Appendix 1: Supplemental methods and results for **"Estimating time-varying cholera transmission and oral cholera vaccine effectiveness in Haiti and Cameroon, 2021-2023"**

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Disclaimer: This appendix accompanies a work-in-progress paper. We welcome feedback and suggestions on the analyses and interpretation, as well as any meaningful additions.

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Section 1: Additional Methods

Schematic of the analysis process

Figure 1: Schematic of the steps in our analysis

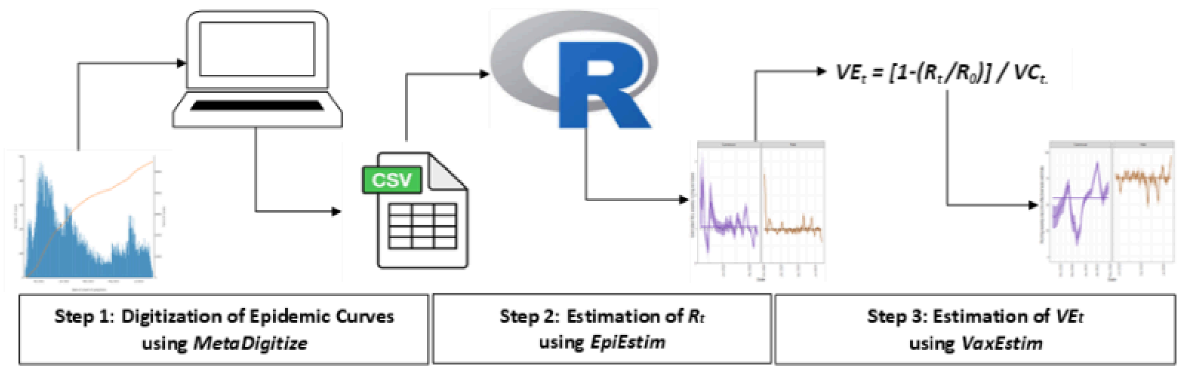


Figure 1 above depicts the steps taken in our analysis. In Step 1, we pulled static non-machine-readable images of epidemic curves from situation and outbreak news reports for our two countries of interest. We then used digitization methods (specifically the *MetaDigitise* package in R[1]) to generate machine-readable case time series data in R and CSV format. In Step 2, we used these machine-readable data and the EpiEstim[2–4] package in R to estimate the time-varying effective reproductive numbers (R_t) in each country. Lastly, in Step 3, we used the R_t time series and the algebraic extension of EpiEstim—dubbed VaxEstim[5] —to estimate the OCV1 effectiveness over time (VE_t) in each country.

Calculating the error rate between static epidemic curves and digitized cholera data

$$Error\ Rate = \frac{|Digitized\ Cumulative\ Case\ Count - Reported\ Cumulative\ Case\ Count|}{Reported\ Cumulative\ Case\ Count}$$

This formula shows how we calculated the error rate between the static, non-machine-readable epidemic curves and the digitized cholera data in our study. The denominator is the "ground truth" (i.e., the cumulative number of cases reported by health agencies in situation and outbreak news reports) and the numerator is the absolute difference between the ground truth and the inferred case count time series, derived from the digitized version of the epidemic curve.

Estimating OCV1 campaign dates in Haiti

While the date of the OCV1 delivery in Haiti was reported as December 12, 2022, the specific date of the campaign was not specified in any published reports. The report mentioned that the campaign was "set to start in the next days".[6] For this analysis, we assumed a vaccine distribution start date of December 19, 2022, one week later; sensitivity analyses altering the campaign start date by two days in either direction revealed minimal differences in our results: the median VE_t estimate was 75.32% [95% CI: 54.00–86.39%] for December 19 versus 75.28% [53.95–86.42%] for December 21 and 75.33% [54.04–86.37%] December 17.

Section 2: Additional Tables

Table 1: Descriptive and modeled statistics from the literature, Cameroon and Haiti

	Cameroon	**Haiti**
2017 % with access to improved water source[7]	73.95 (71.24-76.90)	68.29 (66.32-70.19)
2017 % with access to improved sanitation[7]	52.93 (51.05-55.11)	51.50 (50.31-52.79)
2017 under-5 mortality per 1,000 live births[8]	73.5 (60.5-87.0)	59.3 (50.0-71.0)
2019 one-dose MCV coverage[9]	67.8 (59.2-75.2)	71.6 (65.1-77.4)
% of children with diarrhea taking ORT[10]	19.91 (11.95-31.05)	39.05 (29.17-49.41)
2017 mean years education: female 15-49[11]	7.77 (6.72-8.79)	6.42 (5.70-7.05)
2017 difference in mean years education males to females 15-49 years[11]	0.66 (0.48-0.93)	0.71 (0.66-0.88)
2019 under-5 diarrhea prevalence[12]	43.17 (31.79-58.94)	48.51 (44.42-52.28)
2019 under-5 stunting prevalence[13]	33.07 (26.41-40.55)	23.79 (18.91-29.41)
2019 under-5 wasting prevalence[13]	6.30 (4.31-8.94)	6.25 (3.21-10.41)
2019 under-5 underweight prevalence[13]	12.77 (9.94-16.33)	12.93 (9.70-17.25)
2019 under-5 severe wasting prevalence[13]	1.13 (0.67-1.77)	0.85 (0.38-1.65)
2022 Corruption Perceptions Index[14]	26 / 100	17 / 100
2022 GDP per capita[15]	$1588.5	$1748.3
2015 Healthcare Access and Quality Index[16]	44.4 (35.0-53.3)	38.5 (33.7-43.5)
Gini Index[17]	46.6	41.1
2018 Wellcome Global Monitor: Trust in neighbors[18]	44%	67%
2018 Wellcome Global Monitor: Trust in government[18]	51%	46%
2018 Wellcome Global Monitor: Trust in scientists[18]	49%	62%
Vaccine Confidence Project: Vaccines are important[19]	82.98% (71.83-91.84)	91.18% (82.80-97.49)
Vaccine Confidence Project: Vaccines are safe[19]	56.50% (42.46-72.76)	62.33% (43.10-77.75)
Vaccine Confidence Project: Vaccines are effective[19]	63.24% (45.55-83.46)	71.80% (51.30-88.96)
2020 Average precipitation in depth (mm per year)[20]	1,604	1,440
Population density (people per sq. km of land area)[21]	58	415
Percent of population exposed to high flood risk[22]	19.1	17.5

MCV= Measles containing vaccine; ORT = Oral rehydration therapy; GDP = Gross domestic product

Improved water access includes piped water and other improved sources; improved sanitation access includes sewer and septic as well as other improved sources. For the Corruption Perceptions Index, a lower score indicates more corruption. Gini data were most recently available for 2014 in Cameroon and 2012 in Haiti. Wellcome Global Monitor trust data use “a lot” or “some” trust as survey answers indicating trust. Vaccine confidence data were pulled from modeled estimates and used the midpoint of 2018 as the timestamp; importance, safety, and efficacy were defined as the portion of respondents who replied “strongly agree”.

Table 2: Number and percent of vaccine effectiveness observations outside 0% or 100%, Cameroon and Haiti

	Cameroon (n=196 data points)	**Haiti (n=302 data points)**
Upper 95% CI estimates	3 (1.5%)	2 (0.7%)
Lower 95% CI estimates	24 (12.2%)	3 (1.0%)
Median estimates	5 (2.6%)	2 (0.7%)

We noted a small percentage of estimates that fell outside of the 0 to 100% boundary. This is likely a result of using static estimates of vaccine coverage over the entire duration of the vaccine study period rather than dynamic estimates, which were unavailable for OCV1 campaigns in either country. However, in our study, we were most interested in understanding general patterns of vaccine effectiveness over time and interpreting the median estimates and whether credible intervals overlapped. As such, a small percentage of results out-of-bounds—especially in the credible interval—do not drastically alter our interpretation of the results. In clinically-motivated vaccine effectiveness studies where precision is more important, time-varying vaccine coverage should be considered for similar analysis.

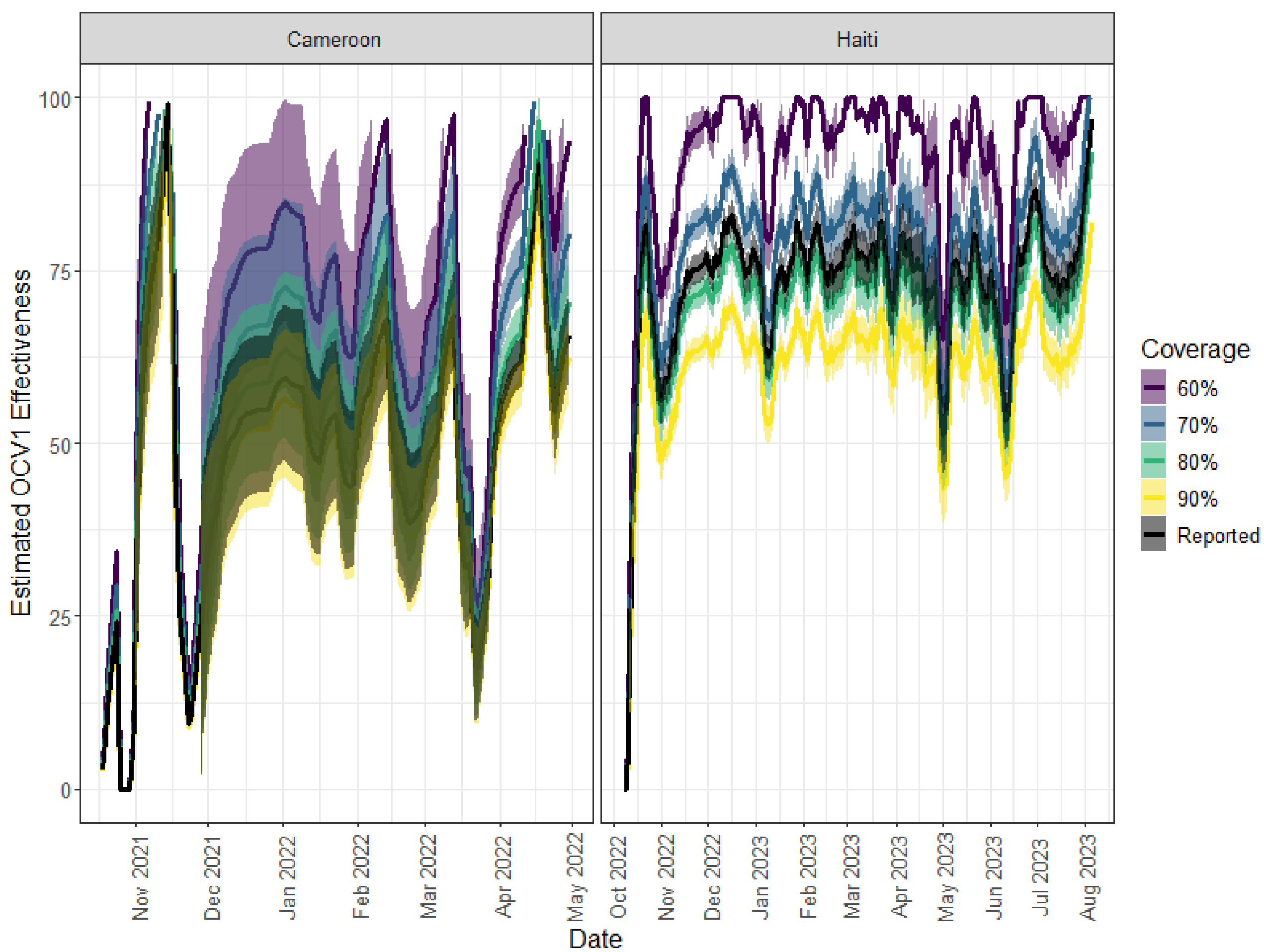
Section 2: Sensitivity Analyses

In order to understand the impact of our assumptions on our findings, we changed our assumptions in a number of ways, each independently while holding all other variables constant.

Artificially changing OCV coverage to understand impact on vaccine effectiveness, Cameroon and Haiti

For our main analysis, we used reported coverage figures for OCV1 campaigns in Cameroon and Haiti. Given that these estimates are highly localized to the targeted locality and do not reflect the coverage status in the whole country, we explored how changing coverage from 60% OCV1 coverage to 90% OCV1 coverage would impact estimated OCV1 effectiveness in both Cameroon and Haiti. When assuming coverage was at 60% rather than the reported 85.50% and 76.00% in Cameroon and Haiti, respectively, as represented by the black line in Figure 2 below, vaccine effectiveness was 76.48% (15.24-122.29%) and 95.23% (66.66-108.07%). In contrast, assuming coverage of 90% revealed vaccine effectiveness estimates of 50.99% (10.16-81.52%) in Cameroon and 63.49% (44.44-72.05%) in Haiti.

Figure 2: Impact of assumed OCV1 coverage on vaccine effectiveness

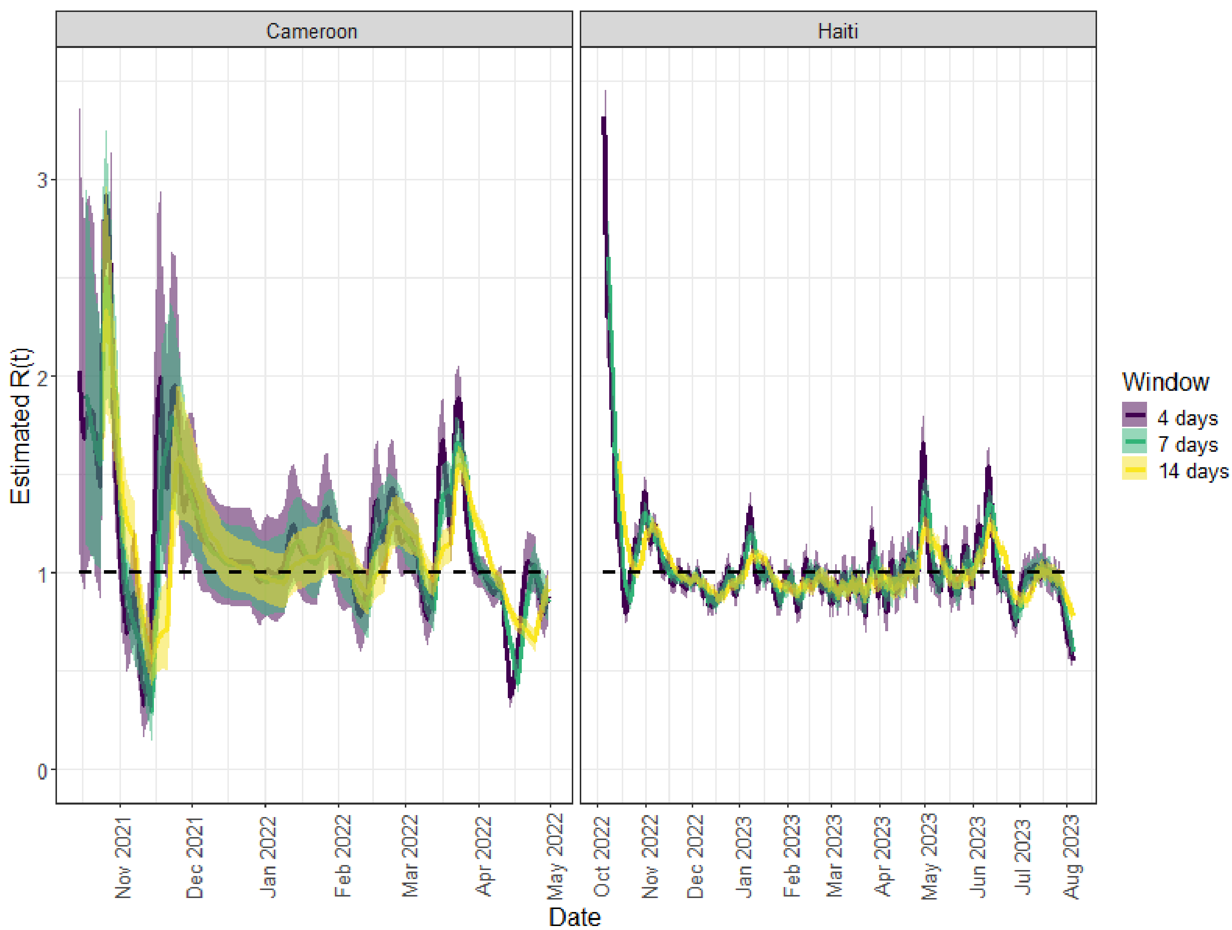


All data in Figure 2 are truncated to 0 or 100% where smaller or greater than these values, respectively

Exploring alternate R_t windows in EpiEstim, Cameroon and Haiti

While we chose a R_t window of one-week to optimize the relationship between too much statistical noise with smaller windows and too much smoothing with larger windows, we explored additional time windows: four days and two weeks. While the shorter window had higher initial R_0 values and the longer window had fewer days under R_t=1, qualitatively the patterns across all three windows analyzed were relatively consistent.

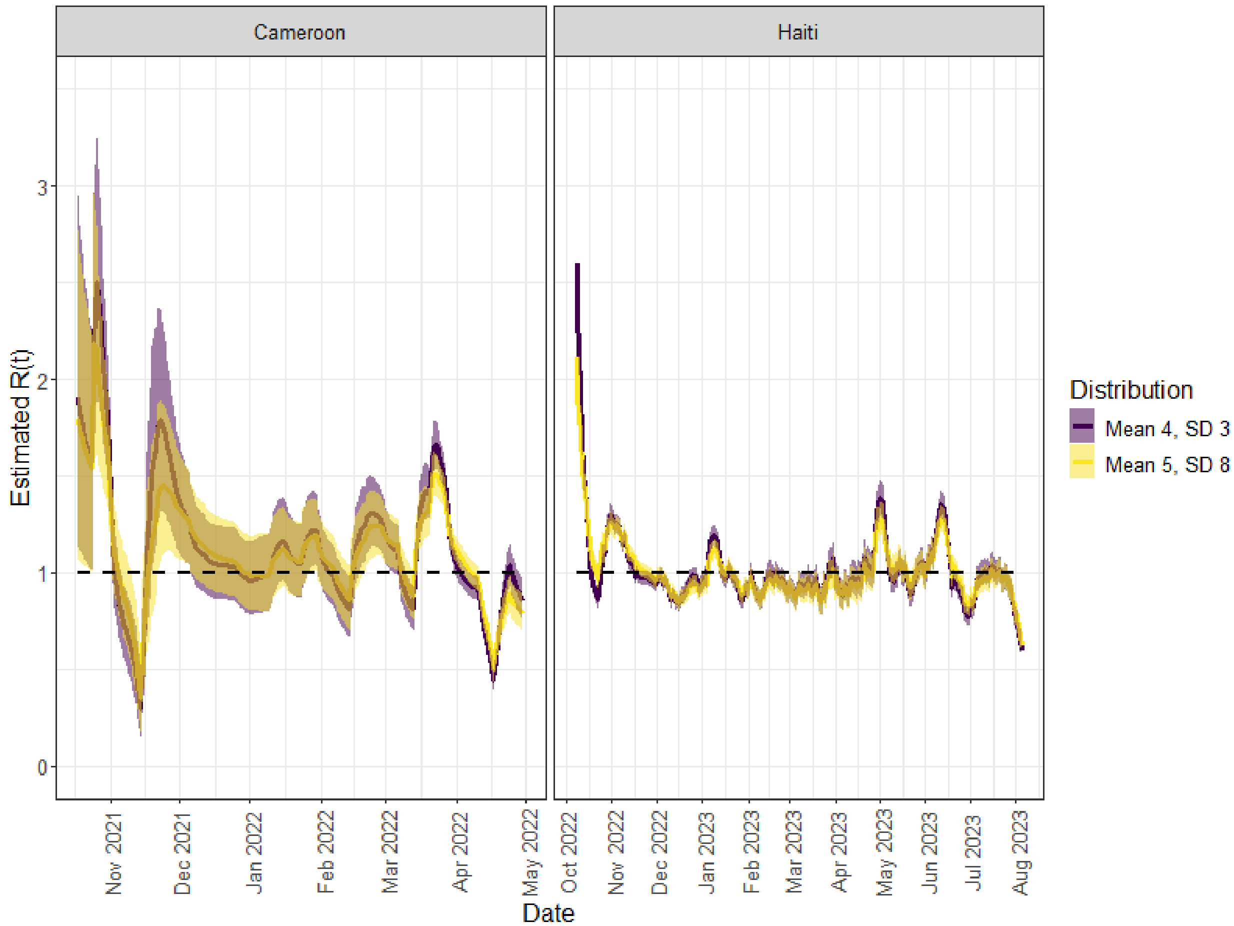
<u>Figure 3: Impact of length of time window on R_t</u>



Exploring alternate SI parameters in EpiEstim, Cameroon and Haiti

For our SI, we used a gamma distribution with a mean of 4 days and a SD of 3 derived from previous studies of cholera among household contacts,[23] historic investigations of cholera,[24] and used among previous EpiEstim analyses of cholera.[25,26] However, studies of cholera in humanitarian and crisis settings used a slightly higher and wider distribution with a mean of 5 and a standard deviation of 8.[27–29] We modified our analysis to use this wider distribution and qualitatively found similar results between the two distributions, with the narrower SI having slightly higher peaks and lower troughs, but generally similar patterns.

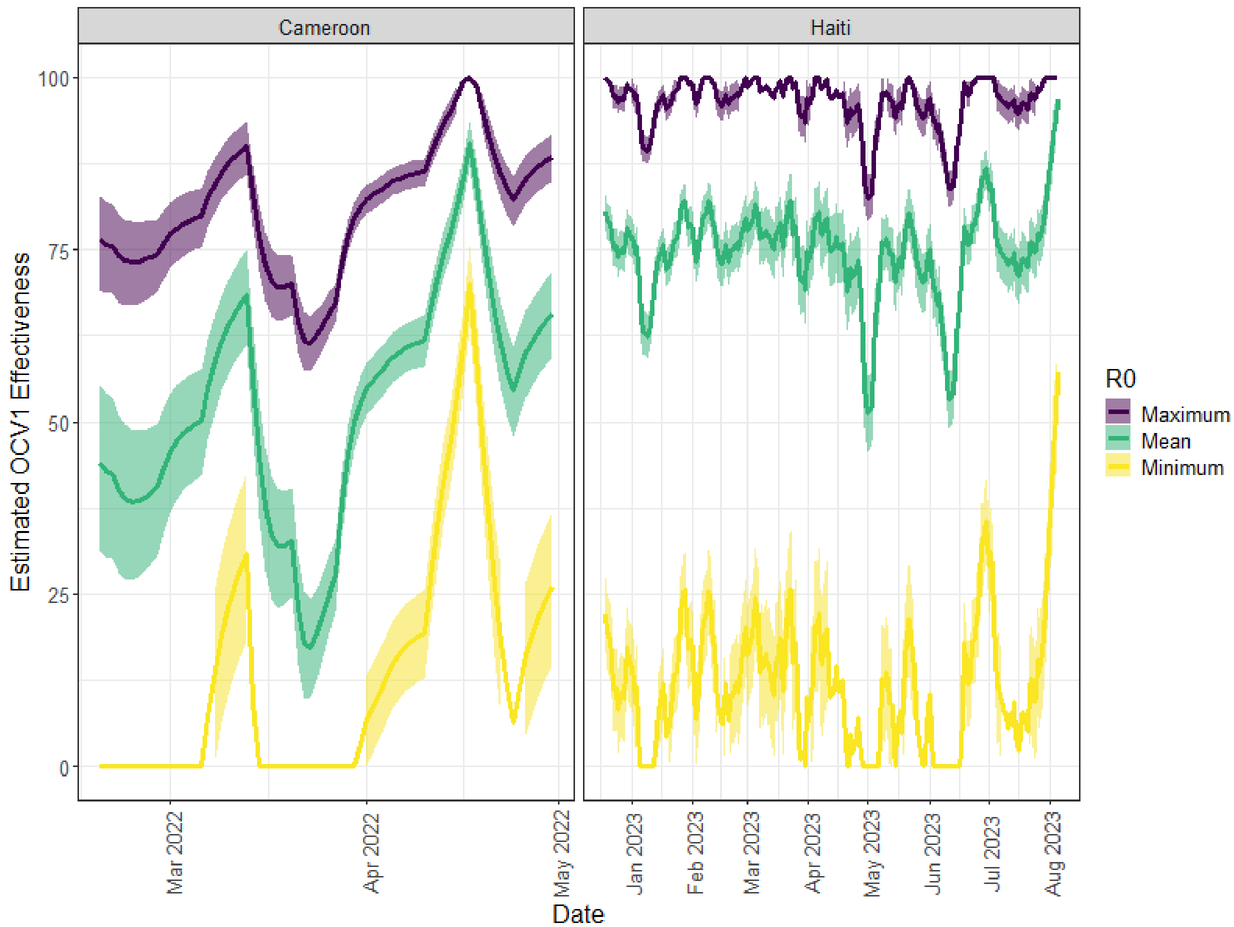
Figure 4: Impact of changing the SI on R_t



Exploring alternate values of R_0 on vaccine effectiveness, Cameroon and Haiti

In our main analysis, we used averages of the published regional and local data for R_0 for our two countries of interest, resulting in a mean R_0 of 1.95 in Cameroon and 2.27 in Haiti, as represented by the teal line in Figure 5 below. For our sensitivity analysis, we considered the minimum R_0 published in the literature (1.10 Cameroon / 1.06 Haiti) and maximum published R_0 (3.5 Cameroon / 3.72 Haiti) in each location. In contrast to the changes to the window and the SI which had few qualitative impacts on our findings, changing R_0 drastically altered the vaccine effectiveness estimates. Using the minimum R_0 value in each Cameroon in Haiti resulted in median estimates of vaccine effectiveness of 19.41% (6.40-61.39%) and 12.22% (1.61-35.78%), respectively, while using the maximum R_0 value in each country resulted in average vaccine effectiveness of 83.08% (62.29-97.69%) and 96.97% (83.88-99.70%) for both Cameroon and Haiti. In addition, in both countries, the relative relationship overtime remained consistent despite the changing magnitude of the estimates. It is important to note that these minima and maxima represent estimates at extreme ends of the credible intervals of the distribution of R_0 and therefore are meant to be considered as the extremes in the analysis of the vaccine effectiveness estimates rather than those that were most probable.[26,30] Notably, such extreme choices of R_0 also resulted in a larger proportion of estimates falling outside of the bounded range of 0 to 100%, suggesting that while these are within the realm of possible choices for R_0, they are unlikely to be the realized values of R_0 during the outbreaks in Cameroon and Haiti.

Figure 5: Impact of changing R_0 on OCV1 effectiveness

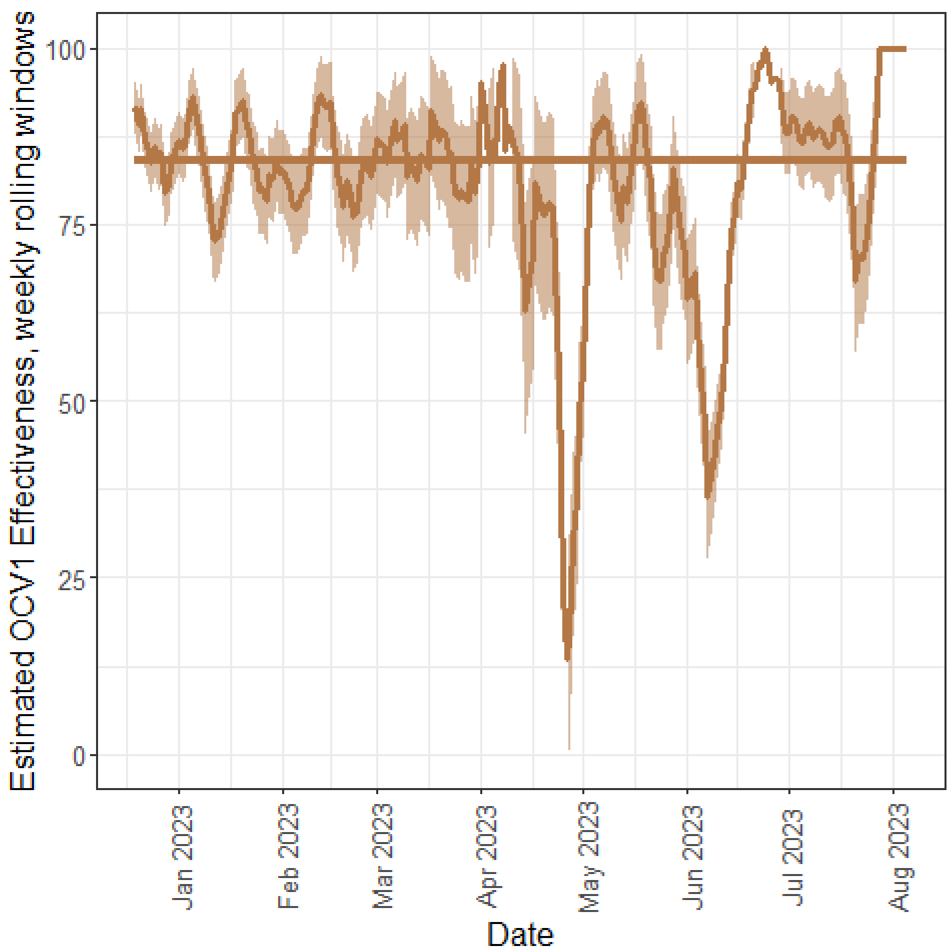


All data in Figure 2 are truncated to 0 or 100% where smaller or greater than these values, respectively

Exploring the vaccine effectiveness in Ouest department, Haiti

In Haiti, where the OCV1 campaign was highly localized to the Ouest and Centre departments, we also conducted a sensitivity analysis using daily cholera data published by department by Haiti's Ministry of Health (MSPP)[31] to understand how localized data influence our results. Our digitization resulted in a cumulative case count of 24,571 versus a reported cumulative sum of 24,245 for an error rate of 1.34%. We consider the vaccine effectiveness in the Ouest department of Haiti using digitized daily cholera data (digitized using WebPlotDigitizer[32]) from October 1, 2022 to August 5, 2023, using reported OCV1 coverage at 69.90%.[33,34,31] This analysis suggests a median vaccine effectiveness of 83.66% (95% UI: 37.80-975.24%) over the entire vaccination period after December 19, 2022, almost 10% higher than the point estimate at the national level; however, the credible interval overlapped with the national level analysis, and thus this difference was not considered statistically significant.

Figure 6: Focusing on Ouest department for vaccine effectiveness in Haiti



All data in Figure 2 are truncated to 0 or 100% where smaller or greater than these values, respectively

Section 3: References

1. Pick, J. L., Nakagawa, S. & Noble, D. W. A. Reproducible, flexible and high throughput data extraction from primary literature: The metaDigitise R package. *BioRxiv* 1–25 (2018) doi:https://doi.org/10.1101/247775.
2. Gostic, K. M. *et al.* Practical considerations for measuring the effective reproductive number, Rt. *PLOS Comput. Biol.* **16**, e1008409 (2020).
3. Cori, A. *et al.* EpiEstim: Estimate Time Varying Reproduction Numbers from Epidemic Curves. (2021).
4. Cori, A., Ferguson, N. M., Fraser, C. & Cauchemez, S. A New Framework and Software to Estimate Time-Varying Reproduction Numbers During Epidemics. *Am. J. Epidemiol.* **178**, 1505–1512 (2013).
5. Martoma, R. A., Washam, M., Martoma, J. C., Cori, A. & Majumder, M. S. Modeling vaccination coverage during the 2022 central Ohio measles outbreak: a cross-sectional study. *Lancet Reg. Health – Am.* **23**, (2023).
6. Pan American Health Organization & World Health Organization. Haiti receives first shipment of cholera vaccines. https://www.paho.org/en/news/12-12-2022-haiti-receives-first-shipment-cholera-vaccines (2022).
7. Deshpande, A. *et al.* Mapping geographical inequalities in access to drinking water and sanitation facilities in low-income and middle-income countries, 2000–17. *Lancet Glob. Health* **8**, e1162–e1185 (2020).
8. Burstein, R. *et al.* Mapping 123 million neonatal, infant and child deaths between 2000 and 2017. *Nature* **574**, 353–358 (2019).
9. Sbarra, A. N. *et al.* Mapping routine measles vaccination in low- and middle-income countries. *Nature* **589**, 415–419 (2021).
10. Wiens, K. E. *et al.* Mapping geographical inequalities in oral rehydration therapy coverage in low-income and middle-income countries, 2000–17. *Lancet Glob. Health* **8**, e1038–e1060 (2020).
11. Graetz, N. *et al.* Mapping disparities in education across low- and middle-income countries. *Nature* **577**, 235–238 (2020).
12. Reiner, R. C. *et al.* Variation in Childhood Diarrheal Morbidity and Mortality in Africa, 2000–2015. *N. Engl. J. Med.* **379**, 1128–1138 (2018).
13. Kinyoki, D. K. *et al.* Mapping child growth failure across low- and middle-income countries. *Nature* **577**, 231–234 (2020).
14. Transparency International. CORRUPTION PERCEPTIONS INDEX. (2019).
15. World Bank Open Data - GDP per capita (USD). *World Bank Open Data* https://data.worldbank.org/indicator/NY.GDP.PCAP.CD.
16. Barber, R. M. *et al.* Healthcare Access and Quality Index based on mortality from causes amenable to personal health care in 195 countries and territories, 1990–2015: a novel analysis from the Global Burden of Disease Study 2015. *The Lancet* **390**, 231–266 (2017).
17. World Bank Open Data - Gini Index. *World Bank Open Data* https://data.worldbank.org/indicator/SI.POV.GINI.
18. Wellcome Trust & Gallup. *Wellcome Global Monitor 2018: Country-Level Data*. https://wellcome.org/reports/wellcome-global-monitor/2018/appendix-country-level-data (2019).
19. de Figueiredo, A., Simas, C., Karafillakis, E., Paterson, P. & Larson, H. J. Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake: a large-scale retrospective temporal modelling study. *The Lancet* **396**, 898–908 (2020).
20. World Bank. Average precipitation in depth (mm per year). https://data.worldbank.org/indicator/AG.LND.PRCP.MM (2023).
21. World Bank. Population density (people per sq. km of land area). *World Bank Open Data*

https://data.worldbank.org (2023).
22. Rentschler, J., Salhab, M. & Jafino, B. A. Flood exposure and poverty in 188 countries. *Nat. Commun.* **13**, 3527 (2022).
23. Weil, A. A. *et al.* Clinical Outcomes in Household Contacts of Patients with Cholera in Bangladesh. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **49**, 1473–1479 (2009).
24. Phelps, M. D. *et al.* The importance of thinking beyond the water-supply in cholera epidemics: A historical urban case-study. *PLoS Negl. Trop. Dis.* **11**, e0006103 (2017).
25. Bi, Q. *et al.* The Epidemiology of Cholera in Zanzibar: Implications for the Zanzibar Comprehensive Cholera Elimination Plan. *J. Infect. Dis.* **218**, S173–S180 (2018).
26. Zheng, Q. *et al.* Cholera outbreaks in sub-Saharan Africa during 2010-2019: a descriptive analysis. *Int. J. Infect. Dis.* **122**, 215–221 (2022).
27. Zhao, S., Musa, S. S., Qin, J. & He, D. Associations between Public Awareness, Local Precipitation, and Cholera in Yemen in 2017. *Am. J. Trop. Med. Hyg.* **101**, 521–524 (2019).
28. Camacho, A. *et al.* Cholera epidemic in Yemen, 2016–18: an analysis of surveillance data. *Lancet Glob. Health* **6**, e680–e690 (2018).
29. Azman, A. S. *et al.* Population-Level Effect of Cholera Vaccine on Displaced Populations, South Sudan, 2014. *Emerg. Infect. Dis.* **22**, 1067–1070 (2016).
30. Chunara, R., Andrews, J. R. & Brownstein, J. S. Social and News Media Enable Estimation of Epidemiological Patterns Early in the 2010 Haitian Cholera Outbreak. *Am. J. Trop. Med. Hyg.* **86**, 39 (2012).
31. Ministere de la Sante Publique et de la Population & Direction d’epidemiologie, des laboratoires, et de la recherche. *SITUATION ÉPIDÉMIOLOGIQUE DU CHOLÉRA,HAÏTI: 04 AOUT 2023*. https://mspp.gouv.ht/site/downloads/Sitrep%20cholera_05_aout_2023.pdf (2023).
32. Rohatgi, A. WebPlotDigitizer. (2022).
33. Pan American Health Organization & World Health Organization. Immunization Newsletter, v.45, n.1. *PAHO* (2023).
34. World Health Organization. Disease Outbreak News: Cholera – Cameroon. https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON374.