What modeling can and cannot bring to impact assessment of vaccines

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Beyond efficacy: the full public health impact of vaccines in addition to efficacy measures in trials

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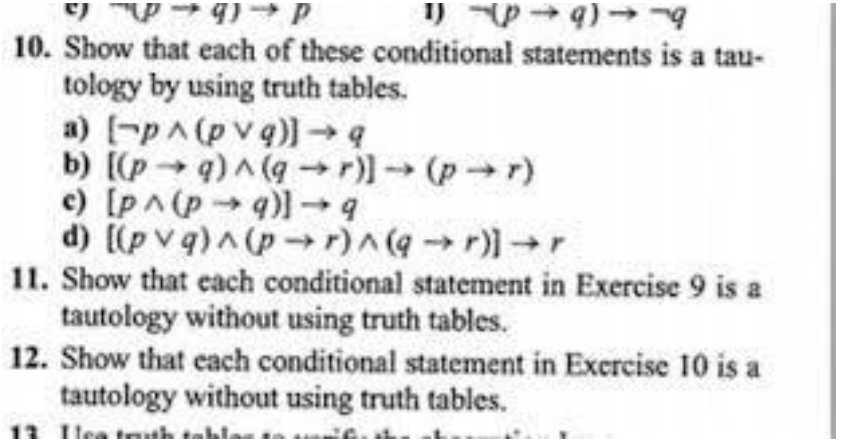
Some useful quotes (maybe)

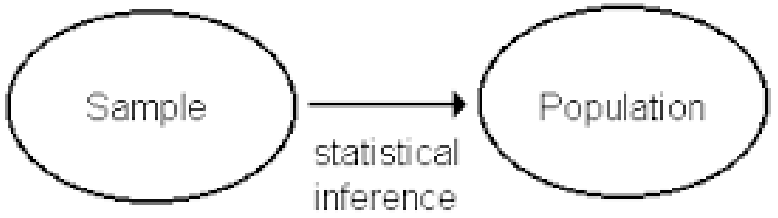
- “All mathematical models are tautologies ….. “



e) $\neg(p \rightarrow q) \rightarrow p$ f) $\neg(p \rightarrow q) \rightarrow \neg q$

10. Show that each of these conditional statements is a tautology by using truth tables.
    a) $[\neg p \wedge (p \vee q)] \rightarrow q$
    b) $[(p \rightarrow q) \wedge (q \rightarrow r)] \rightarrow (p \rightarrow r)$
    c) $[p \wedge (p \rightarrow q)] \rightarrow q$
    d) $[(p \vee q) \wedge (p \rightarrow r) \wedge (q \rightarrow r)] \rightarrow r$
11. Show that each conditional statement in Exercise 9 is a tautology without using truth tables.
12. Show that each conditional statement in Exercise 10 is a tautology without using truth tables.
13. Use truth tables to verify the absorption laws.

- “All statistical models are inferential engines …. “



- Therefore, “combining mathematical and statistical models results in tautological inferential engines“ *i.e.*, integrating observation and theory

Statistics for Biology and Health

M. Elizabeth Halloran • Ira M. Longini, Jr. • Claudio J. Struchiner

Design and Analysis of Vaccine Studies

Widespread immunization has many different kinds of effects in individuals and populations, including in the unvaccinated individuals. The challenge is in understanding and estimating all of these effects. This book presents a unified conceptual framework of the different effects of vaccination at the individual and at the population level. The book covers many different vaccine effects, including vaccine efficacy for susceptibility, for disease, for post-infection outcomes, and for infectiousness. The book includes methods for evaluating indirect, total and overall effects of vaccination programs in populations. Topics include household studies, evaluating correlates of immune protection, and applications of casual inference. Material on concepts of infectious disease epidemiology, transmission models, casual inference, and vaccines provides background for the reader. This is the first book to present vaccine evaluation in this comprehensive conceptual framework.

This book is intended for colleagues and students in statistics, biostatistics, epidemiology, and infectious diseases. Most essential concepts are described in simple language accessible to epidemiologists, followed by technical material accessible to statisticians.

Elizabeth Halloran and Ira Longini are professors of biostatistics at the University of Washington and the Fred Hutchinson Cancer Research Center in Seattle. Claudio Struchiner is professor of epidemiology and biostatistics at the Brazilian School of Public Health of the Oswaldo Cruz Foundation in Rio de Janeiro. The authors are prominent researchers in the area. Halloran and Struchiner developed the study designs for dependent happenings to delineate indirect, total, and overall effects. Halloran has made contributions at the interface of epidemiological methods, causal inference, and transmission dynamics. Longini works in the area of stochastic processes applied to epidemiological infectious disease problems, specializing in the mathematical and statistical theory of epidemics. Struchiner has contributed to understanding the role of transmission in interpreting vaccine effects.

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Stockholm University

Vaccine Efficacy and Direct Effects

Measures of Vaccine Efficacy

- $\{VE(t)_S , VE(t)_P , VE(t)_I\}$
- VE_S Vaccine Effect on Susceptibility
  - Classical III vaccine trials
    - Many times observe

    $VE_{SP} = 1 - (1 - VE_S)(1 - VE_P)$
  - Phase I and II vaccine trials
    - Correlates of immunity
  - Challenge studies in humans or animals
  - Leaky vs all-or-none

Measures of Vaccine Efficacy

- VE_P Vaccine Effect on Clinical Disease
  - Possible phase III vaccine trials if infection in both symptomatic and asymptomatic are included
  - Usually only VE_{SP} is available
  - Challenge studies in humans or animals
  - All-or-none

Measures of Vaccine Efficacy

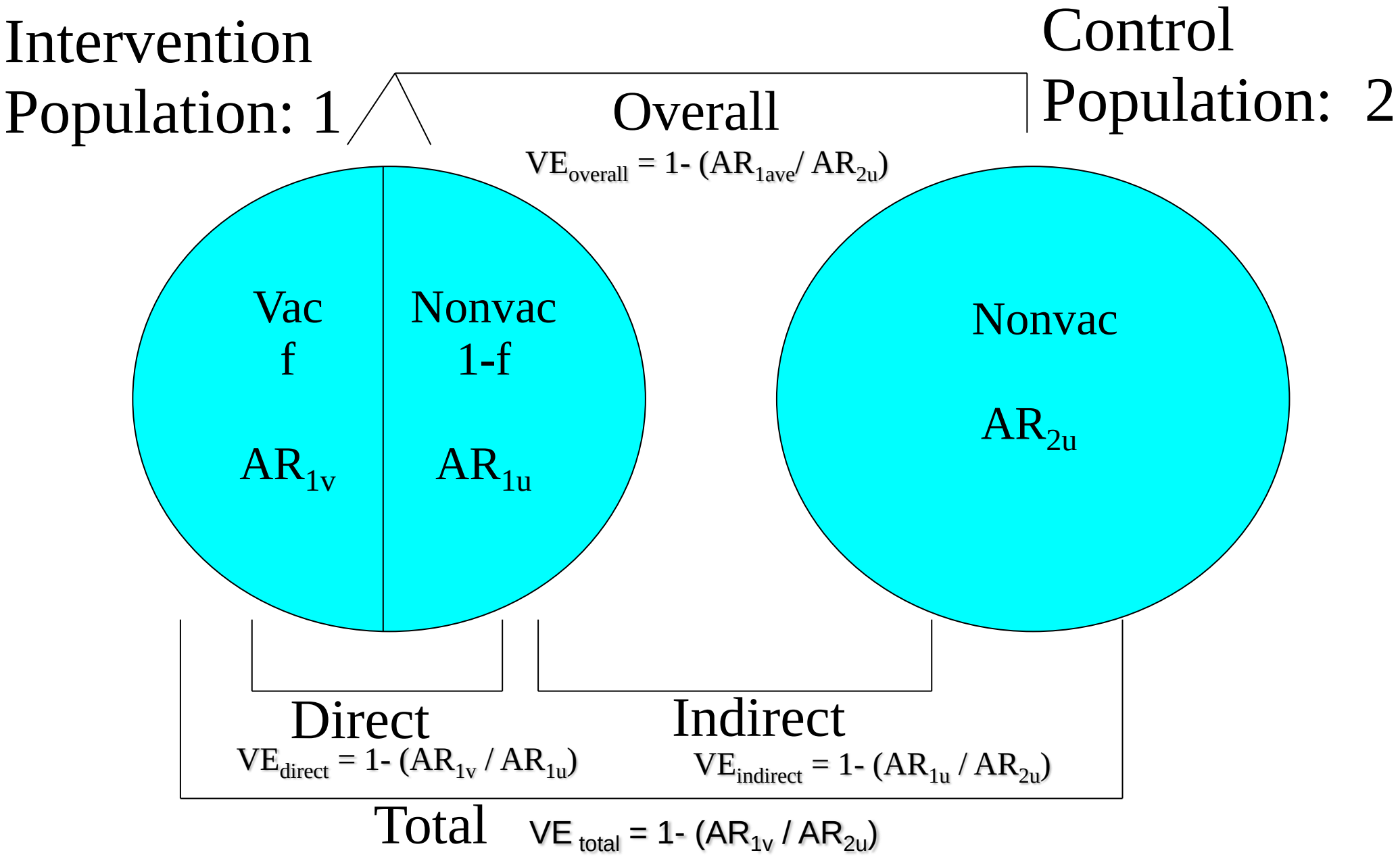
- VE_I Vaccine Effect on Infectiousness
  - Vaccine trials in households or other small transmission groups
    - Whole cell pertussis vaccine:

      $VE_I = 0.85\ (0.46 – 0.95)\ 95\%\ CI^*$
  - Teased out of indirect effects (community randomized vaccine trials, modeling)
  - Challenge studies in humans or animals, however challenge dose is usually too large

*Preziosi and Halloran. Effects of pertussis vaccination on transmission: Vaccine Efficacy for infectiousness, *Vaccine,* 21:1853-1861 (2003).

Indirect, total and overall effects

Vaccine Effectiveness



Effectiveness and impact

- Effectiveness
  - $VE_X = 1 - (r_{vac}/r_{novac})$
    - r_{vac} overall incidence rate with vaccination campaign
    - r_{novac} overall incidence rate with no vaccination in a comparable population

  - $VPDI_X = (\#risk)\ r_{novac} VE_X$, cases averted

    $= (\#risk)\ (r_{novac} - r_{vac})$

What models can do

- Provide reasonable simulations and analysis of vaccine effects on populations
  - Direct, indirect (heard immunity, overall and total effects)
- Be used to compare different vaccination strategies and find optimal strategies
- Help with design and analysis of vaccine trials and impact field studies

What models can do (continued)

- Provide hypotheses that can be tested in the field
- Provide impact numbers for cost effectiveness calculations
- Make accurate short term forecasts of vaccine program impact in particular populations
  - Probabilistic format
- Sensitivity analysis for poorly determined parameters and data

What models can not do

- Generate critical data on actual vaccine efficacy and impact in populations
  - This can only be done with real vaccine trials and, effectiveness trials and studies
  - Models will never replace field trials and studies
- Make accurate forecasts of vaccine program impact in particular populations
  - Long term forecasting is not possible except in very probabilistic forms

Case study of successful creation of a tautological inferential engine, i.e, successful integration of observation and theory

- Killed oral cholera vaccine impact
  - Licensed vaccine Shanchol
  - Phase IV vaccine effectiveness trials
  - Potential use of cholera vaccines

Start in the field $\longrightarrow$ modeling

- Killed oral cholera vaccine trial in Matlab Banglesh, 1985-1989.
  - Clemens, et al. *Lancet* **335** (1990)
    - $VE_{SP} \approx 0.65$, waning protection, about 2.5 years
  - Ali, et al. *Lancet* **366** (2005) – Create CRT!
    - GIS mapping of cases, evidence of indirect protections
  - Longini, et al. PLoS Med (2007)
    - Mathematical model projecting indirect, total and overall effectiveness for one year

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

Vaccination Coverage (%)		Mean Cases/1000 (95% CI)				Mean Direct Effectiveness (%) (95% CI)	
		Placebo		Vaccinated			
Target Population	Overall Population	Observed	Simulated	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)

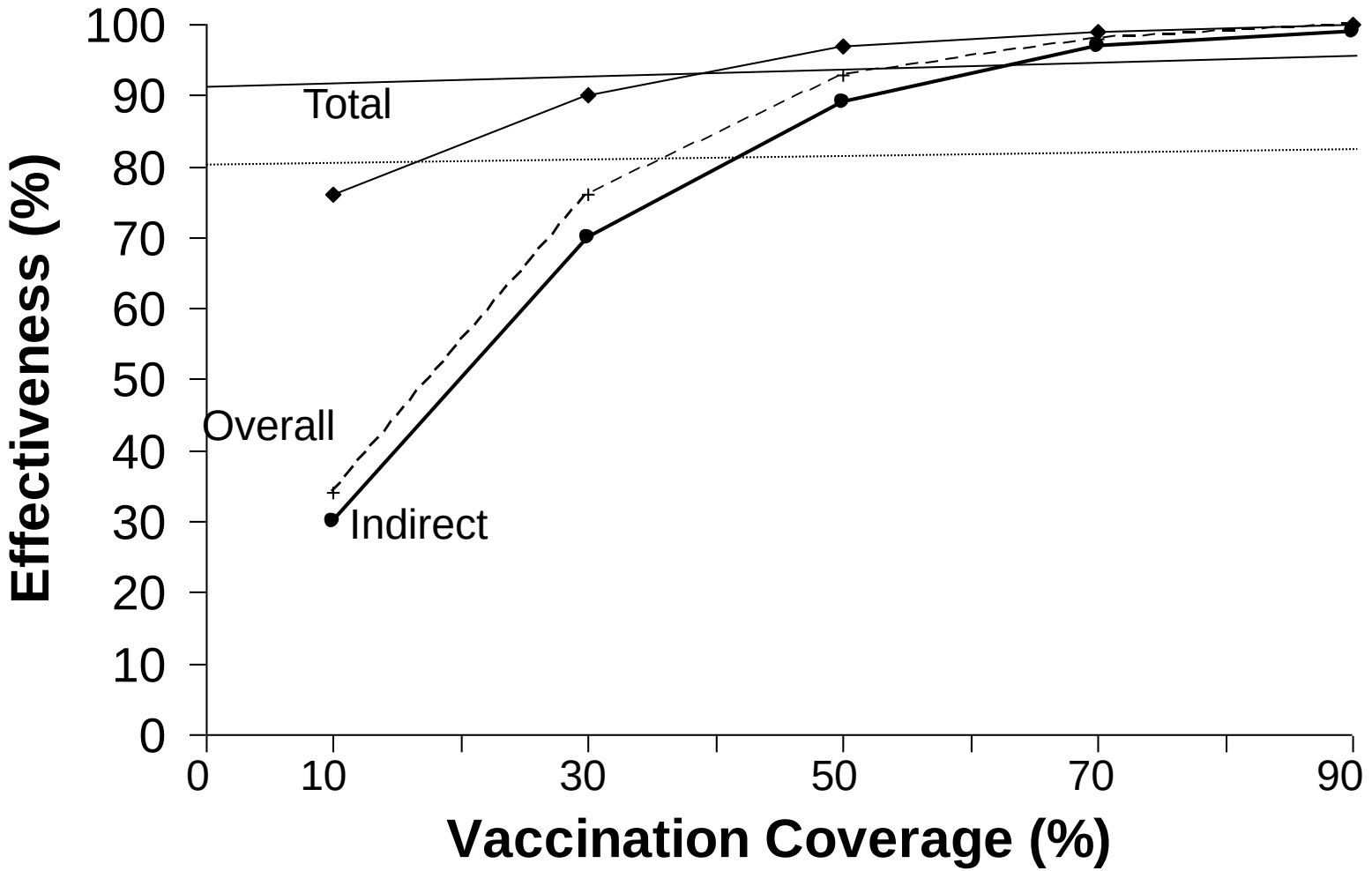
χ^2 goodness-of-fit test for frequency data p = 0.84

Source: Longini, et al. Controlling endemic cholera with oral vaccines. PloS Med (2007)

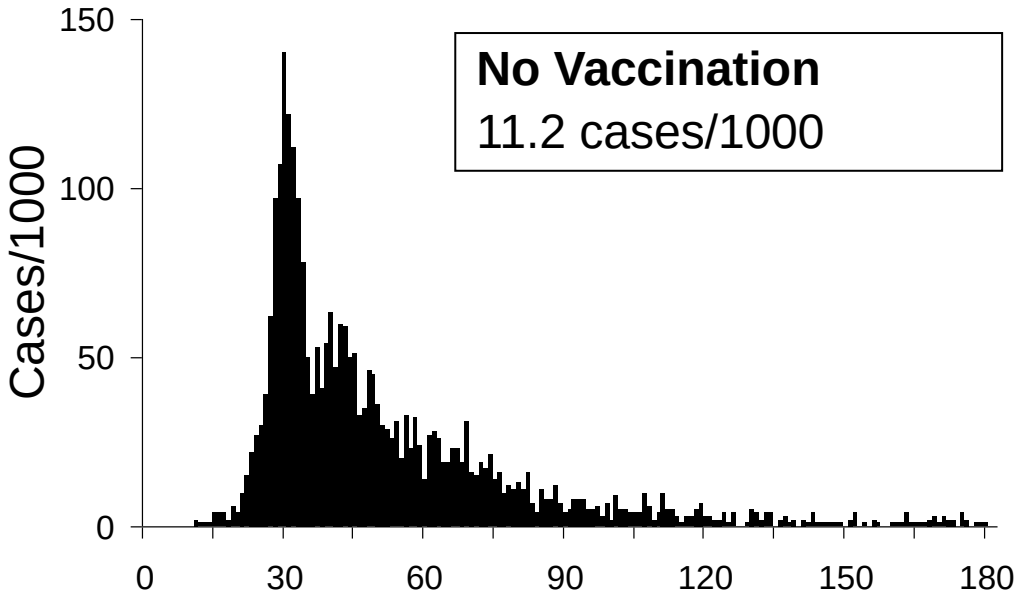
Average Indirect, Total and Overall Effectiveness of Vaccination, and Cases Prevented 10,000 Per Doses

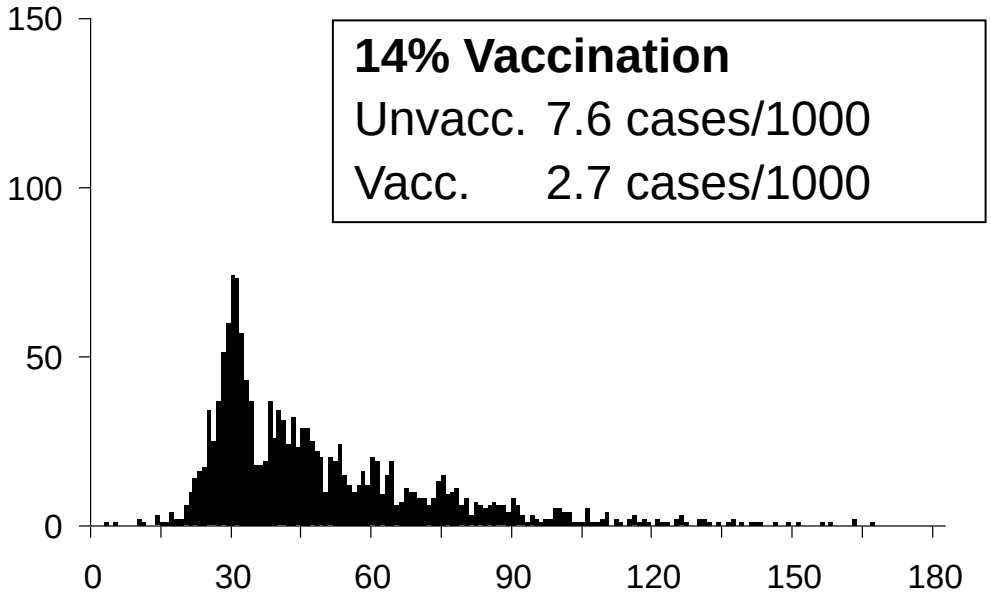
Vaccination Coverage (%)	Mean Effectiveness (%) (95%CI)			Mean # Cases Prevented per 10,000 Doses
	Indirect	Total	Overall	
10	30 (-39, 83)	76 (47, 95)	34 (-30, 84)	50
30	70 (31, 93)	90 (76, 98)	76 (44, 95)	40
50	89 (72, 98)	97 (91, 99)	93 (82, 99)	30
70	97 (91, 99)	99 (97, 100)	98 (95, 100)	20
90	99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

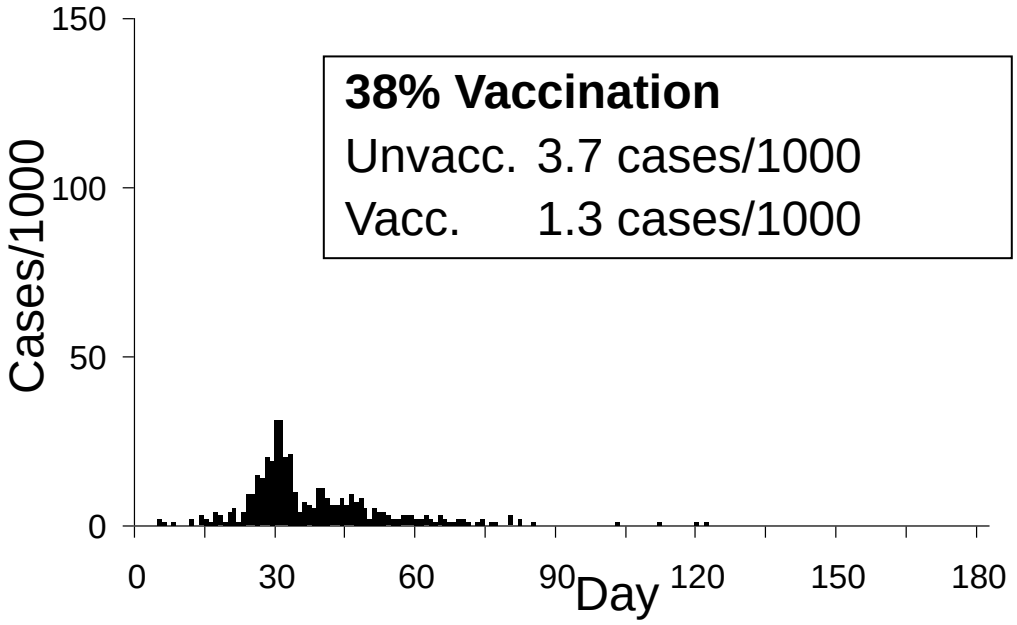
Source: Longini, et al. Controlling endemic cholera with oral vaccines. PloS Med (2007)

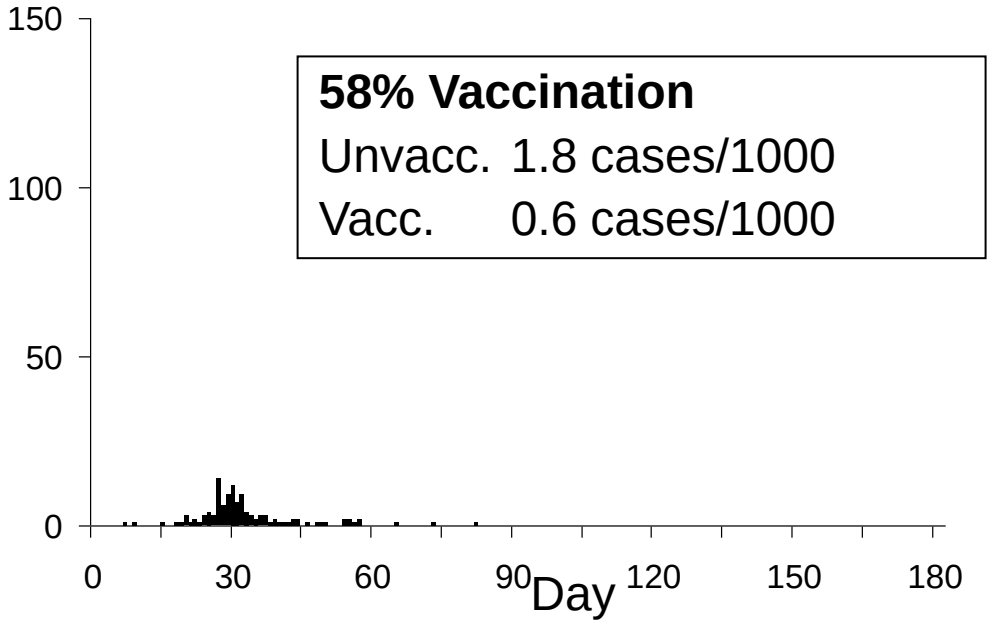


Source: Longini, et al. Controlling endemic cholera with oral vaccines. PloS Med (2007)


No Vaccination
11.2 cases/1000
Cases/1000
150
100
50
0
0
30
60
90
120
150
180

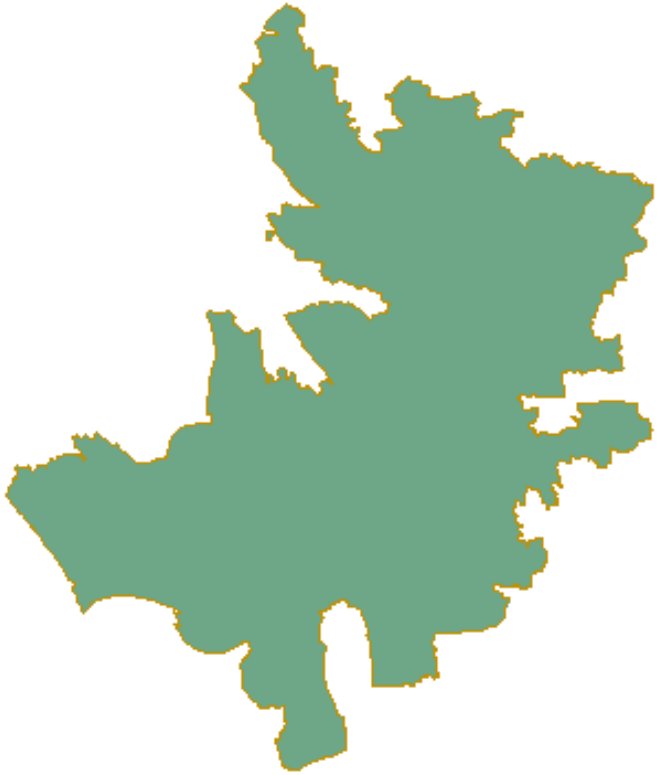

14% Vaccination
Unvacc. 7.6 cases/1000
Vacc. 2.7 cases/1000
150
100
50
0
0
30
60
90
120
150
180


38% Vaccination
Unvacc. 3.7 cases/1000
Vacc. 1.3 cases/1000
Cases/1000
150
100
50
0
0
30
60
90
120
150
180
Day


58% Vaccination
Unvacc. 1.8 cases/1000
Vacc. 0.6 cases/1000
150
100
50
0
0
30
60
90
120
150
180
Day

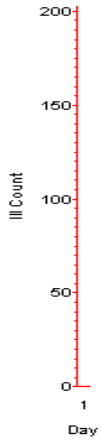
Mass Vaccination: 0 % Day 1

Red: Ill Yellow:Recovered



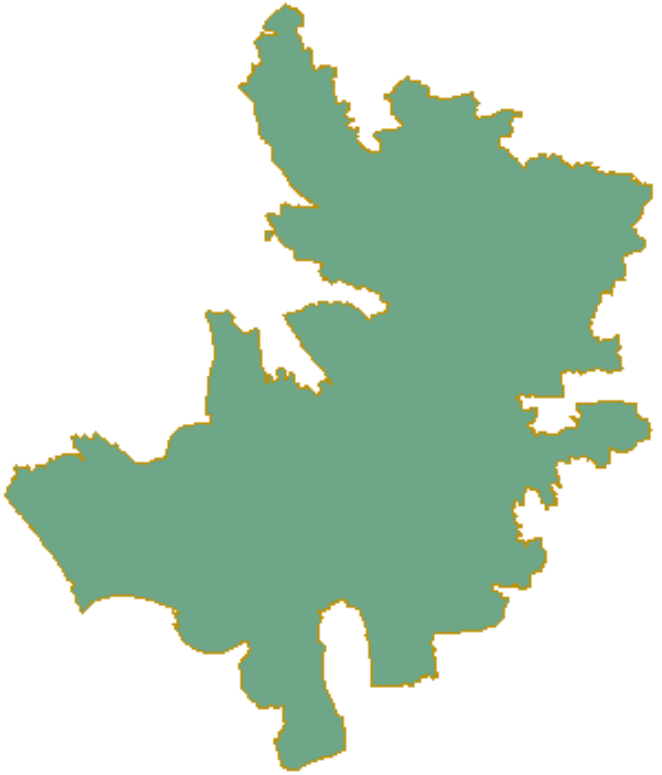
Epidemic curve: Day 1

Mass Vaccination:0 %



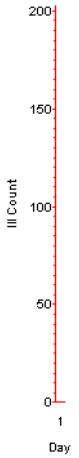
Mass Vaccination: 58 % Day 1

Red: Ill Yellow:Recovered



Epidemic curve: Day 1

Mass Vaccination:58 %



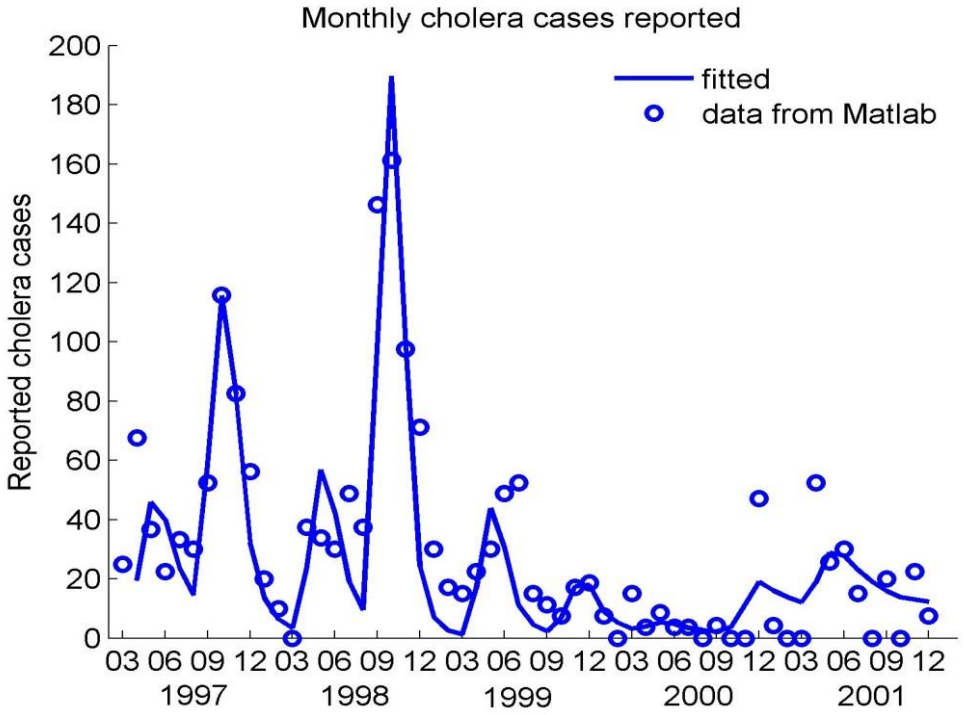
Field first → model → back to the field

- Development of killed oral cholera vaccine Shanchol by International Vaccine Institute and partners
- Large scale cluster-randomized trial of Shanchol in Kolkata, India, 2006 - present
  - Bhattacharya, et al.: *Lancet* **13** (2013) (5 yrs follow-up)
    - $VE_{SP,\ older\ than\ 5\ yrs} \approx 0.65$, $VE_{SP,\ 1\text{-}5\ yrs} \approx 0.40$
    - at least 5 years of protection
  - Dimitrov, et al.: *PLoS* (2014).
    - Mathematical modeling of the indirect, total and overall effectiveness over a 20 year horizon

Modeling to implement policy

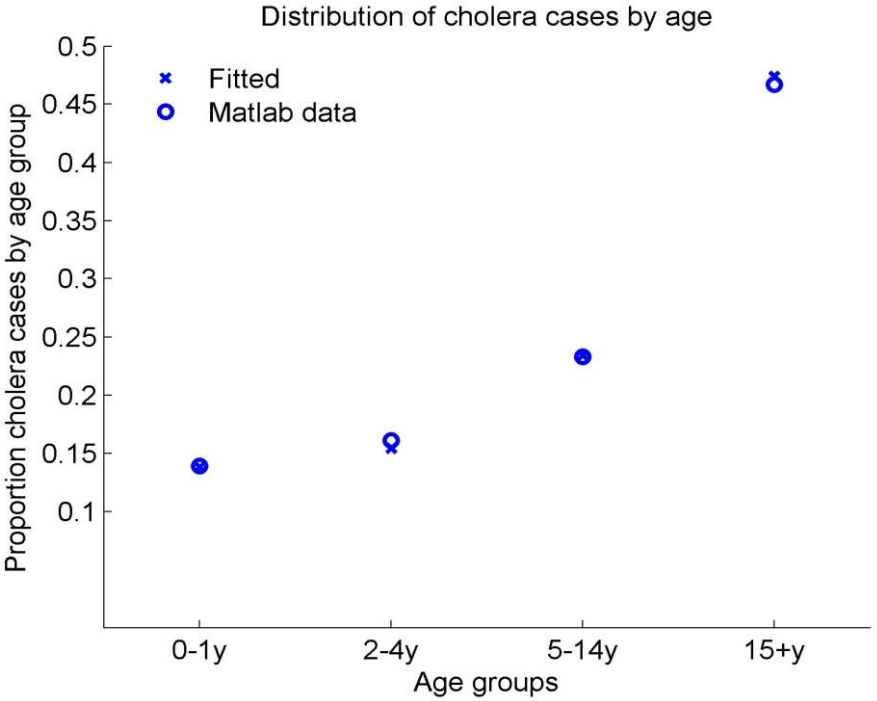
Dimitrov DT, Troeger C, Halloran ME, Longini IM, Chao DL. Comparative effectiveness of different strategies of oral cholera vaccination in Bangladesh: A modeling study. PLoS Negl Trop Dis. DOI: 10.1371/journal.pntd.0003343 (2014).

Model calibration 1997-2001(Matlab, Banglash



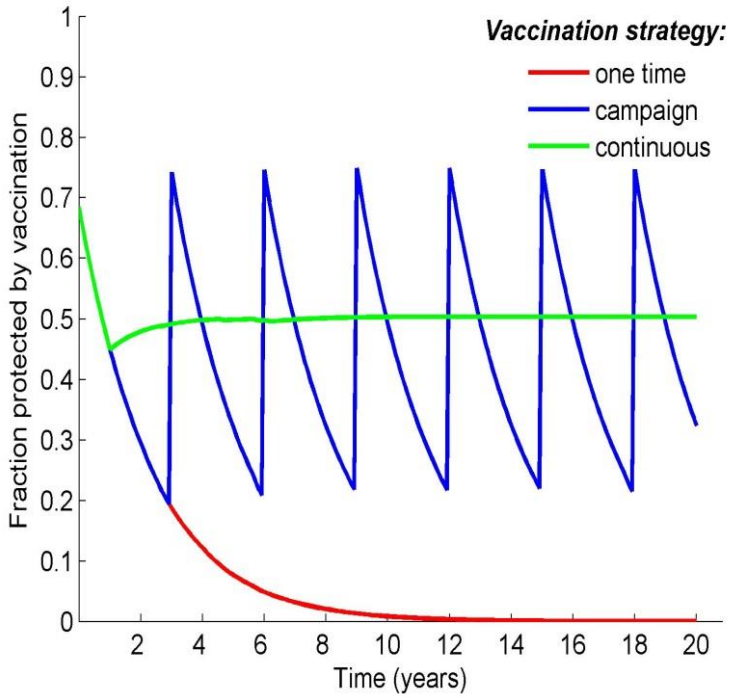
Relative susceptibility		
0-1y	2-4y	5-14y
6.274	5.253	1.845

Magnitude I period	Magnitude II period	Delay II period
10-80	15-150	0-60



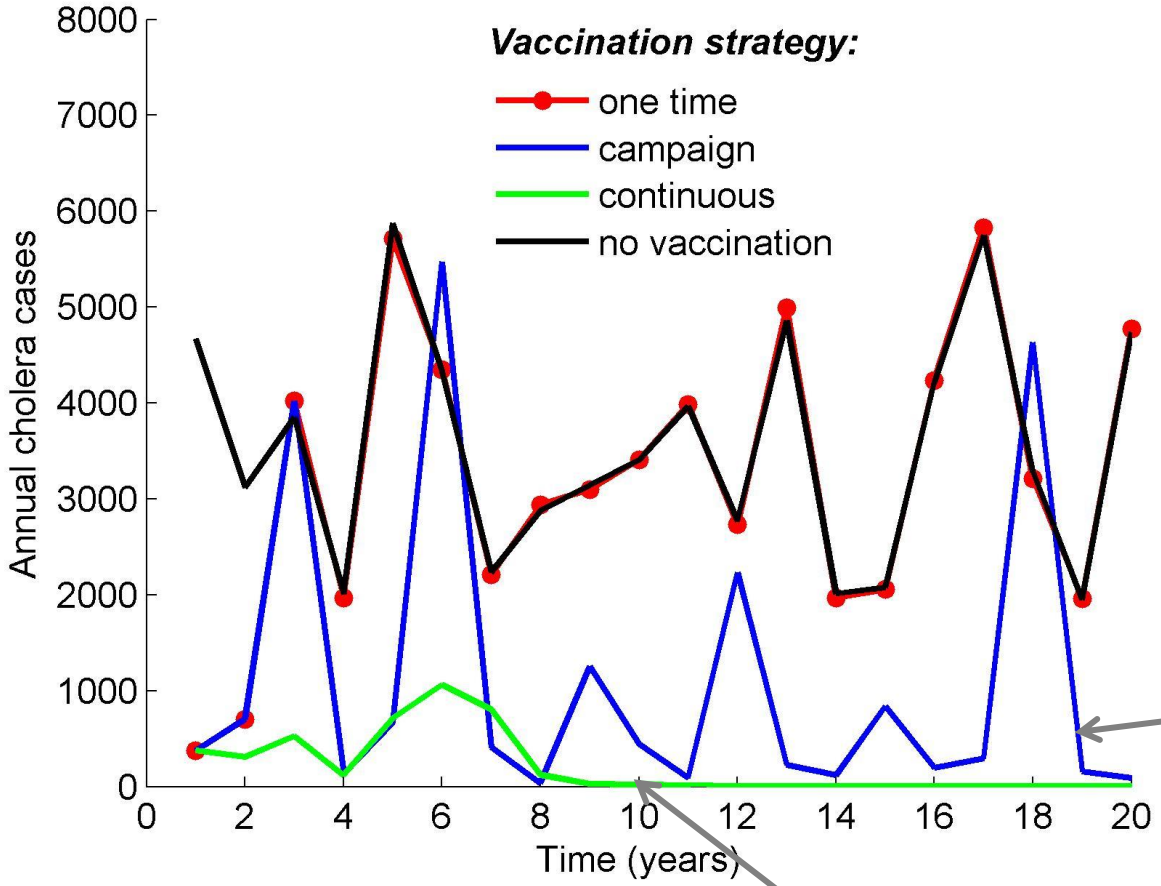
Vaccination strategies

- **One time vaccination**. A proportion (coverage) of the targeted population is vaccinated once at the start of the simulation.
- **Periodic campaigns.** A proportion of the targeted population is vaccinated every three years.
- **Continuous vaccination.** A proportion of the targeted population is vaccinated initially After the first year, a continuous revaccination is in place at a fixed rate.



- **Periodic campaign with limited doses.** A limited number of vaccine doses are distributed to the targeted population, as mass vaccination campaigns every three years. The vaccine supply is assumed to be sufficient to vaccinate 5,000, 10,000, and 15,000 individuals per campaign.

Results: Annual cholera cases

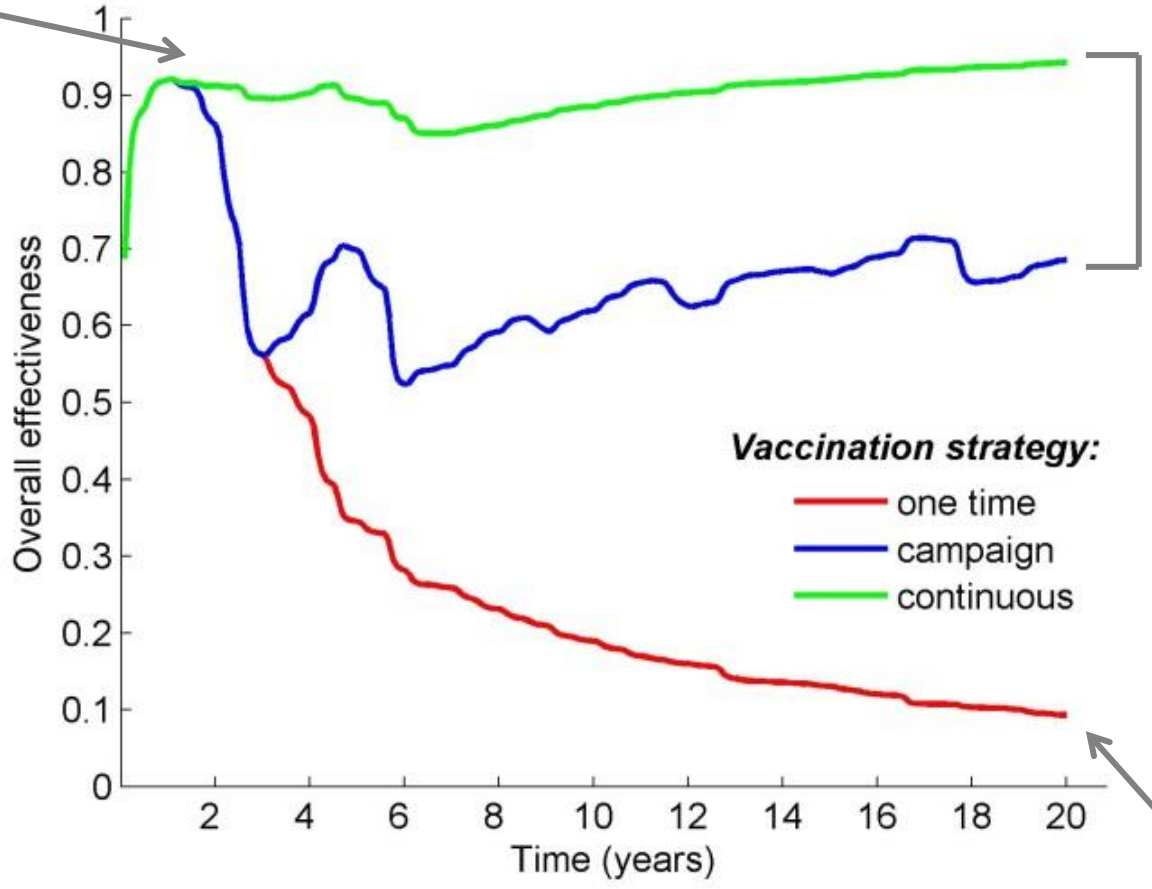


cholera incidence oscillates and peaks in the years preceding each campaign

cholera transmission is basically stopped after 10 years

Results: Overall effectiveness

70% vaccination coverage averts more than 90% of the cholera cases in the first year



continuous strategy achieves 20% higher effectiveness

Effectiveness of one-time vaccination is only about 10% after 20 years

Summary for cholera vaccines: What models and data can do

- Our results indicate that maintaining 50% vaccine coverage in the population is required to stop cholera transmission.
- Vaccination campaigns every three years may be easier to implement, but large cholera outbreaks can occur due to protection waning and adding new susceptible individuals to the population between campaign.
- Vaccinating young children, ages 1-4 years, requires the fewest number of vaccinations per case averted compared to vaccinating all children (1-14 years) or the general population (ages 1 year and older) but may not be enough to interrupt the circulation of cholera.

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Thank You