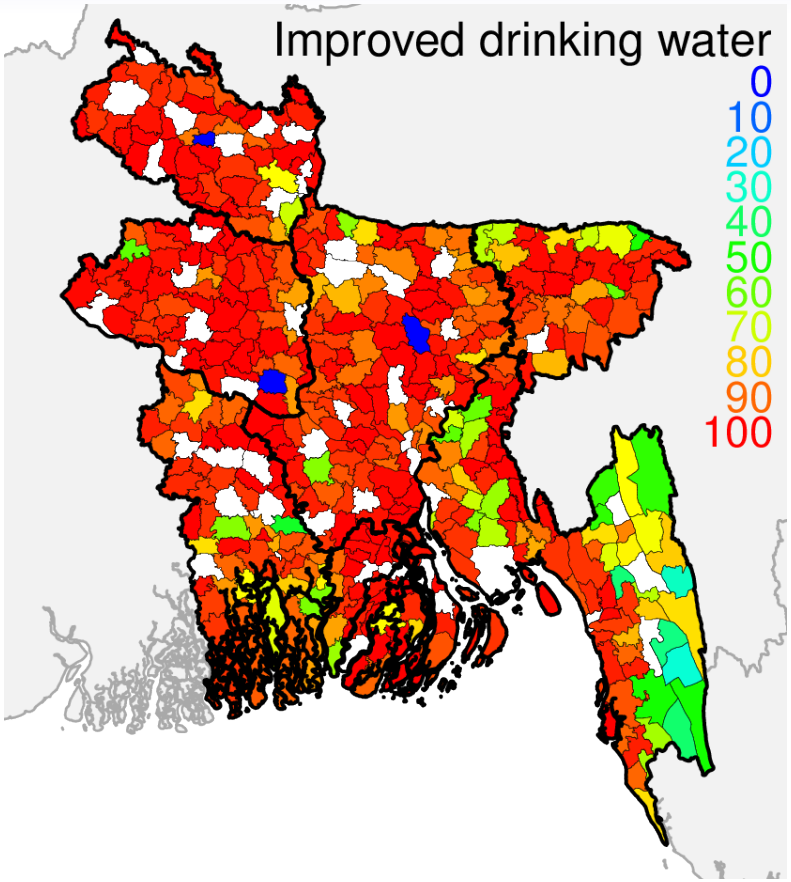
*International Vaccine Institute. Country investment case study on cholera vaccination: Bangladesh. 2012.

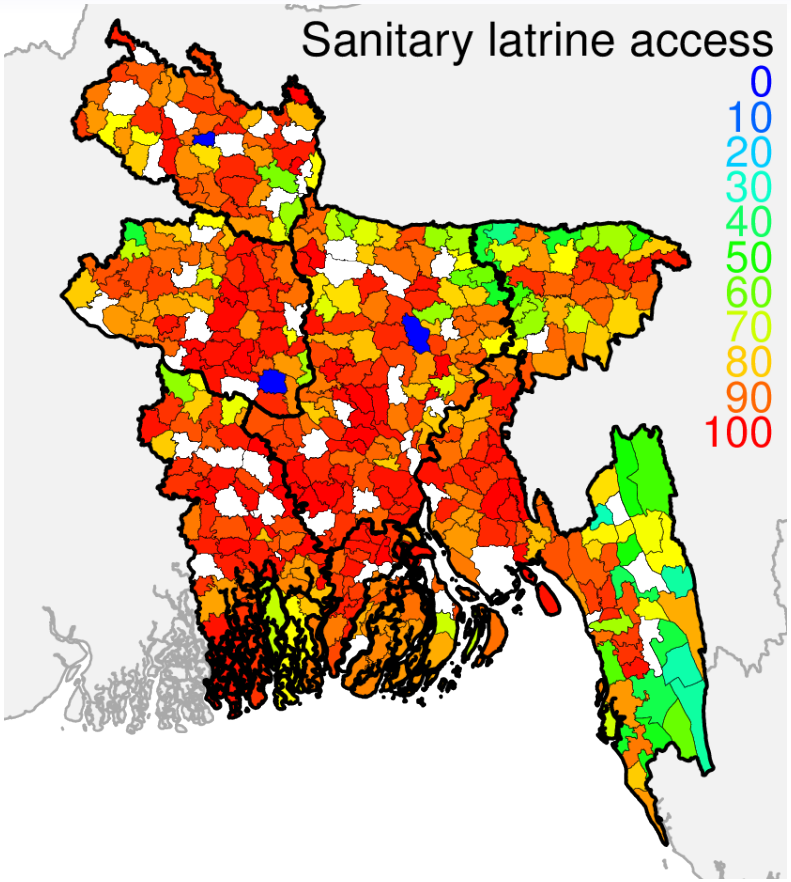


Glass et al. Endemic cholera in rural Bangladesh, 1966–1980. Am J Epidemiol 116(6):959–70. 1982.

- Estimated 350,000 cases and 5,300 deaths per year in Bangladesh.
- Cholera incidence is about 1–4 per 1000 per year.
- Cholera activity peaks before or after monsoons.

How can cholera transmission be stopped?





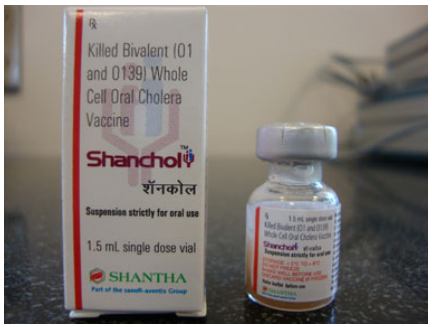
Data from http://app.dghs.gov.bd/localhealthBulletin2015/publish/

- The long-term solution is improved hygiene and sanitation (WASH).
- Oral cholera vaccine (OCV) may be part of a short-term solution.

Cholera vaccine

3 World Health Organization pre-qualified vaccines:

Dukoral (2001)



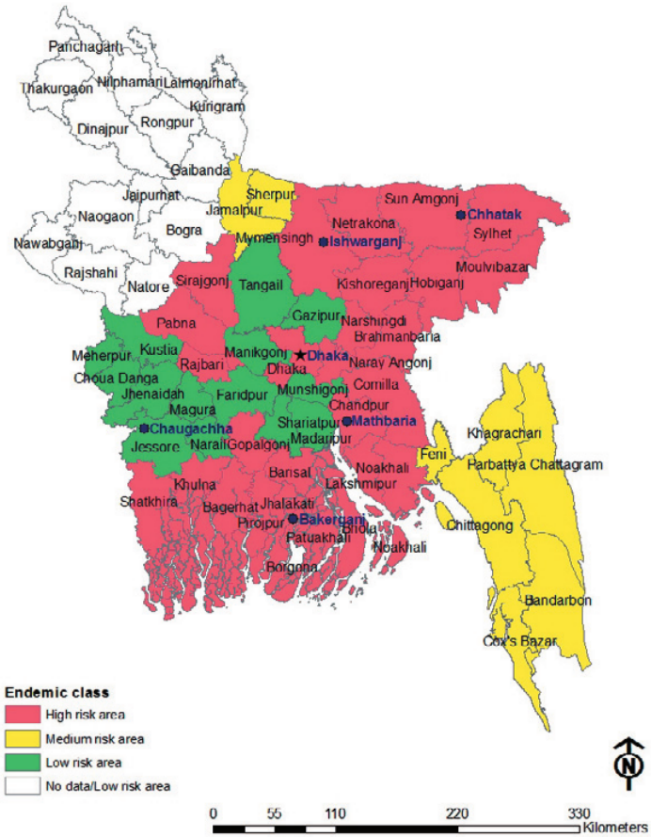
Shanchol (2011)

Euvichol (2015)

- Cholera vaccine is not expensive (about $1.85 per dose), and having a local manufacturer would make it even cheaper.
- Good acceptability in Bangladesh.

Cholera vaccination in Dhaka, Bangladesh by Orlando de Guzman and Andrew Marshall

Using cholera vaccine efficiently

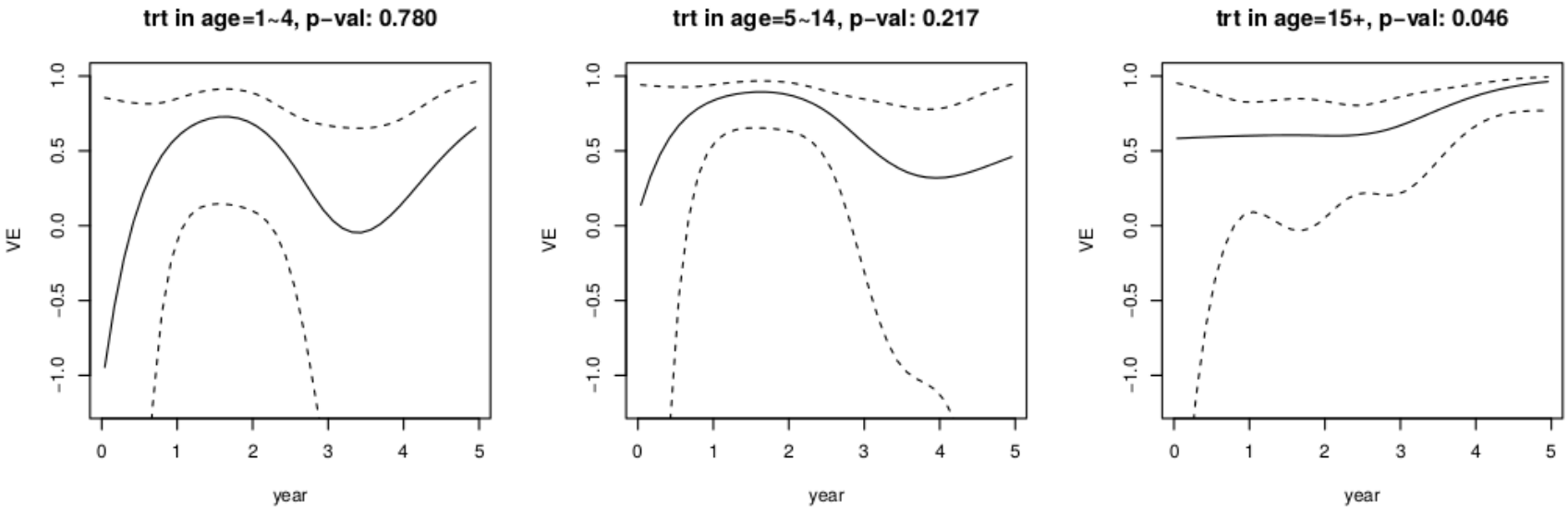


An investment case for the accelerated introduction of oral cholera vaccines. The International Vaccine Institute. 2012

- Bangladesh has 166 million people.
- 1–2 million doses of OCV available worldwide.
- Target cholera hot-spots?
  - About half of Bangladesh can be considered “high-risk”.
- Prioritize children for vaccination?
  - About 50 million children under 15 years old.
  - Birth cohort is over 3 million.

- Cholera vaccine has moderate efficacy (65%) that may last 3 to 5 years. Need for regular boosters could be expensive.
- Lowest efficacy among young children, who have the highest incidence of disease.

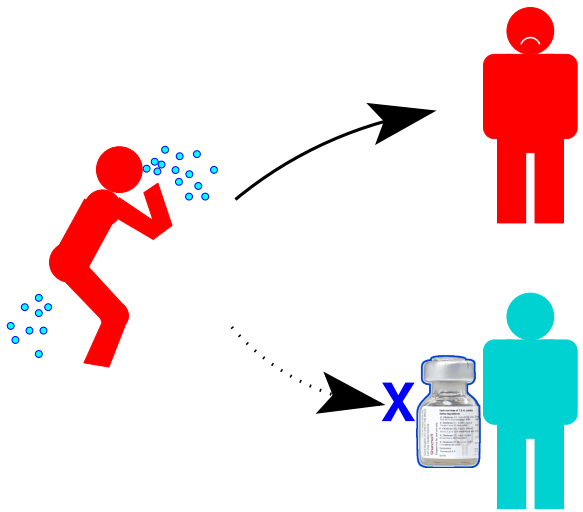
What is the efficacy of cholera vaccine?



Fong, Halloran, Park, Marks, Clemens, Chao. Efficacy of a Bivalent Killed Whole-Cell Cholera Vaccine Over Five Years: A Re-analysis of a Cluster-Randomized Trial. In submission.

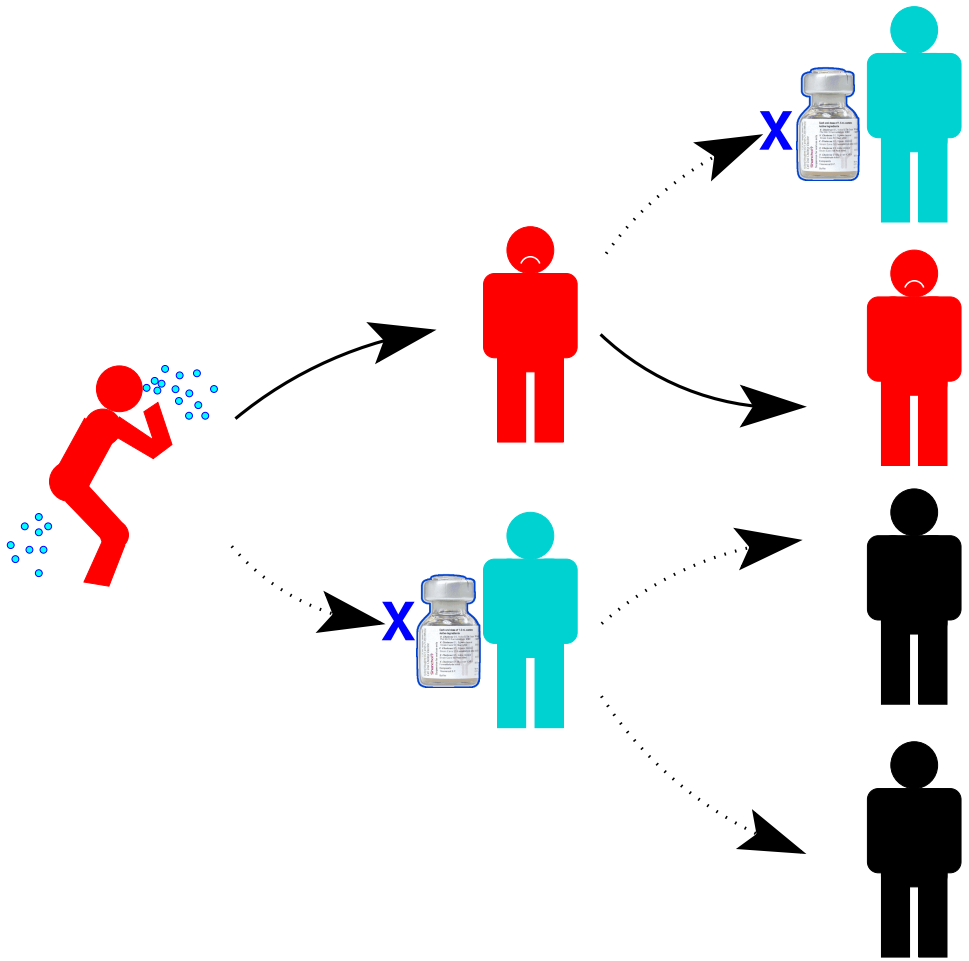
- We re-analyzed cholera vaccine trial data to study efficacy by age and over time.
- Vaccine is less effective in those vaccinated when under 5 years old (38%) and most effective in older children (85%).
- Didn't see evidence of waning efficacy among adults.
- Adults might not require boosters after only 5 years.

“Direct protection” from vaccine



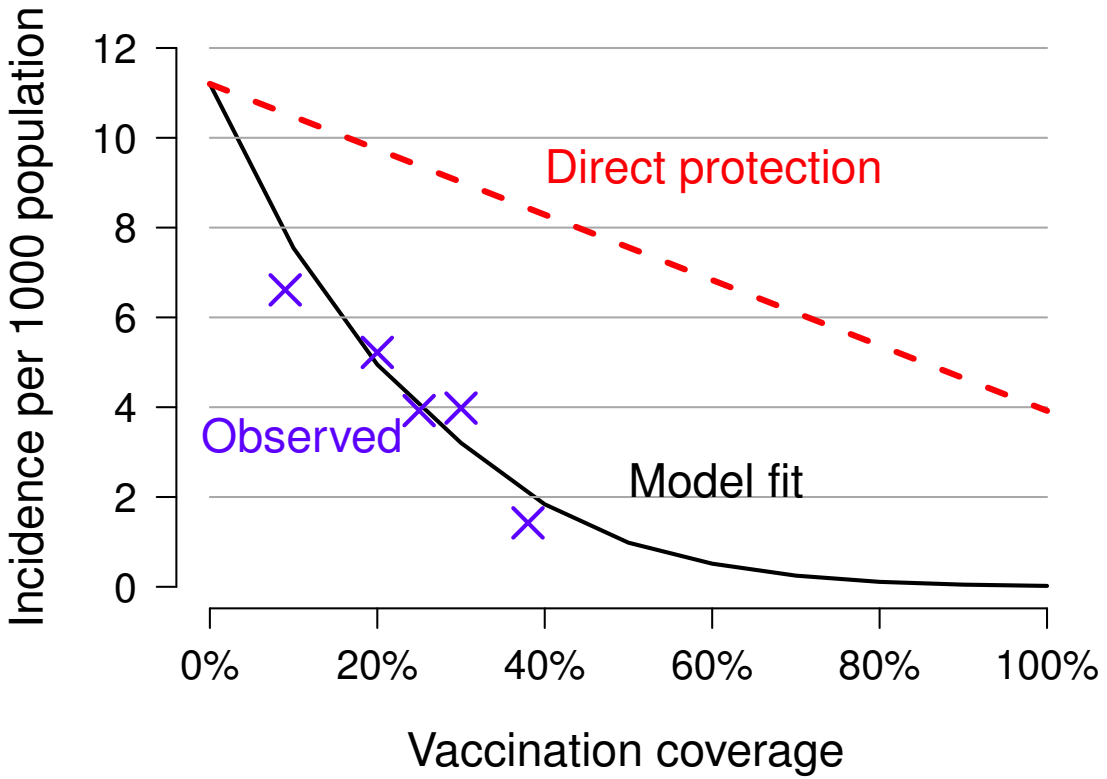
Vaccinated people are less likely to become infected. (about 65% less)

"Indirect protection" from mass vaccination



Vaccinated people are less likely to become infected *and* less likely to infect others. Therefore, vaccines can protect vaccinated *and* unvaccinated people. (Also applies to WASH interventions.)

"Herd immunity", or protecting the unvaccinated



- 1985 OCV trial in Matlab: 49336 vaccinees, 24667 placebo.
- If a vaccine is 65% effective, then one should avert at least 65% of cases.
- The observed reduction in a large-scale trial was greater.

High levels of vaccination (but below 100%) can basically stop cholera transmission ("herd immunity").

Mathematical model of cholera in Bangladesh

$$\frac{dS_i}{dt} = \lambda_i N + a_{i-1}S_{i-1} + \gamma_3 R_i + \nu_2 V_i - (\nu_1 + \mu + a_i)S_i - (\sum_{i=1}^{4} I_i + \beta_{asymp}\sum_{i=1}^{4} A_i)\frac{s_i b_H S_i}{N} + \frac{s_i b_W W}{k+W} S_i$$

$$\frac{dV_i}{dt} = \nu_1 S_i + a_{i-1}V_{i-1} - (\sum_{i=1}^{4} I_i + \beta_{asymp}\sum_{i=1}^{4} A_i)\frac{(1-VE_S)s_i b_H V_i}{N} + \frac{(1-VE_S)s_i b_W W}{k+W} V_i - (\mu + \nu_2 + a_i)V_i$$

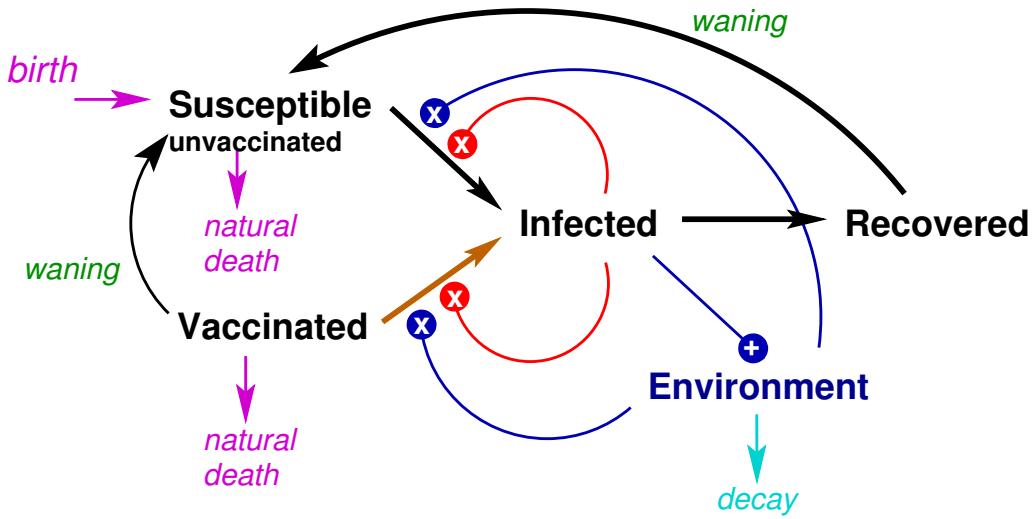
$$\frac{dI_i}{dt} = p\left((\sum_{i=1}^{4} I_i + \beta_{asymp}\sum_{i=1}^{4} A_i)\frac{s_i b_H S_i}{N} + \frac{s_i b_W W}{k+W} S_i\right) + q\left((\sum_{i=1}^{4} I_i + \beta_{asymp}\sum_{i=1}^{4} A_i)\frac{(1-VE_S)s_i b_H V_i}{N} + \frac{(1-VE_S)s_i b_W W}{k+W} V\right) + a_{i-1}I_{i-1} - (\mu + d + \gamma_1 + a_i)I_i$$

$$\frac{dA_i}{dt} = (1-p)\left((\sum_{i=1}^{4} I_i + \beta_{asymp}\sum_{i=1}^{4} A_i)\frac{s_i b_H S_i}{N} + \frac{s_i b_W W}{k+W} S_i\right) + (1-q)\left((\sum_{i=1}^{4} I_i + \beta_{asymp}\sum_{i=1}^{4} A_i)\frac{(1-VE_S)s_i b_H V_i}{N} + \frac{(1-VE_S)s_i b_W W}{k+W} V\right) + a_{i-1}A_{i-1} - a_i A_i - (\mu + \gamma_2)A_i$$

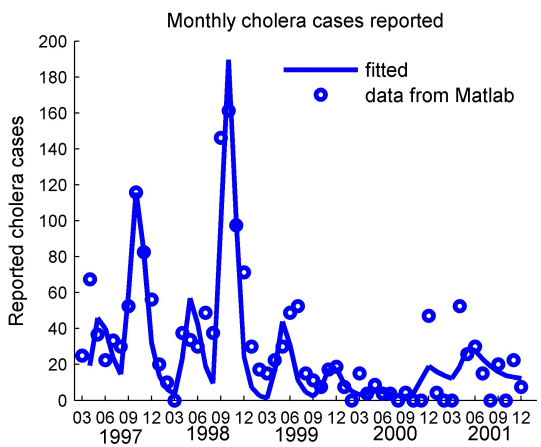
$$\frac{dR_i}{dt} = \gamma_1 I_i + \gamma_2 A_i + a_{i-1}R_{i-1} - (\mu + \gamma_3 + a_i)R_i$$

$$\frac{dW}{dt} = \sigma_1 \sum_{i=1}^{4} I_i + \sigma_2 \sum_{i=1}^{4} A_i - \theta W$$

$$b_w = \begin{cases} b_w^{\min}(1+\delta_1) & rem(t,360) < 60 \\ b_w^{\min}(1+\delta_2) & \delta_3 + 150 < rem(t,360) < \delta_3 + 210 \\ b_w^{\min} & otherwise \end{cases}$$

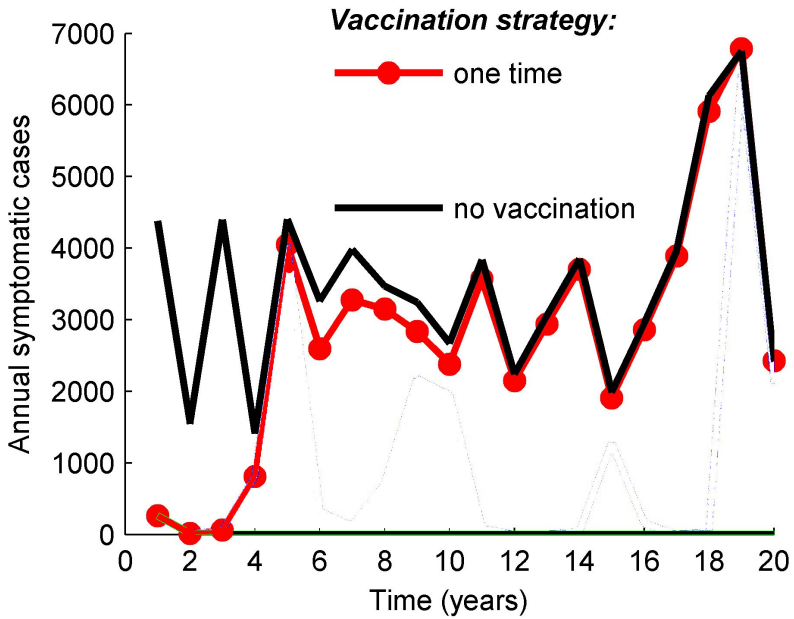


- We developed a mathematical model of cholera transmission calibrated to the dynamics and epidemiology of cholera in Matlab, Bangladesh.
- Mathematical models can capture direct and indirect protection.
- Includes waning immunity (Recovered to Susceptible transition) and vital dynamics.

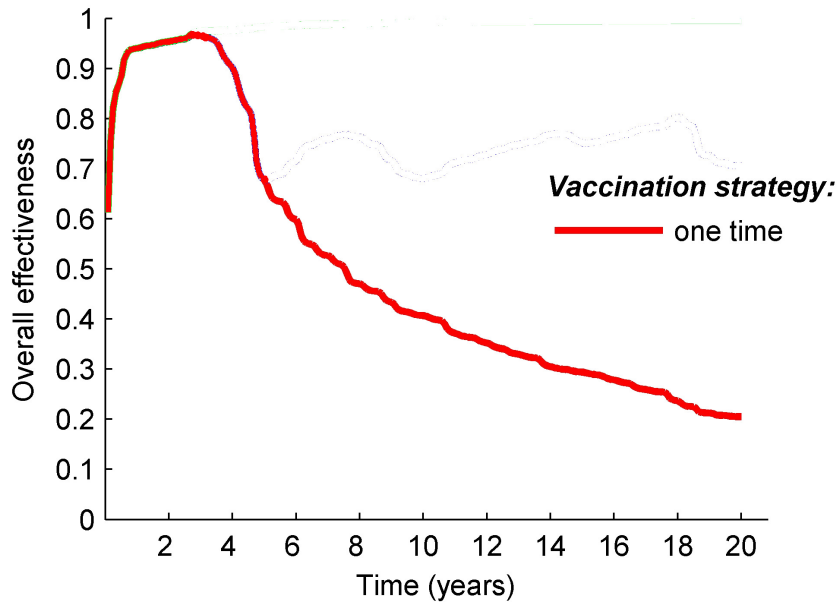


Dimitrov, Troeger, Halloran, Longini, Chao. Comparative effectiveness of different strategies of oral cholera vaccination in Bangladesh: A modeling study. PLoS Negl Trop Dis 8(12): e3343.

Modeling mass vaccination



Epidemic curves

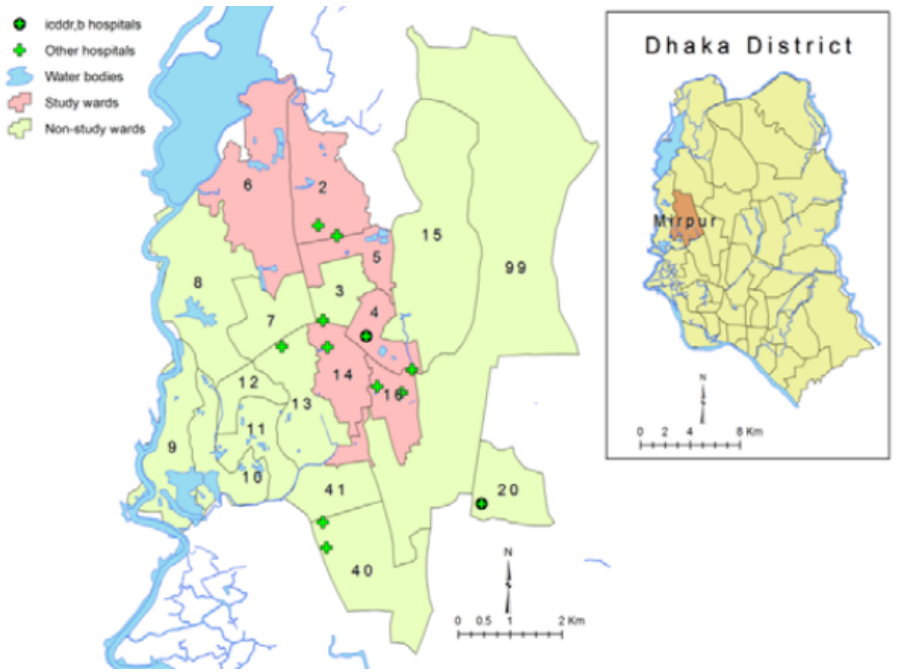


Overall effectiveness

Dimitrov DT, Troeger C, Halloran ME, Longini IM, Chao DL. Comparative effectiveness of different strategies of oral cholera vaccination in Bangladesh: A modeling study. PLoS Negl Trop Dis 8(12): e3343.

- We assumed that vaccine protects for 5 years on average.
- After mass vaccination, incidence goes down for the first year then returns to pre-vaccination levels a few years later.
- Overall effectiveness starts high then declines.

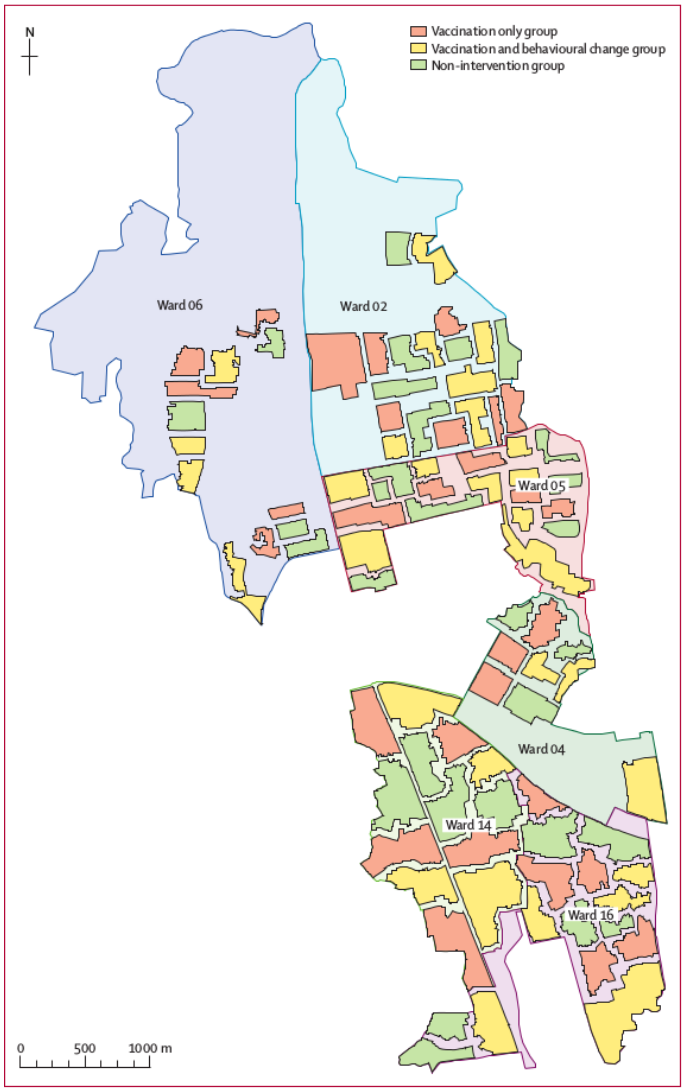
Targeting geographic "hotspots"



Qadri et al. Feasibility and effectiveness of oral cholera vaccine in an urban endemic setting in Bangladesh: a cluster randomised open-label trial. Lancet 386:1362–71. 2015.

- Mirpur (Dhaka, Bangladesh) had the highest incidence of cholera (4 per 1000).
- Non-pregnant individuals 1 year old and older were invited to participate in a demonstration project.
- 3 arms: Vaccination, Vaccination+Behavioural, No intervention.
- 65% coverage was achieved.

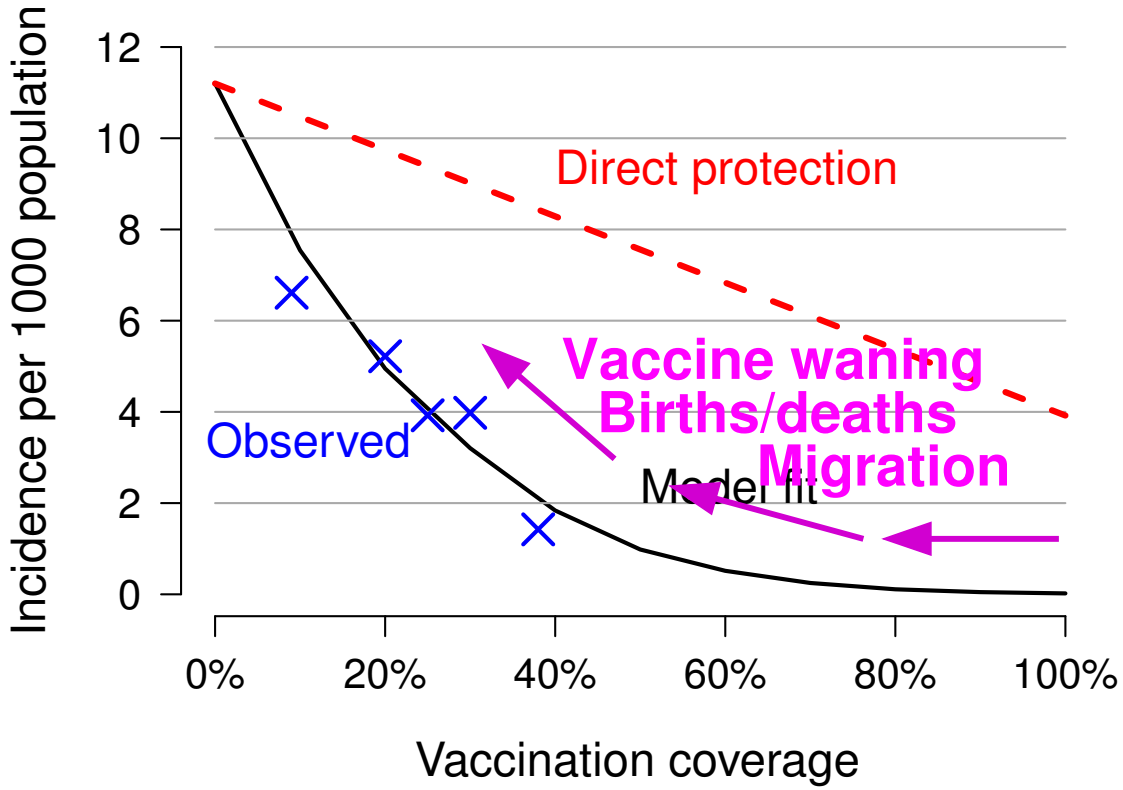
Barriers to effective mass vaccination



Qadri et al. Feasibility and effectiveness of oral cholera vaccine in an urban endemic setting in Bangladesh: a cluster randomised open-label trial. Lancet 386:1362–71. 2015.

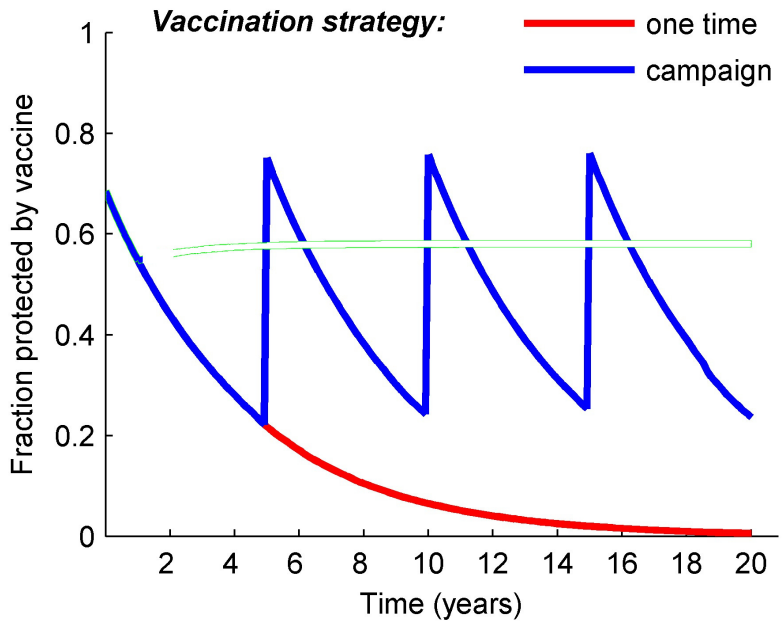
- **Only 37% overall protection in vaccination only arm.**
- Vaccinated clusters were small and surrounded by untreated individuals.
  - Clusters with 3,000 people.
  - 30-meter buffer zones around clusters.
- High population mobility.
  - 58% of participants migrated out or died during the two year trial.

Maintaining OCV coverage levels

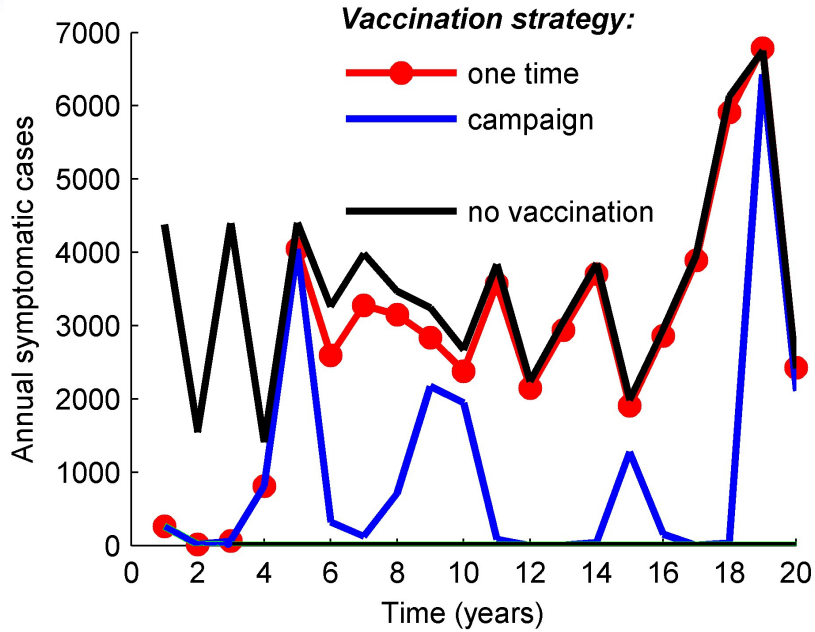


- Erosion of coverage can have a disproportionately large (or small) effect on indirect protection.
- To prevent large outbreaks, coverage must remain consistently high.

Vaccinate every few years



Vaccine coverage

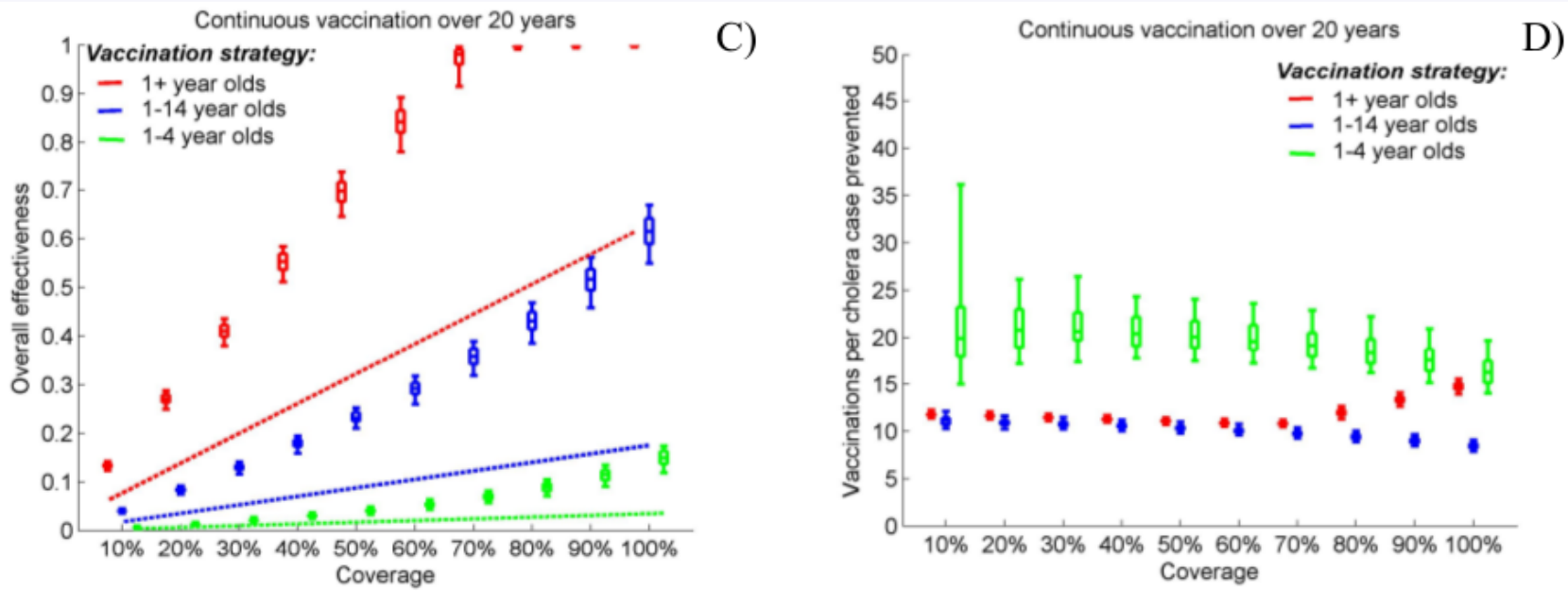


Epidemic curves

Dimitrov DT, Troeger C, Halloran ME, Longini IM, Chao DL. Comparative effectiveness of different strategies of oral cholera vaccination in Bangladesh: A modeling study. PLoS Negl Trop Dis 8(12): e3343.

- Vaccinate every few years to compensate for waning and population turnover (births, deaths, and migrations).
- Average incidence is reduced but large outbreaks still occur when coverage is lowest.
- How often do we need to vaccinate? Do we need routine vaccination of children between campaigns?

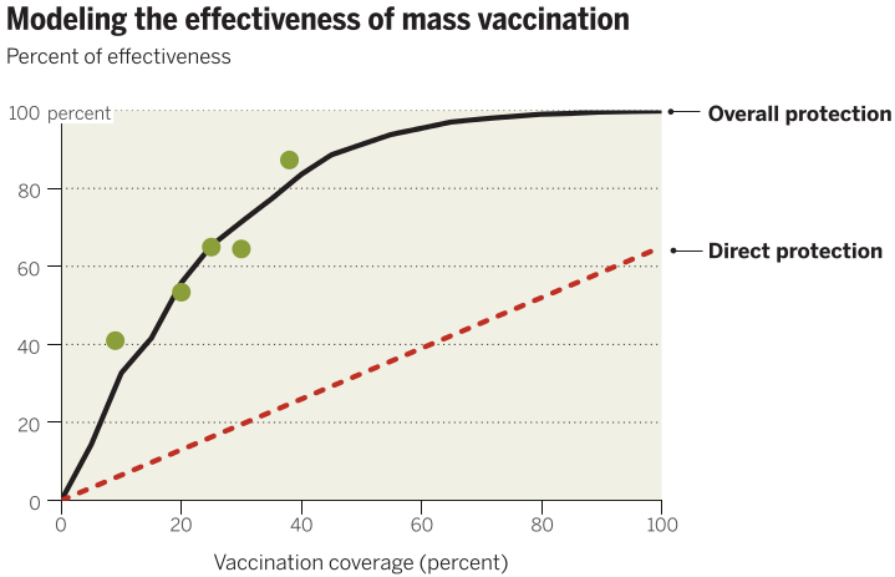
Community-level benefits from protecting children

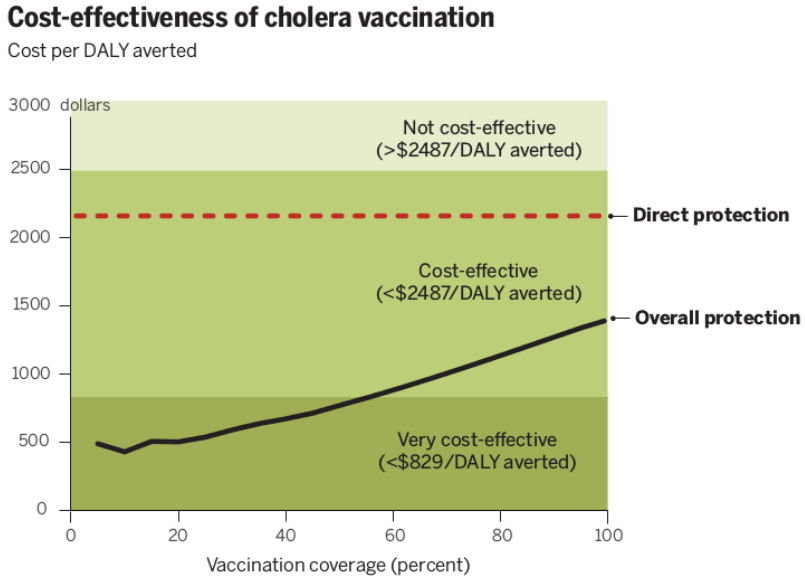


Dimitrov DT, Troeger C, Halloran ME, Longini IM, Chao DL. Comparative effectiveness of different strategies of oral cholera vaccination in Bangladesh: A modeling study. PLoS Negl Trop Dis 8(12): e3343.

- Young children have the highest incidence of cholera.
- Vaccinating young children is probably easiest logistically.
- Vaccinating the whole population, including adults, may prevent the most cases per vaccination. But it may be more difficult and expensive to reach adults.
- **Ongoing trial in Mirzapur will show the community-level protection from vaccinating children (ages 1–15 years).**

Cost effectiveness





Halloran and Longini. Emerging, evolving, and established infectious diseases and interventions. *Science* 345(6202):1292–4. 2014.

- To prevent large outbreaks, coverage must remain consistently high.
- Even “sub-optimal” coverage levels can be cost-effective.
- $3.93 to vaccinate each person (2 doses). Vaccine was 58.5% of the total cost.
  Khan IA, Saha A, Chowdhury F, Khan AI, Uddin MJ, Begum YA, Riaz BK, Islam S, Ali M, Luby SP, Clemens JD, Cravioto A, Qadri F. Coverage and cost of a large oral cholera vaccination program in a high-risk cholera endemic urban population in Dhaka, Bangladesh. Vaccine. 2013 Dec 9;31(51):6058-64.
- We are talking to public health officials about actual vaccination strategies being considered and the associated costs.

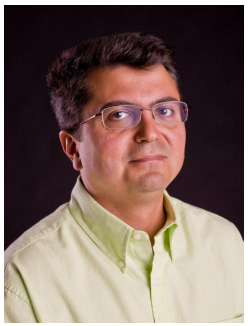
Summary

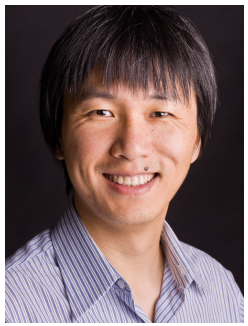
- Mass cholera vaccination is feasible in Bangladesh.
- Developing a cost-effective strategy is challenging.
  - Where to vaccinate?
  - Who to vaccinate?
  - How often to vaccinate?
- Mathematical models can be informed by trial results.
  - High levels of OCV coverage should produce “herd immunity”.
  - Will we see high levels of indirect protection from vaccinating only children?
- How can we maintain high levels of OCV coverage in mobile populations?
- How to integrate WASH into mathematical models?

Thank you!

Colleagues


Betz Halloran


Dobromir Dimitrov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