Achieving coordinated national immunity and cholera elimination in Haiti through vaccination

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1 Introduction

The primary objective of this modeling exercise was to forecast the potential for oral cholera vaccination (OCV) campaigns to eliminate cholera from Haiti. We formed a modeling consortium of research teams that had previously modeled cholera transmission dynamics in Haiti (*1–3*). For ease of comparison, we decided upon common parameters and assumptions related to vaccine protection and vaccine campaign logistics. We shared common data sources, used a common definition of elimination across models and produced comparable outputs for figures and analyses. All other modeling decisions and assumptions were left to the discretion of each team.

All teams adapted and improved upon their previously published models of Haiti transmission dynamics for this new modeling effort. In brief, teams fit their models to a common cholera incidence data source, using the different slices of the data according to their model structures and assumptions. Then they generated model projections of true and reported cholera incidence 10 years past the end of the data available for model fitting. Multiple 10-year projections were produced by each model; a *status quo* scenario and five primary vaccination campaign scenarios that differ by deployment and vaccination coverage. To coordinate the modeling efforts, we held bi-weekly phone calls to discuss progress, troubleshoot problems, and settle on common assumptions and timelines.

We discussed the goals of the project and methods with partners in the Haiti Ministry of Public Health and Population (MSPP) at the onset of this initiative for feedback on the approach and primary assumptions. Once work had started, we had multiple consultative meetings in Haiti and by teleconference with epidemiologists, researchers and clinicians that had were involved in the cholera response in Haiti in their individual capacities.

2 Methods

2.1 Data Sources

All teams fit their models to publicly available weekly department-level cholera reports of suspected cases from the MSPP website (*4*). Data were available for the week of October 23, 2010 through the week of January 12, 2019.

Teams also had the option to use the following additional shared data sources, formally or informally in to calibrate or validate the models:

1. The number of confirmatory tests (culture) conducted and the number positive in 2016 and 2017 from US CDC and MSPP;

2. The number of doses administered and fully vaccinated persons from coverage surveys of historical deployments of OCV in Haiti among selected communes in Grand'Anse (first round: November 2016; second round: May to June 2017), Sud (first round: November 2016 to January 2017; second round: May to June 2017), Ouest (first round: July 2017; second round: August 2017), Centre (first round: November 2017; second round: December 2017), and Artibonite (first round: April 2018; second round: May 2018).

2.2 Vaccine Campaign Logistics

2.2.1 Rollout

We implemented four vaccine campaign deployment scenarios, each starting the day or week (depending on model implementation) after the last data point used for model calibration (week of January 12, 2019). Campaigns targeted departments in order of 2017-2018 cumulative incidence from highest to lowest (Table 1).

Campaign Order	Department	Population (2015)	Incidence per 1K (2017/18)
1	Centre	746,236	4.30
2	Artibonite	1,727,524	2.73
3	Ouest	4,029,705	1.60
4	Nord Ouest	728,807	1.14
5	Nord	1,067,177	1.02
6	Sud	774,976	0.65
7	Nippes	342,525	0.62
8	Nord Est	393,967	0.42
9	Sud Est	632,601	0.36
10	Grand'Anse	468,301	0.25

Table 1: Departments in Haiti, ordered by cumulative incidence from 2017-2018

In our rollout scenarios, we aimed to capture the potential impacts of three general types of vaccination approaches: (1) rapid vaccination of a limited geographic area; (2) rapid vaccination of the entire country; and (3) national vaccination over a longer rollout period. Specifically, the campaign scenarios are:

- **Two-department**: Vaccination limited to the departments of Centre and Artibonite over a 2-year period, similar to plans outlined in the national cholera elimination plan for Haiti (*5*).

- **Three-department**: Vaccination limited to the departments of Centre, Artibonite, and Ouest (which includes the populous Port-au-Prince) over a 2-year period.

- **Fast national** (named 'National' in the main text): Countrywide vaccination implemented over a 2-year period.

- **Slow national**: Countrywide vaccination implemented over a 5-year period.

2.2.2 Vaccination Coverage

Killed OCVs are licensed as a two-dose regimen, with doses taken at least two weeks apart (*6*). All simulated campaigns aimed to vaccinated everyone with two doses, however, following data from previous vaccination campaigns, a fraction of individuals only received a single dose and some remained unvaccinated. In our primary simulations, we assume that vaccine coverage is the same in all departments with 70% two-dose coverage, 10% one-dose coverage and 20% receiving no vaccine. We also simulated one 'high coverage' campaign, where departments achieved 95% two-dose coverage, 1.67% one-dose coverage and 3.33% unvaccinated at the end of the campaign.

Combining vaccination rollout and coverage scenarios, we had simulated results for five vaccination scenarios that required different numbers of vaccines (Table 2).

Scenario	Number of OCV Doses Needed
2-department	3.71 million
3-department	9.76 million
slow national	16.37 million
fast national	16.37 million
high coverage fast national	20.91 million

Table 2: Roughly, the number of vaccines needed to complete each vaccination deployment scenario.

2.3 Protection from Vaccination

2.3.1 Vaccine efficacy among adults

Two data sources were used to develop the model of vaccine efficacy used for our study. Using the raw data from a published meta-analysis (excluding a single outlier estimate of vaccine efficacy in India after 5 years to be conservative) (*6*), where vaccine efficacy was reported for short, discrete, time windows, we performed a log-linear weighted regression model to describe the monthly waning efficacy of vaccine (Figure 1 and Table 3). Using these data points, we modeled vaccine efficacy estimates to decline from 64% after initial vaccination to 15% after five years. A subsequent 4-year case-control study in Haiti conducted over four years did not find evidence for decreased vaccine effectiveness (average cumulative vaccine effectiveness of 76%) over the time period, although the sample size was limited after 2 years (*7*).

In simulations, all teams used the early vaccine effectiveness estimate from the case-control study in Haiti (76%) and assumed that vaccine efficacy waned at the rate we estimated in the efficacy meta-analysis described above (Table 3). We assumed that the vaccine afforded no protection after the end of five years.

Months after vaccination	2-Dose Efficacy, Adults (%)	1-Dose Efficacy, Adults (%)	2-Dose Efficacy, Children (%)	1-Dose Efficacy, Children (%)
0	76	76	36	36
6	72	72	34	34
12	68	68	32	32
18	63	0	30	0
24	58	0	27	0
30	52	0	24	0
36	46	0	22	0
42	39	0	18	0
48	32	0	15	0
54	24	0	11	0
60	15	0	7	0

Table 3: Vaccine efficacy assumptions for adults and children used in modeling scenarios.

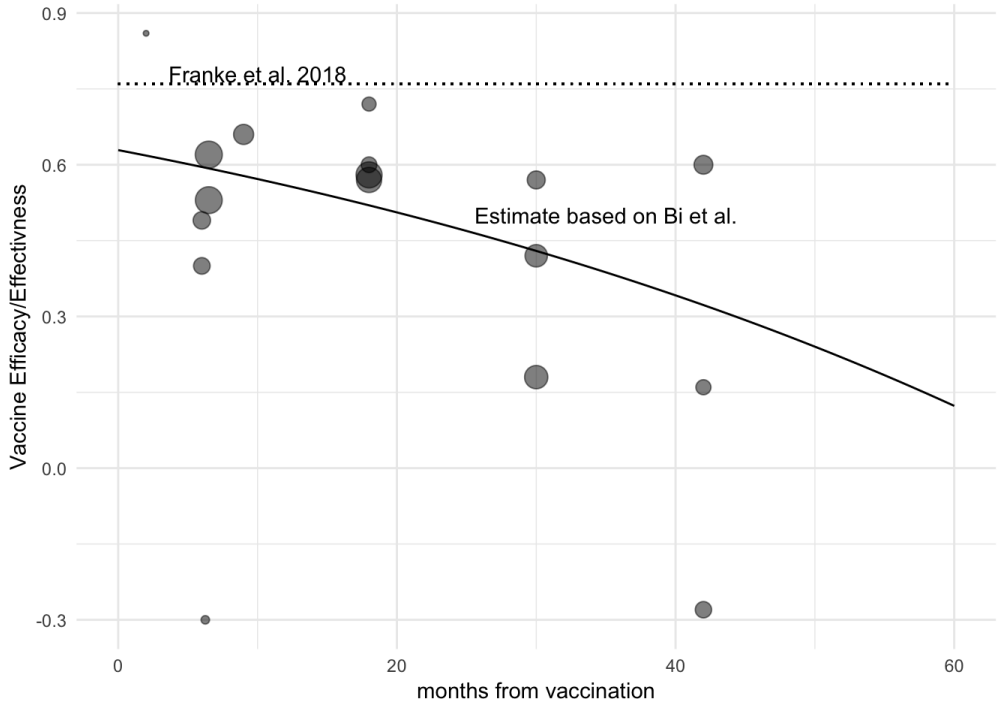

Figure 1: Inputs to the model of vaccine efficacy among adults over time. A simple log-linear model was fit to vaccine efficacy data from a the meta-analysis by Bi et al. (black line). Circles represent individual estimates from studies with the size proportional to the standard error of the original vaccine efficacy estimate. The dotted line represents the data reported by the Franke et al. observational study of vaccine effectiveness in Haiti. Our models assumed that early vaccine efficacy achieved the level of protection observed in Franke et al. and that vaccine efficacy decayed over time at the same rate as modeled from data in Bi et al.

2.3.2 Vaccine efficacy among children

Following estimates from a recent meta-analysis, the average efficacy among children under five years old was 46.88% (0.30/0.64) as effective as that in adults (*6*). As there are limited data on vaccine efficacy among children, we used this ratio as a conservative multiplier to adjust the adult vaccine efficacy for vaccine efficacy among children under five (Table 3).

2.3.3 Vaccine efficacy from a single dose

In the first year after vaccination, individuals who received a single dose of vaccine were assumed to have the same protection as those with two doses, after which period the single dose efficacy drops to zero (Table 3).

2.4 Model outcomes

Teams aimed to estimate the probability of "true" elimination within ten years after the start of vaccination campaigns, defined as less than one cholera infection (includes reported and unreported cases) over at least 52 consecutive weeks. The ten-year period without resurgence was deemed adequate to limit the possibility of cholera reseeding from human or environmental reservoirs. As defined in these experiments, elimination represents a state of "no transmission," not a state of "no reporting."

For each simulation and scenario, teams produced outputs according to common modeling templates: (1) Weekly time series of reported cholera cases (median and upper and lower uncertainty interval bounds); (2) Weekly time series of true cholera infections (median and upper and lower uncertainty interval bounds); (3) Elimination date (the date that represents the start of the period where true cholera infections dips below one and remains there through the end of the ten year simulation timeframe)

2.5 Additional model assumptions

The four models ranged from simple stochastic compartmental models to agent-based models of cholera dynamics in the entire country, as summarized in Table 4. Model-1, from the Johns Hopkins Bloomberg School of Public Health, represents all of Haiti as a single population in a stochastic compartmental model. Model-2, from Fred Hutchinson Cancer Research Center and University of Florida, is a deterministic metapopulation model with inter-departmental connectivity through human movement and bacteria flow on river networks. Model-3, from École Polytechnique Fédérale de Lausanne, is a stochastic metapopulation model with calibrated, non-specific inter-departmental connectivity and rainfall-driven seasonal transmission. Model-4, from the Institute for Disease Modeling, is an agent-based model that uses a synthetic representation of the Haitian population, including household structure, age structure and a transmission function driven by human mobility, river network connectivity, and human interaction with environmental reservoirs. Additional details on model structure, calibration and fit are described in the individual team supplements and .

Model	Spatial Scale	Seasonality Function	Environmental Transmission	Age Structure	Spatial Transmission Dynamics
1	National	Basis splines	No	None	None
2	Department	Sinusoidal	Yes	None	Road and river networks
3	Department	Rainfall	Yes	None	Calibrated human mobility
4	1 km x 1 km grid	Rainfall	Yes	Yes	Road and river networks, commuting

Table 4: Summary of key model features across teams

2.6 Data and model access and detailed model supplements

All modeling teams have provided a detailed supplementary methods and results section, which are assembled collectively at the summary DOI: 10.5281/zenodo.3361800. We performed an internal review of these supplementary documents in order to enhance the readability of these materials. Teams have also made available input data and model code at the following DOIs:

- Model-1, Johns Hopkins Bloomberg School of Public Health: 10.5281/zenodo.3360991
- Model-2, Fred Hutchinson Cancer Research Center and University of Florida: 10.5281/zenodo.3360857
- Model-3, École Polytechnique Fédérale de Lausanne: 10.5281/zenodo.3360723
- Model-4, Institute for Disease Modeling: 10.5281/zenodo.3360885

3 Results

3.1 Projections of true cholera infection

We present the median projections of true cholera infections for the status quo and five vaccination scenarios (Figures 2, 3, 4, 5, 6, 7). Here, 'cholera infections' include all cases that may result in onward transmission of disease (e.g., reported and unreported cases, symptomatic and potentially asymptomatic cholera).

There was substantial variation across models in the estimated reporting rate of surveillance, which led to orders-of-magnitude differences in the estimated projections of true cholera infections (e.g., Model-4 had much lower estimated reporting rates than the other models).

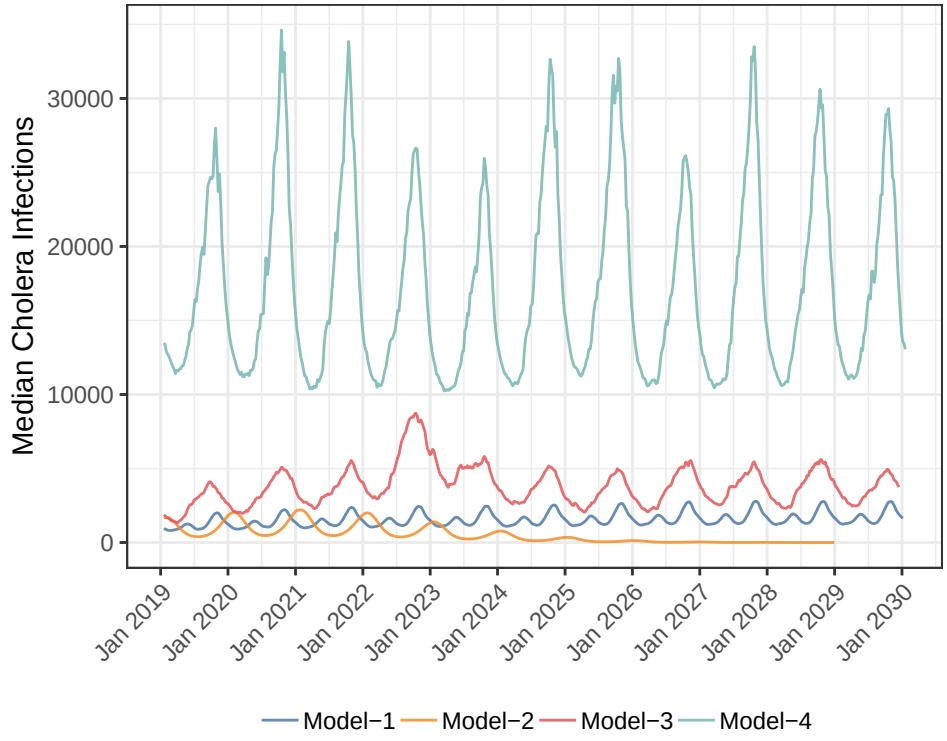

Figure 2: Median projections of true cholera infections for the no vaccination (status quo) scenario across teams.

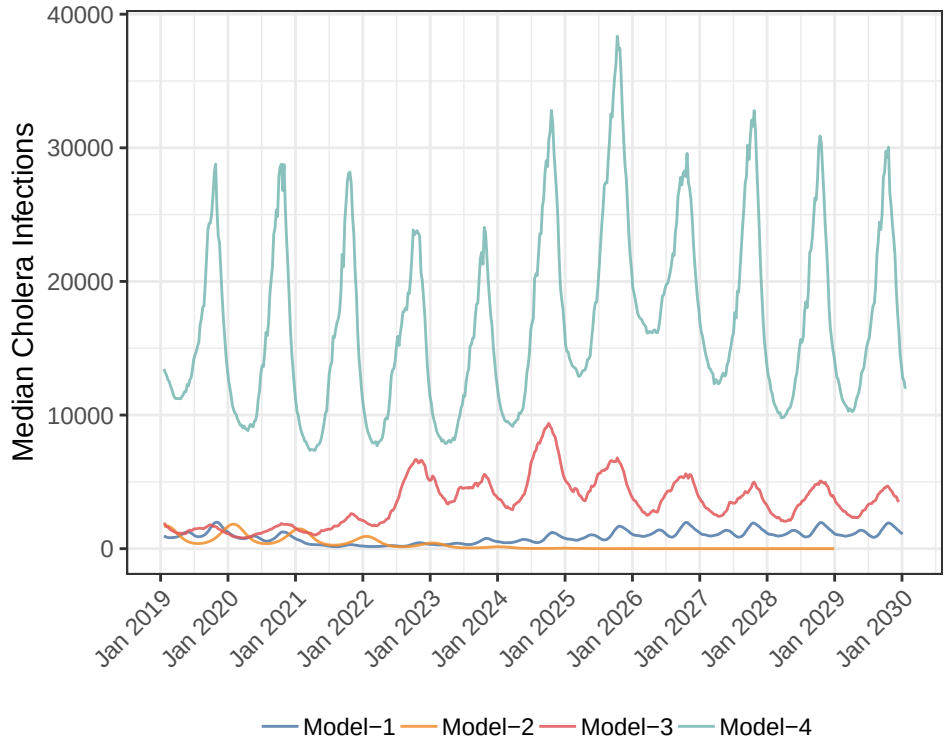

Figure 3: Median projections of true cholera infections for the 2 department vaccination campaign across teams.

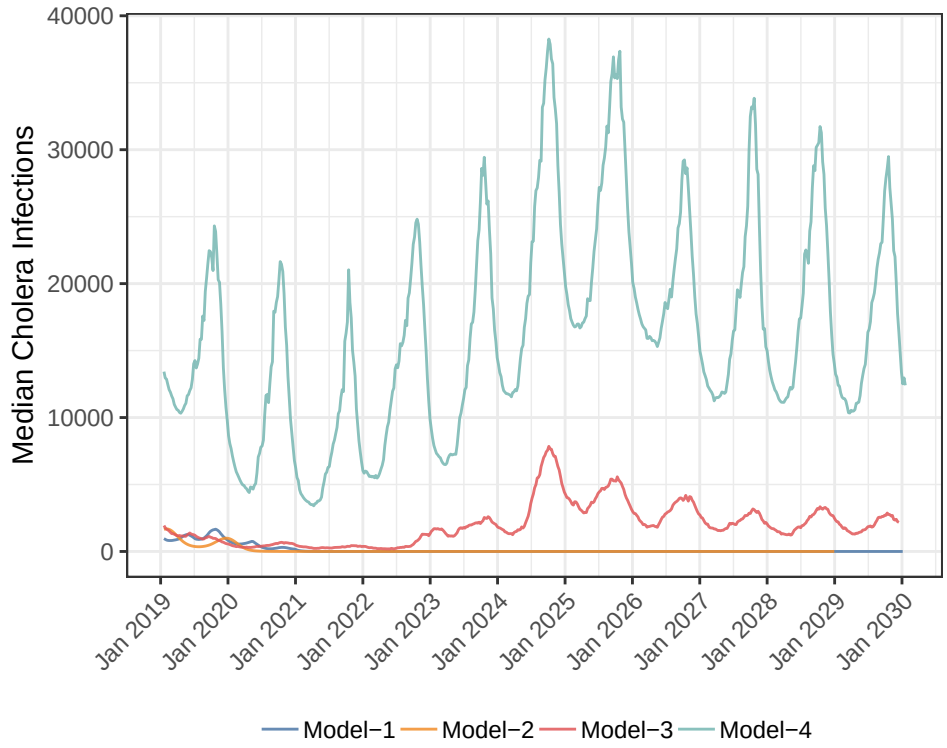

Figure 4: Median projections of true cholera infections for the 3 department vaccination campaign across teams.

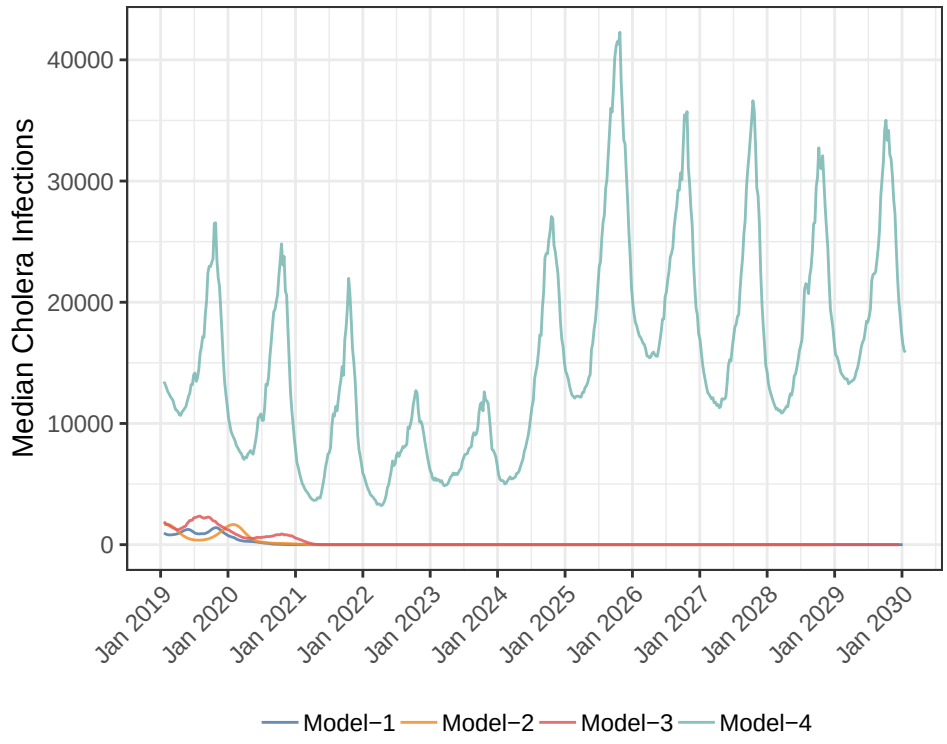

Figure 5: Median projections of true cholera infections for the slow national vaccination campaign across teams.

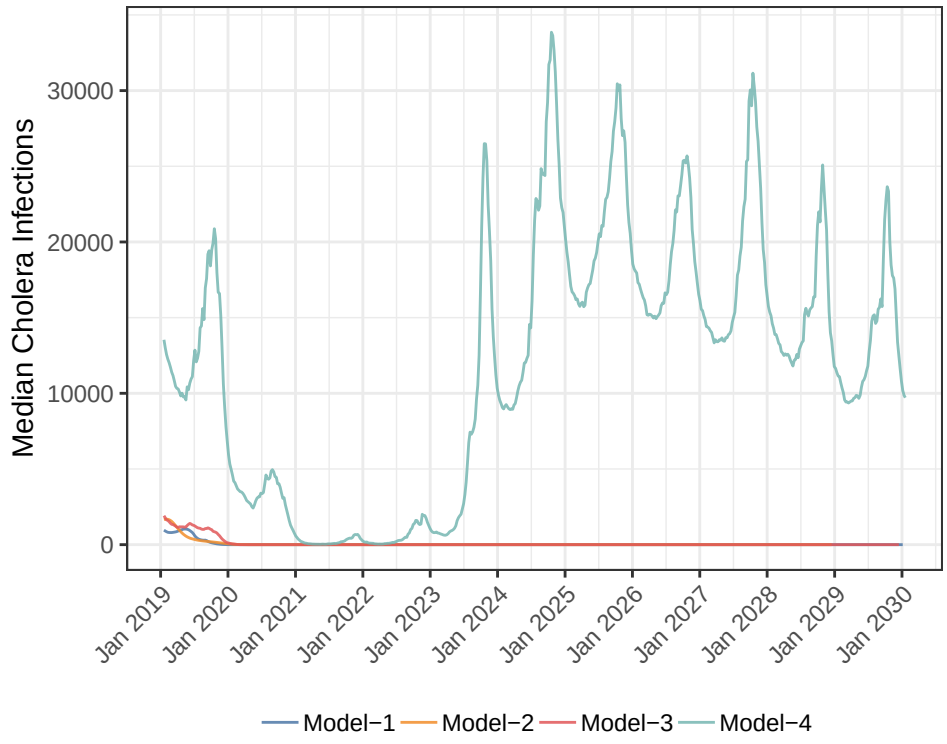

Figure 6: Median projections of true cholera infections for the baseline coverage fast national vaccination campaign across teams.

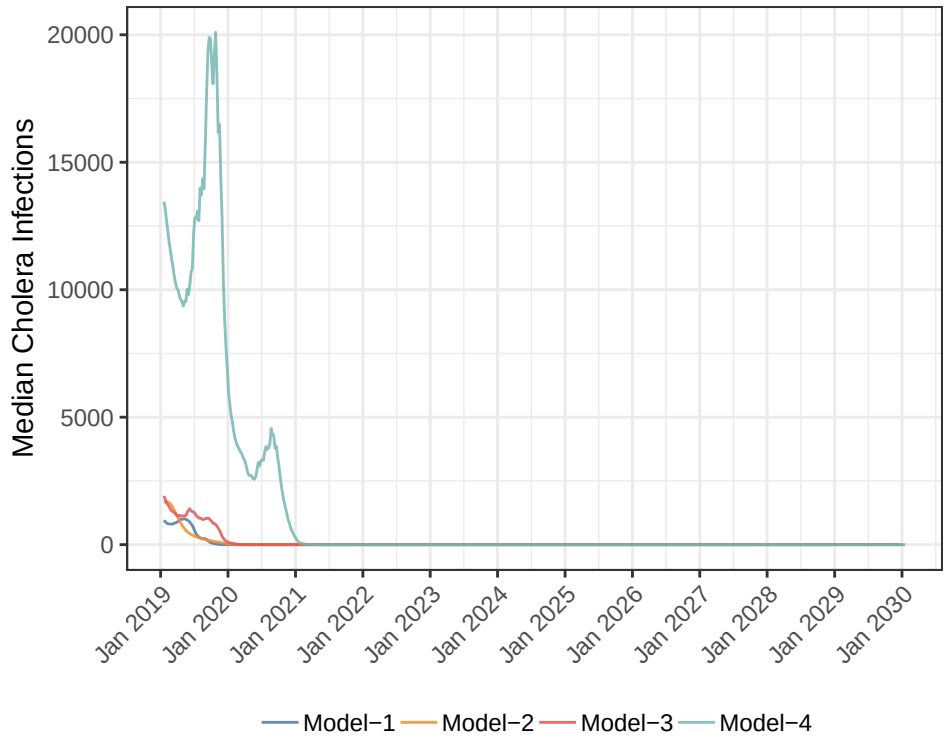

Figure 7: Median projections of true cholera infections for the high coverage fast national vaccination campaign across teams.

3.2 Probability of Elimination

Next we present summaries of probability of elimination for the no vaccination (status quo) and five vaccination scenarios (Figures 8, 9 and Table 5). There was divergence across models for all scenarios. As might be expected, models with higher reporting rate estimates (Model-1, Model-2, and Model-33) had greater probability of elimination than the model with low reporting rate estimates (Model-4). Model-2 was the only one that projected stochastic outbreak die-offs in the status quo and 2-department scenarios (demonstrated with the increasing probability of elimination over time).

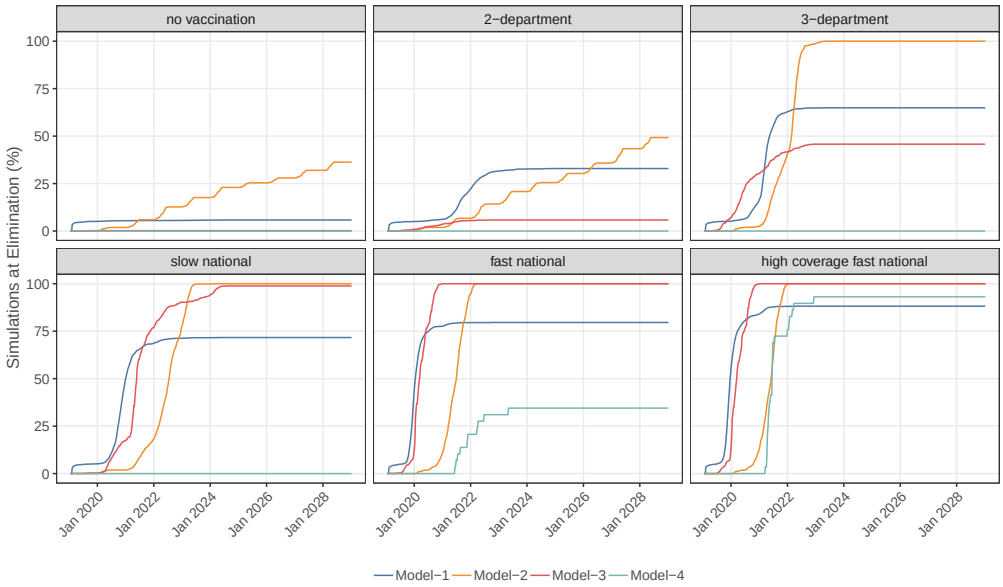

Figure 8: Percentage of simulations achieving elimination over time across scenarios and teams.

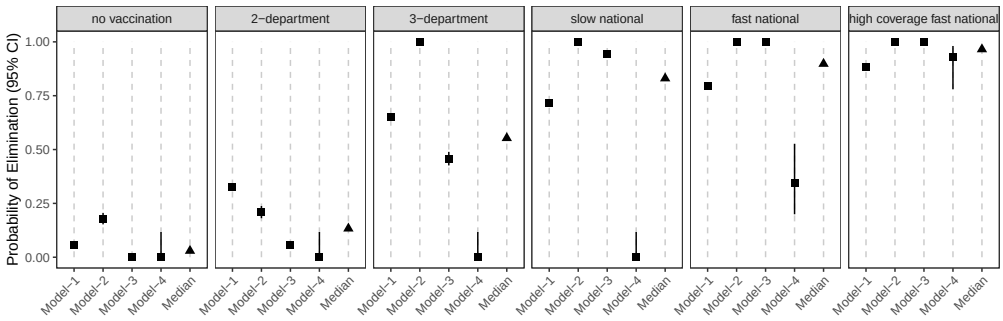

Figure 9: Probability of elimination 5 years after the start of vaccination campaigns across scenarios and teams.

Model	no vaccination	2-department	3-department	slow national	fast national	high coverage fast national
1	6 (5-7)	33 (31-34)	65 (63-66)	72 (70-73)	80 (78-81)	88 (87-89)
2	18 (15-21)	21 (18-24)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)
3	0.2 (0.06-0.8)	6 (5-7)	46 (43-49)	94 (93-96)	100 (100-100)	100 (100-100)
4	0.0 (0-12)	0 (0-12)	0 (0-12)	0 (0-12)	34 (20-53)	93 (78-98)

Table 5: Median percentage probability of elimination (95% CI) 5 years after the start of vaccination campaigns across scenarios and teams.

3.3 Time to Elimination

Simulations that achieved elimination always did so during or shortly after the end of vaccination campaigns (Figures 8 top row and 10)

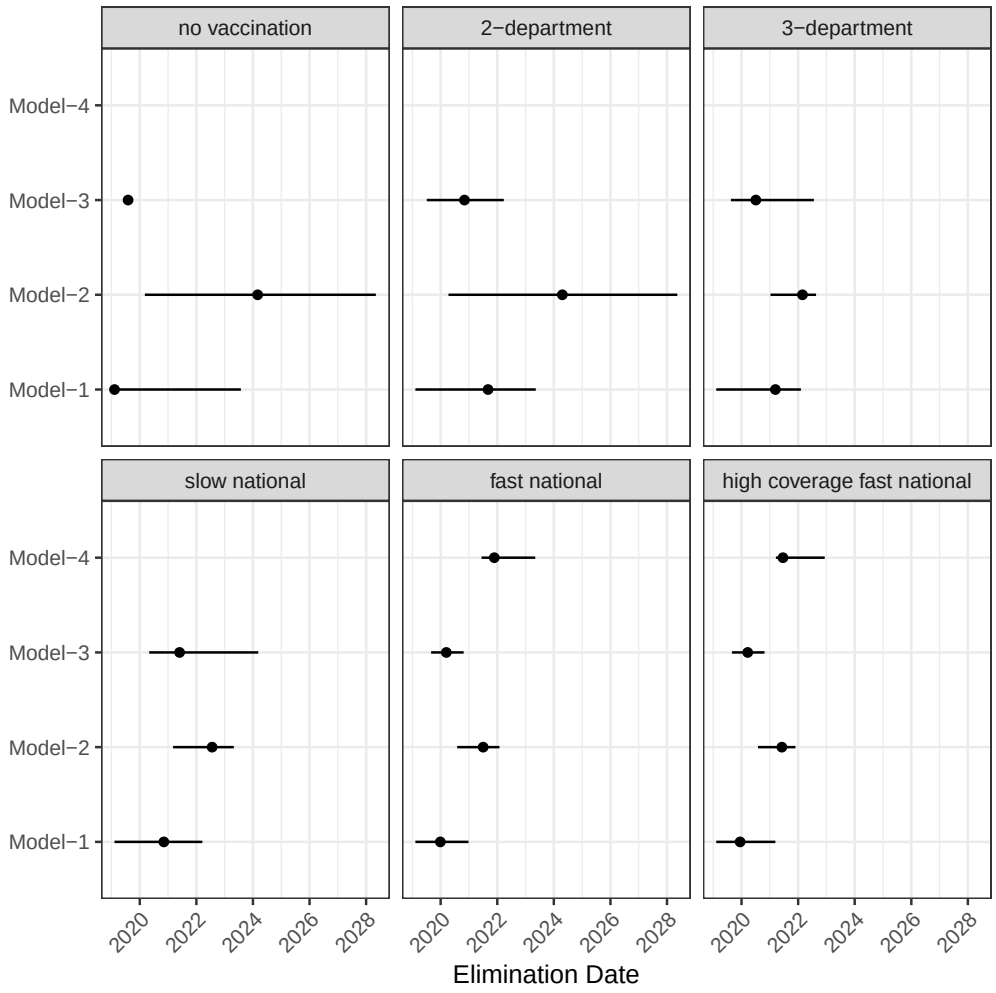

Figure 10: Among eliminated simulations, date that elimination was achieved. The point is the median, and the error bars are the 2.5% and 97.5% range of elimination dates. Model-4 had 0% probability of elimination in several scenarios, and no data are displayed on those panels.

3.4 Cases Averted

We calculated the median infections averted (includes observed and unobserved cholera cases) 5 years after the start of vaccination campaigns across scenarios (Figures 11, 12). Fast national campaigns were the most effective in reducing cases, but a 3-department campaign averted roughly twice as many cases as a 2-department campaign. The slow national campaign and 3-department campaigns have relatively similar health outcomes, thus highlighting the trade-offs between a smaller and faster rollout versus a larger and prolonged campaign.

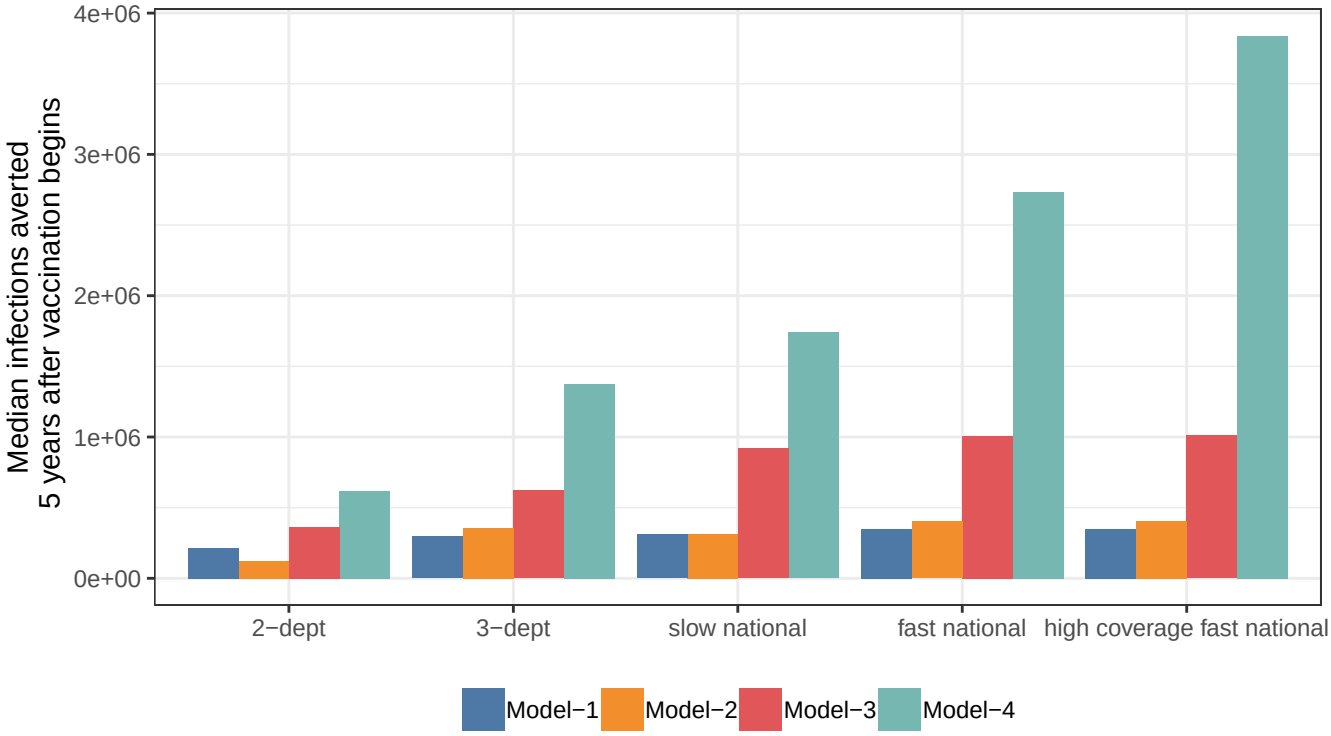

Figure 11: Median infections averted 5 years after the start of vaccination campaigns across scenarios and teams.

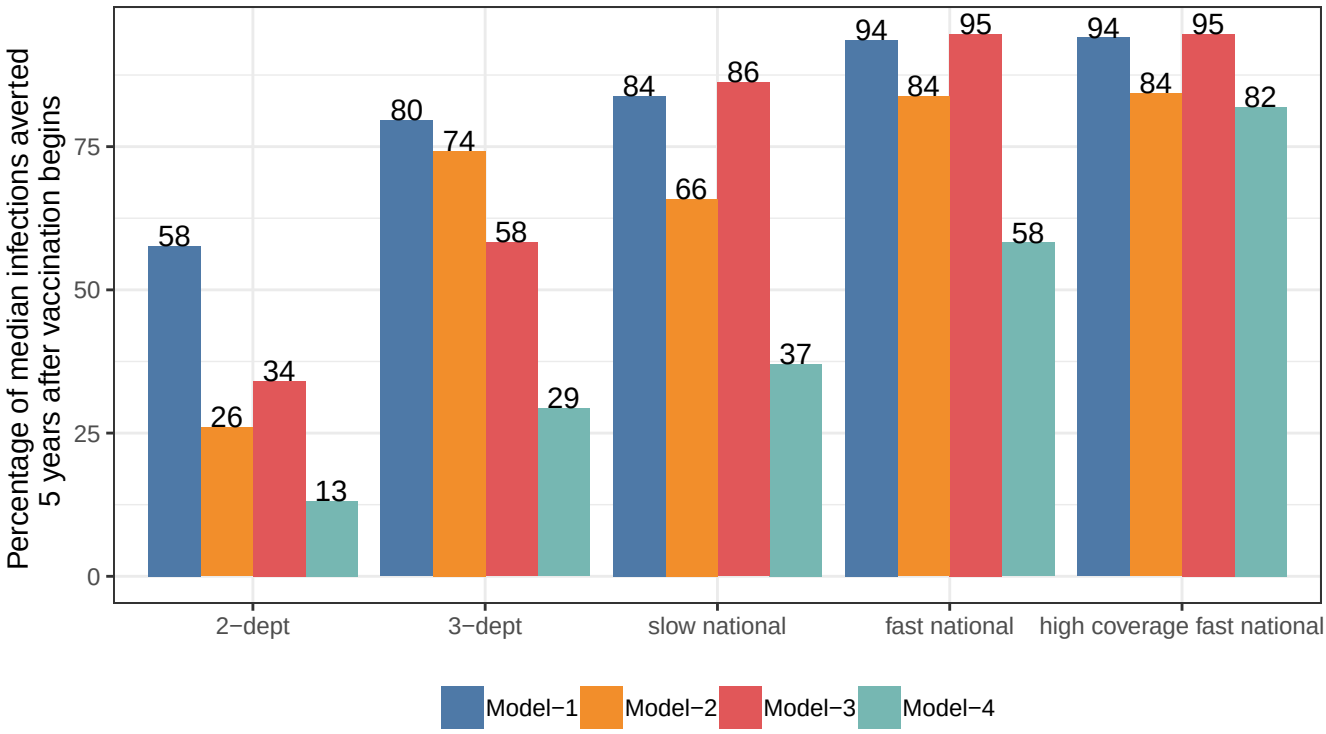

Figure 12: Percentage of median infections averted 5 years after the start of vaccination campaigns across scenarios and teams. This is calculated as the median infections averted divided by the total infections in the no vaccination (status quo) scenario case projections.

References

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