The impact of geographic targeting of oral cholera vaccination in sub-Saharan Africa: a modeling study

Elizabeth C. Lee[1], Andrew S. Azman[1], Joshua Kaminsky[1], Sean M. Moore[2,3], Heather S. McKay[1], and Justin Lessler[1]

[1] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
[2] Department of Biological Sciences, University of Notre Dame, Notre Dame, IN, USA
[3] Eck Institute for Global Health, University of Notre Dame, Notre Dame, IN, USA

Correspondence to:
Elizabeth C. Lee
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD, 21205, USA
elee154@jhu.edu

Abstract

Background: In May 2018, the World Health Assembly committed to reducing worldwide cholera deaths by 90% by 2030. Oral cholera vaccine (OCV) plays a key role in reducing the near-term risk of cholera, although global supplies are limited. Characterizing the potential impact and cost-effectiveness of mass OCV deployment strategies is critical for setting expectations and developing cholera control plans that maximize chances of success.

Methods: We compared the projected impacts of vaccination campaigns across sub-Saharan Africa from 2018 through 2030 when targeting geographically according to historical cholera burden and risk factors. We assessed the number of averted cases, deaths, disability-adjusted life-years, and cost-effectiveness with models that account for direct and indirect vaccine effects and population projections over time.

Findings: Under current vaccine supply projections, an approach that balances logistical feasibility with targeting historical burden is projected to avert 620,000 cases cumulatively (9-26% of cases annually). Targeting by access to improved water and sanitation prevents one-half to one-seventh as many cases as targeting by burden. We find that effective geographic targeting of OCV campaigns can have a greater impact on cost-effectiveness than improvements to vaccine efficacy and moderate increases in coverage.

Conclusions: Oral cholera vaccines must be targeted strategically in order for campaigns to be cost-effective and impactful. While OCV campaigns will improve cholera control in the near-term, we need a greater supply of vaccines and rapid progress in developing safely managed water and sanitation services in order to achieve the 2030 goals.

Introduction

Cholera remains a significant global public health threat, causing more than 100,000 deaths per year globally, with sub-Saharan Africa bearing the majority of the burden [1–3]. In May 2018, the 71st World Health Assembly adopted a resolution aimed at reducing global cholera deaths by 90% by 2030 [4]. Achieving major reductions in morbidity and mortality in sub-Saharan Africa are essential to reaching this goal.

Due to successful campaigns conducted in over 15 countries since 2013 [5], countries that regularly experience cholera are beginning to integrate vaccination with oral cholera vaccine (OCV) into regular public health activities, as recommended by the Global Task Force on Cholera Control (GTFCC) *Roadmap to 2030* and general WHO guidance [6]. These vaccines have 49-67% efficacy in protecting vaccine recipients against cholera infection for up to five years [7], thus presenting an important near-term solution to rapidly reducing cholera risk while long-term improvements to safely managed and sustainable water and sanitation services are made.

Nevertheless, OCV presents several challenges to traditional approaches to vaccine deployment. OCV does not provide lifelong immunity; while the length of protection is uncertain, it is thought to wane significantly after five years [7]. Further, the vaccine appears to be half as protective in children under five years old [7]. Together, these factors suggest that inclusion of OCV in a childhood vaccination schedule would have limited impact. Similarly, the high degree of clustering of cholera risk, both geographically and demographically [8,9], makes large-scale (e.g., country-wide) vaccination campaigns inefficient.

The limited supply of OCV further complicates its integration into routine cholera control activities. In 2018, 23 million doses of OCV were produced globally (enough to provide the recommended two-dose course to 11.5 million people) [8]. This is only a fraction of what would be needed to cover the 87.2 million people living in high-risk areas of sub-Saharan Africa alone [8]. Consequently, efficient strategies are needed if the limited vaccine supply is to play a significant role in cholera control.

While previous work has examined the impact of targeting OCV to specific age groups [10], an alternate strategy for efficient OCV use is to target vaccines geographically to high-risk areas. Here, we use simulation studies to explore the impact of different approaches to conducting geographically targeted OCV campaigns from 2018 to 2030 in sub-Saharan Africa. We quantify the impact of targeted strategies over untargeted OCV use and compare targeting according to historical cholera burden to that of cholera risk factors. The ultimate aim of these analyses is to provide guidance in how this critical cholera control tool may be used efficiently to accomplish global cholera control goals.

Methods

Epidemiologic and Demographic Data Sources

Methods for mapping cholera incidence have been previously described [8]. Briefly, our estimates of cholera incidence were based on suspected and clinically confirmed cholera case reports from 2010 to 2016 obtained from multiple sources, including the World Health

Organization (WHO), Médecins Sans Frontières, ProMED, situation reports from ReliefWeb and other websites, several Ministries of Health, and the scientific literature [3,8]. These cholera reports were combined with ecological risk factors such as access to improved drinking water and sanitation and distance to nearest major body of water to estimate average annual cholera incidence at the 20 km x 20 km grid resolution in a Bayesian modeling framework [3,8]. The cholera incidence estimates were then disaggregated to the 5 km x 5 km grid resolution for more accurate characterization of cells at country and district (i.e., ISO administrative level 2 units) borders. We did not obtain water and sanitation data for Botswana, Djibouti, and Eritrea, and these countries were excluded from our analyses. Summaries of all cholera data sets, including 20 km x 20 km resolution estimates of cholera cases and incidence and instructions for requesting access are available at http://www.iddynamics.jhsph.edu/projects/cholera-dynamics.

Population estimates for each administrative area were derived from WorldPop's population density rasters for Africa [11]. A log-linear (exponential) growth assumption was applied to these WorldPop population projections for 2000, 2005, 2010, 2015, and 2020 at the 5 km x 5 km grid cell scale to estimate yearly populations from 2018 through 2030.

Vaccine Properties

Campaign Coverage

We conducted a review of published literature on post-OCV campaign vaccination coverage surveys and identified seven studies related to 24 two-dose campaigns conducted globally from 2003 through 2016 (Table S1) [12–20]. For each of the seven studies, we resampled two-dose

(the standard vaccine regimen) coverage estimates 5000 times from a Gaussian distribution using estimates of the mean and standard error of coverage; for studies with multiple locations, we first drew a single location randomly and then sampled from a Gaussian distribution of coverage estimates for that location. We pooled these 35,000 draws across studies and used the median (68%) of the samples as the baseline coverage estimate for our model (Figure S1). These estimates give studies equal weight to the distribution regardless of the number of campaign locations.

Vaccine Efficacy

We fit a log-linear decay function to two-dose vaccine efficacy data reported one to five years after vaccination in a recent meta-analysis [7] and used the median point estimates for each year as (direct) vaccine efficacy in our model. In this framework, the initial vaccine efficacy is 66% declining to 0% after six years (Figure S2). We assumed that individuals who received a single vaccine dose were not protected.

Vaccine Indirect Effects

OCV has been shown to induce indirect protection across multiple settings [20–22]. We modeled indirect protection as a function of the vaccination coverage in a given grid cell using data from trials in India and Bangladesh [21,22]. Specifically, the phenomenological association between the relative reduction in incidence among unvaccinated (placebo) individuals and OCV coverage in their ‘neighborhood’ was fit to a logistic function (Figure S3). Under this model of indirect vaccine protection, individuals not protected by vaccine and residing in grid cells with 50% and 70% vaccination coverage experienced an 80% and near 100% reduction in cholera risk, respectively.

Vaccine Supply Projections

Current global supplies of OCV are limited. In 2017, approximately 17 million bivalent killed whole-cell OCV doses of ShanChol (Shantha Biotech, Hyderabad, India) and Euvichol-Plus/Euvichol (Eubiologics, Seoul, Republic of Korea) were produced. Based on estimates from experts within the GTFCC and data from vaccine manufacturers in the first half of 2018, we assumed that global OCV supply would increase linearly from 23 million doses in 2018 to 59 million doses in 2030 (Figure S4).

Vaccination Deployment Strategies

We modeled eight OCV deployment strategies: untargeted distribution, four historical burden-based strategies (*rate optimized*, *rate-logistics optimized*, *case optimized*, and *case-logistics optimized*) (Figure 1), and three based on access to improved water and sanitation (*water optimized*, *sanitation optimized*, and *watsan optimized*). For all targeted strategies, a given district was targeted fully (i.e., achieving 68% vaccination coverage) only once every three years, as suggested by WHO guidelines for OCV deployment [23].

Untargeted distribution

OCV is distributed proportional to population throughout the study region (i.e., everyone has equal likelihood of receiving vaccine).

Rate optimized

We ranked all districts across countries in the study area by estimated cholera incidence rate (i.e., cases per unit population) and targeted them in decreasing order with vaccine until the annual global vaccine supply was depleted (Figure S5).

Rate-logistics optimized

It may not be logistically feasible to target districts in multiple, potentially geographically non-adjacent countries at once. Thus, in the *rate-logistics optimized* strategy, we first ranked countries according to the size of the population residing in high-risk districts, and then targeted vaccines to all high-risk districts in those countries. The highest risk districts were defined as those where cholera incidence exceeded a threshold of 1 case per 1000 persons for at least 100,000 residents or 10% of the population; subsequent tiers of “high-risk districts” employed incidence thresholds of 1 case per 5000, 10,000, and 100,000 persons successively (Figure S6) [3]. Within each incidence threshold tier, districts were ranked from highest to lowest by estimated cholera incidence rate (hence, *rate-logistics*). Some districts with high incidence rates may not meet the definition of “high-risk district” because fewer than 100,000 people or less than 10% of the district population reside in cells achieving the given incidence threshold tier; this can lead to differences in targeting between the *rate optimized* and *rate-logistics* optimized strategies.

Case optimized and Case-logistics optimized

These are the same as their rate optimized counterparts, except districts were ranked according to raw cholera case numbers instead of estimated cholera incidence rate (Supplement only).

Water optimized, *Sanitation optimized*, and *Watsan optimized*

We ordered districts across all countries according to their estimated coverage of access to improved water, improved sanitation, and improved water or sanitation ("Watsan", Supplement only), and then targeted them from worst to best coverage. District-level coverage was derived from previously modeled estimates of access to improved water and improved sanitation [24].

Measuring Public Health Impact and Costs

We estimated the public health impact of conducting OCV campaigns from 2018 to 2030 as the number of cholera cases, deaths, and disability-adjusted life-years (DALY) averted over the period from 2018 to 2030 (See Supplementary Material for details).

We reviewed four cost surveys for mass OCV campaigns that reported the vaccine delivery and vaccine procurement costs per fully vaccinated person (i.e., receiving two vaccine doses) in non-refugee African settings [25–28] (Table S2). All costs were adjusted to 2017 US dollars (USD) according to the World Bank Consumer Price Index. The median delivery and procurement costs ($2.33 and $5.49 per fully vaccinated person, respectively) were used to calculate vaccination campaign costs.

Program costs were measured as the cost per DALY averted (2017 USD) and discount rates for health benefits and costs were set to 0% and 3%, respectively [29]. An intervention is defined as cost-effective if the cost per DALY averted is less than 3 times the GDP of a country and highly cost-effective if it is less than or equal to the GDP of a country [29].

Sensitivity Analyses for Vaccine Parameters

We performed one-way sensitivity analyses of differences in vaccination deployment strategy, vaccine efficacy, vaccination campaign coverage, and the time between vaccination campaigns in a given location (Table 1). Sensitivity parameters for vaccine efficacy were taken directly from the upper and lower 95% confidence interval bounds from a recent meta-analysis (Figure S2) [7]. Sensitivity parameters for vaccination coverage were taken from the 10th and 90th percentile resampled distribution of published coverage survey estimates from previous OCV campaigns (Figure S1, Table S1) [12–20].

Projected Cases Averted Due to Vaccination Campaigns

For our study period years of 2018-2030, we assumed that cholera incidence remained constant at the mean annual incidence rates observed from 2010-2016 in the absence of vaccination.

We assume that cholera vaccination is the only mechanism that confers immunity to cholera. The proportion of the population not protected by vaccine, and hence susceptible to cholera infection ('susceptibles'), in location *i* in year *t* is:

$$S^*_{i,t} = \Pi^{t}_{k=1}(1 - V_{i,k} f_v\,(t-k+1)\,p_{i,k,t})\,,$$

where $V_{i,k}$ is the proportion of the population vaccinated in year *k* at location *i*. The function $f_v\,(n)$ represents the direct vaccine efficacy *n* years after vaccine was administered to the population. We modeled demographic changes in the population as

$$p_{i,k,t} = (N_{i,k}\,(1-(t-k)\,\mu\,)) / N_{i,t}\,,$$

where $p_{i,k,t}$ is the proportion of the population in location *i* from year *k* that is still present in year *t*. This proportion is calculated as a function of the population *N* in years *k* and location *i*, and the location's net loss of vaccinated individuals due to migrations and deaths μ. We assumed that the net loss of vaccinated individuals due to migrations and deaths was the same for all locations (65 years^{-1}). The expected number of cholera cases at time *t* and location *i*, $Y_{i,t}$, is then calculated as

$$Y_{i,t} = S_{i,t} \lambda_i N_{i,t} ,$$

where $S_{i,t}$ is the susceptible proportion of the population after accounting for both direct and indirect vaccine effects, and λ_i is the projected baseline cholera incidence for location *i*. The total proportion of effective susceptibles $S_{i,t}$ may be represented as $S_{i,t} = S^*_{i,t} \times g_v(S^*_{i,t})$, where g_v is a function that models the indirect effects of vaccination, as described in the 'Vaccine Properties' section (Figure S3). To estimate the potential reductions in cases attributable to OCV use, we calculated

$$Y^*_{i,t} - Y_{i,t} ,$$

where $Y^*_{i,t}$ represents the counterfactual scenario where no vaccines were deployed.

Role of the Funding Source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of this report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Absent substantial changes to cholera prevention and control, or secular trends in incidence, we expect 2.4 million reported cholera cases from 2018 through 2030 in sub-Saharan Africa; with nearly 50% of these cases in just four countries -- the Democratic Republic of the Congo, Nigeria, Somalia, and Sierra Leone. Given this clustering of disease burden, we examined practical deployment strategies targeting the highest risk districts across sub-Saharan Africa according to historical cholera burden (*rate optimized* and *rate-logistics optimized*) and to water and sanitation coverage (*water optimized* and *sanitation optimized*) and assessed the sensitivity of our results to different vaccine-related assumptions.

When targeting districts ranked by expected cholera incidence rate (*rate optimized*), 34.1% (95% CI: 33.0-35.3%) of cases that would have otherwise occurred without vaccination from 2018 through 2030 were averted (Figure 2, Figure S9, Figure S10, Table S3). This reduction translates to 831,000 cases, 32,000 deaths, and 762,000 DALYs averted after vaccination campaigns from 2018 through 2030. Taking a logistically simpler approach to incidence rate based targeting, where high-risk districts within high-risk countries are targeted together (*rate-logistics optimized*), 25.5% (95% CI: 24.6-26.4%) of cases that would have otherwise occurred without vaccination were averted cumulatively, translating to 620,000 cases, 24,000 deaths, and 584,000 DALYs averted after 13 years of vaccination campaigns.

Targeting districts geographically by lack of access to improved water and sanitation was not as effective as targeting by historical cholera disease burden. When targeting districts by lack of access to improved water (*water optimized*), 11.3% (95% CI: 11.1-11.4%) of cases were averted; this translates to 274,000 cases, 11,000 deaths, and 255,000 DALYs averted after 13

years of vaccination campaigns (Figure 2, Table S3). Targeting by lack of access to improved sanitation was substantially less effective (*sanitation optimized*); 4.6% (95% CI: 4.3-4.7%) of cases were averted, representing 111,000 cases, 4,000 deaths, and 85,000 DALYs that would have otherwise occurred without vaccination from 2018 through 2030.

Across all years with vaccination campaigns, the *rate optimized* strategy averted 21-34% of annual cholera cases and the *rate-logistics optimized* strategies averted 9-26% of annual cholera cases. Burden based deployment strategies substantially out-performed the *water optimized* and *sanitation optimized* strategies, which averted 6-11% and 3-5% of annual cholera cases, respectively. The *untargeted* strategy, where vaccine was deployed at equal coverage across all districts, saw a 0.7-3% annual case reduction from 2018 to 2030.

The most effective vaccination deployment strategies were also the most cost-effective in our simulations. We projected median costs of $2,197 and $2,866 per DALY averted (USD 2017) for the *rate optimized* and *rate-logistics optimized* strategies, respectively (Figure 3). Targeting by risk factors was much more expensive; median costs for the *water optimized* and *sanitation optimized* strategies were $6,559 and $19,711 per DALY averted (USD 2017), respectively. The 2017 gross domestic products (GDPs) of countries within our study area ranged from roughly $300 to $10,000, with a median around $800 (2017 USD) [30]. Mass OCV campaigns would be cost-effective (17-23 of 39 study area countries) or highly cost-effective (7-9 countries) for only burden-based targeting strategies.

We examined the sensitivity of our results to alternate parameters for vaccine efficacy, vaccination campaign frequency, vaccination coverage, and campaign deployment strategies

when taking the *rate-logistics optimized* strategy as the primary scenario (Table 1, Figure 3). Changing the vaccination deployment strategy affected the greatest variation in cost per DALY averted, from $1,851 to $20,803 for the *rate optimized* and *untargeted* strategies, respectively. Vaccine efficacy affected the second-largest variation among model parameters, where the 97.5 and 2.5 percentile vaccine efficacy estimates (Table 1) from a recent meta-analysis cost $2,275 and $5,425 per DALY averted, respectively.

Discussion

This study shows the essential role of geographic targeting in guaranteeing that extended cholera vaccination campaigns across sub-Saharan Africa would have a measurable impact on cholera incidence. When considering the direct and indirect protective effects of oral cholera vaccines, our results suggest that, under projected resource constraints, campaigns that are geographically targeted according to disease burden may avert roughly 9 to 13 times more cholera cases, deaths, and DALYs than untargeted (i.e., general population) approaches. Vaccination deployment strategy can have a greater impact on health impact and cost-effectiveness than substantial improvements to vaccine efficacy, vaccination campaign frequency, and vaccination coverage.

Two vaccination deployment strategies with different disease burden-based criteria for identifying high-risk districts in Africa yielded similarly effective results. We believe the *rate-logistics optimized* approach to be the most practical deployment strategy considered. In this approach, countries are ranked by population living in high-risk districts and then only these high-risk districts are targeted for vaccination. While the less practical *rate optimized* strategy

(which prioritized districts based on burden regardless of country) does prevent more cases, the resulting benefit would not likely outweigh the unmeasured, added costs in logistical implementation. In targeting the highest risk geographic locations, vaccination can be a cost-effective cholera treatment strategy, thus complementing more comprehensive analyses that suggest the importance of targeting high-risk demographic groups for cost-effective cholera vaccination [31].

Improved access to safe water and sanitation (WatSan) is necessary for long-term cholera control and reductions in overall diarrheal disease burden [32–34]. We examined the impact of vaccination deployment strategies that targeted districts with the lowest access to improved water and sanitation as measured by WHO/UNICEF Joint Monitoring Programme for Water Supply, Sanitation and Hygiene (JMP) indicators [24,35]. Targeting by WatSan access for the same number of deployed vaccines averted one-half to one-seventh as many cholera cases as targeting by disease burden-based criteria. However, our analyses were based on indicators that have been criticized for their focus on access to water and sanitation infrastructure as opposed to safely managed and sustainable water and sanitation use [36], which may explain the relatively poor performance of the *water* and *sanitation optimized* strategies. The JMP recently adopted new indicators, which may prove to be more specific indicators of cholera risk [37].

Our simulations are based on conservative assumptions about the effect of mass oral cholera vaccination in sub-Saharan Africa, yet there are several limitations. Our models do not account for immunity due to natural cholera infection, and the indirect effects of vaccination are captured only at the grid-cell level, which limits the estimated impact of the vaccination at critical hubs of

cholera transmission. Our projections assume that baseline cholera incidence remains constant throughout the study period, which may not capture secular trends or inter-year variability in cholera incidence. We also assume that vaccine supply will increase only incrementally over our study period despite large jumps in production capacity over the past three years. We caution that all of our incidence estimates represent only reports of suspected cholera cases and make no explicit adjustments for biased reporting or measurement error.

Our results show how geographic targeting can play an essential role in ensuring that mass OCV use leads to substantial reductions in the global burden of cholera, even under current supply constraints. Continued increases in global OCV production would enable a greater proportion of high-risk populations to be targeted with vaccination with greater regularity. Strategic targeting of resources can play an essential role in making cholera control efforts cost-effective, a message that may be generalized to the entire suite of cholera control activities, including those to increase access to safe water and improved sanitation. The importance of targeting underscores the critical role of surveillance and assessment of the cholera risk landscape in achieving the ambitious goals set forth by the World Health Assembly resolution and the *Roadmap to 2030* to reduce the global burden of cholera.

Tables

Table 1**. Parameters for primary model and sensitivity analyses for vaccination campaign performance and costs**. The lower and upper bound parameters for vaccine efficacy and costs were derived from the 2.5 and 97.5 percentiles of the available data. The lower and upper bound parameters for vaccination coverage were derived from the 10 and 90 percentiles of the estimated coverage distribution based on published OCV campaign coverage surveys.

Model parameter	Primary Scenario	Sensitivity Lower Bound	Sensitivity Upper Bound
Vaccine efficacy (% after 1-5 years)	60, 52, 43, 32, 20	49, 44, 29, 4, 0	68, 59, 54, 52, 51
Vaccine coverage (%)	68	50	84
Periodicity of vaccination campaigns	Every 3 years	Every 5 years	Every 2 years
Vaccine delivery cost per FVP (2017 USD)[1]	2.33	Not applicable	Not applicable
Vaccine procurement cost per FVP (2017 USD)[2]	5.49	Not applicable	Not applicable

[1] Vaccine delivery costs are related to program preparation, administration, and adverse events following immunization.
[2] Vaccine procurement costs are related to vaccine price, shipment, and storage.

Figures

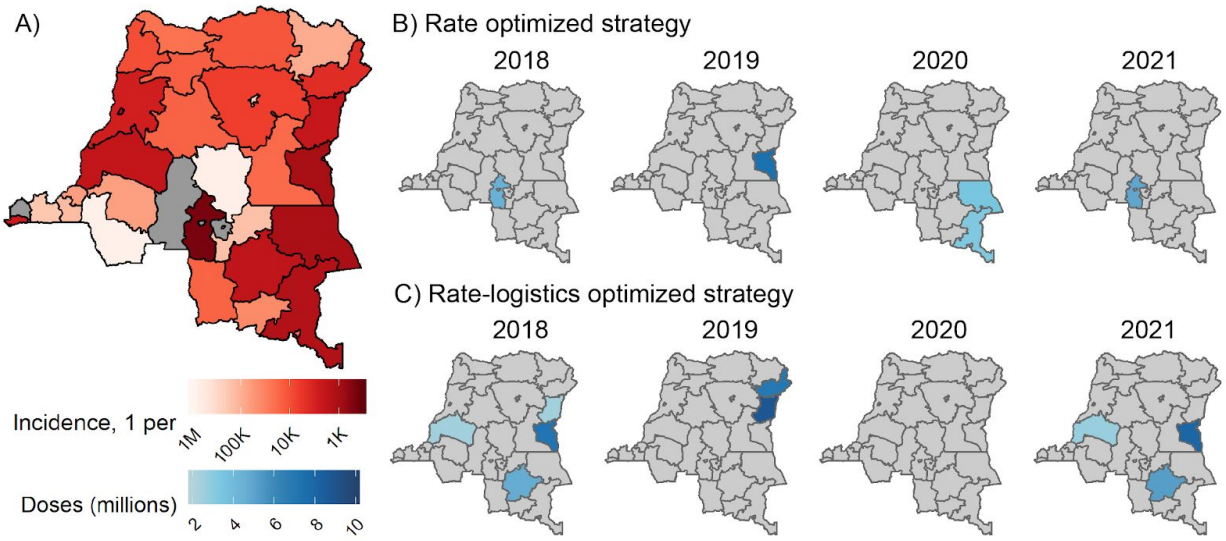

Figure 1. **Demonstration of district-level vaccination deployment strategies in the Democratic Republic of the Congo (DRC).** A) Estimated annual incidence rate by district from 2010-2016. Districts (ISO admin 2) in grey had an annual incidence rate less than one per million people. Vaccine allocations in the DRC by year according to the B) *rate optimized* and C) *rate-logistics optimized* strategies. Districts were targeted in a second consecutive year if they first year's campaign did not have enough vaccine to cover the target population. Districts in grey were not targeted in DRC that year and there were no districts targeted in the DRC in 2020 in the *rate-logistics optimized* strategy.

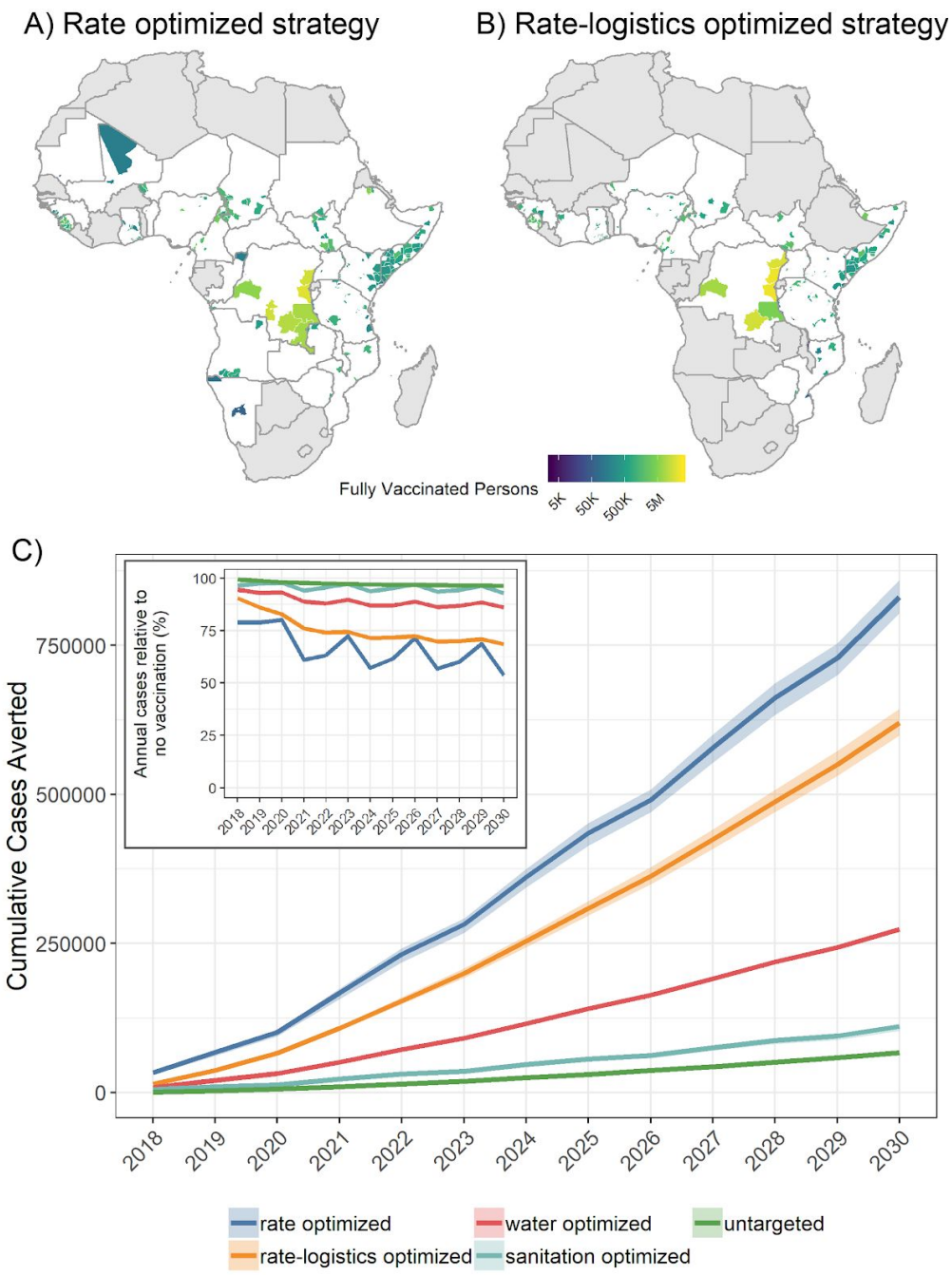

Figure 2. **Health outcomes after vaccination under primary model assumptions.** Cumulative number of fully vaccinated persons in sub-Saharan Africa as a result of campaigns from 2018 through 2030 according to the A) *rate optimized* and B) *rate-logistics optimized* vaccination deployment strategies. Countries in grey had no districts targeted by a given vaccination deployment strategy. C) Cumulative cases averted from mass oral cholera vaccination campaigns across five deployment strategies in sub-Saharan Africa from 2018 through 2030. The inset figure shows the annual percentage of cholera cases averted in our models according to each deployment strategy.

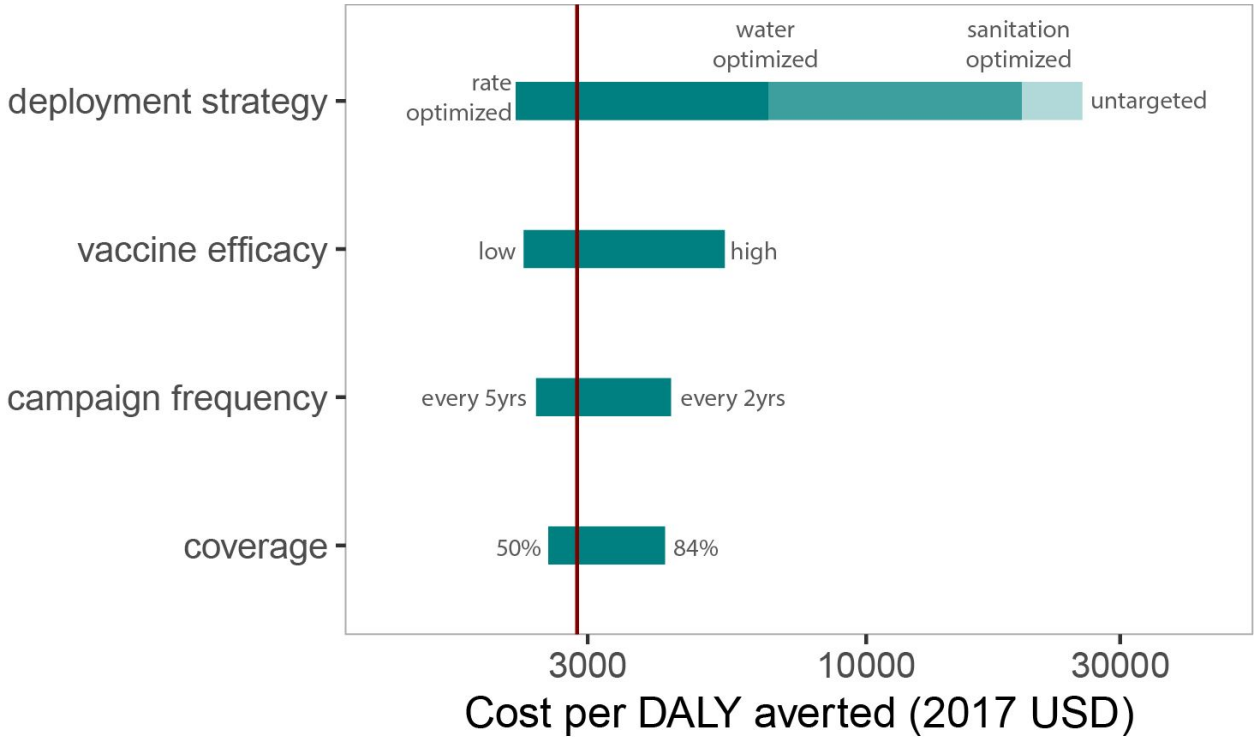

Figure 3. **Sensitivity analysis of the median cost per DALY averted to alternate parameters for vaccination deployment strategy, vaccine efficacy, vaccination campaign frequency, and vaccination coverage.** The red vertical line indicates the cost per DALY averted for the *rate-logistics optimized* scenario with the primary model parameters ($2866). The *untargeted* and *rate optimized* strategies represented the highest and lowest cost vaccination deployment strategies, respectively.

Contributors

ECL, ASA, and JL designed and conceived the study, interpreted data, and wrote the manuscript. ECL analysed data and prepared the figures. JK contributed code and facilitated data management. JK, SMM, and HSM supervised data entry and integrity. SMM developed baseline maps of cholera incidence. All authors provided writing input and reviewed the final draft.

Competing Interests

The authors declare no conflicts of interest.

Supplementary Material

Vaccination Deployment Strategies

The *case optimized*, *case-logistics optimized*, and *watsan optimized* results were not reported in the main text. The *case optimized strategy* performed worse than the *rate optimized* but better than the *rate-logistics optimized* strategies; 28.7% (95% CI: 26.6-29.7%) of cases that would have otherwise occurred without vaccination from 2018 through 2030 were averted. This reduction translates to 698,000 cases, 28,000 deaths, and 657,000 DALYs averted after 13 years of vaccination. In the *case-logistics optimized strategy*, 25.4% (95% CI: 24.5-26.4%) of cumulative cases that would have otherwise occurred without vaccination were averted, thus translating to 619,000 cases, 24,000 deaths, and 581,000 DALYs averted after 13 years of vaccination.

The *watsan optimized* strategy was similar to the *water optimized* and *sanitation optimized* strategies, but the districts were prioritized according to those with the lowest access to improved water or sanitation. As a combination of the water and *sanitation optimized* strategies, the *watsan optimized* strategy performed better than the *sanitation optimized* strategy and less well than the *water optimized* strategy; 8.2% (95% CI: 7.7-8.4%) of cases that would have otherwise occurred without vaccination from 2018 through 2030 were averted, which translates to 199,000 cases, 7,000 deaths, and 171,000 DALYs averted after 13 years of vaccination campaigns.

The *rate optimized* and *rate-logistics optimized* vaccination campaign deployment strategies are described in greater detail in Figure S5 and Figure S6.

Measuring Public Health Impact and Cost Benefit

We calculated the number of cases averted as the difference in cases between vaccination and no vaccination scenarios. To estimate the number of deaths averted, we multiplied a country-specific case-fatality ratio (CFR) with the expected cases outputs. We estimated country-level CFRs as the inverse-variance-weighted CFR across all years where cholera cases were reported in the WHO Global Health Observatory database [38] (Figure S7). For countries where the estimated CFR exceeded 7% (often based on outbreaks with a small total number of cases) or where no data were available, we applied the mean CFR across all remaining countries (3.4%).

We also estimated the disability-adjusted life-years (DALYs) for the vaccination and no-vaccination scenarios, where DALYs are defined as the sum of years of life lost (YLLs) and years of life disabled (YLDs). YLLs were calculated as $YLL_i = CFR_i \times (Y_{i,t} - Y^*_{i,t}) \times (\kappa_{i,t-\rho_c} - \rho_i)$, where ρ_i is the average age of cholera infection in location *i* and $\kappa_{i,t-\rho_i}$ is the average life expectancy for someone of average cholera infection age in year *t*. Country-level estimates of life expectancy for each projected year in our study period were obtained from the United Nations [39] and average age of cholera infection was calculated as the inverse-variance-weighted mean age among cases identified in OCV trials in Africa and the Caribbean (25.75 years old) [20,40–42]. YLDs were calculated as the product of the proportion of the year disabled with illness (assumed at 4/365) and a disability weight for severe

diarrheal disease as estimated from the 2016 IHME Global Burden of Disease Study (0.247) [43]. Disability weights range from 0 to 1 and represent the magnitude of the health loss associated with a specific health status.

Supplemental Tables

Table S1. **Published coverage survey estimates from previous OCV campaigns**. Median point estimates and standard errors were used to resample coverage from a normal distribution for each campaign.

Study	Vaccination campaign (2-doses only)	Coverage (SE)
Lam et al. 2017 [12]	Dahuk, Iraq	90 (.026)
	Erbil, Iraq	93 (.015)
	Sulaymaniya, Iraq	93 (.018)
	Anbar, Iraq	98 (.015)
	Wasit, Iraq	91 (.026)
	Salah Addin, Iraq	81 (.031)
	Najaf, Iraq	74 (.036)
	Baghdad Karkh, Iraq	37 (.038)
	Kerbala, Iraq	30 (.041)
	Babil, Iraq	21 (.031)
Tohme et al. 2015 [13]	Petit Anse, Haiti	62.5 (.023)
	Cerca Carvajal, Haiti	76.8 (.027)
Luquero et al. 2013 [14]	Boffa, Guinea	78 (.046)
	Douprou, Guinea	76 (.041)
	Koba, Guinea	69 (.046)
	Mankountan, Guinea	84 (.036)
	Tamita, Guinea	78 (.051)
	Tougnifili, Guinea	77 (.056)
	Kaback, Guinea	74 (.036)
	Kakossa, Guinea	78 (.046)
Uddin et al. 2014 [15]	Dhaka, Bangladesh	79 (.027)
Massing et al. 2018 [17]	Kalémie (Strata 1), DR Congo	67.2 (.026)
Baltazar et al. 2018 [44]	Nampula, Mozambique	51.2 (.067)
Cavailler et al. 2006 [27]	Beira, Mozambique	53.6 (.015)

Table S2. **Published cost survey estimates (adjusted to 2017 USD) per fully vaccinated person (FVP) for previous vaccination campaigns in Africa**.

Study	Country	Procurement cost per FVP (2017 USD)	Delivery cost per FVP (2017 USD)
Ilboudo et al. 2017 [25]	Malawi	5.32	1.98
Ciglenecki et al. 2013 [26]	Guinea	5.66	2.41
Cavailler et al. 2006 [27]	Mozambique	1.33	2.26
Schaetti et al. 2012 [28]	Tanzania	30.75	6.55

Table S3. **Summary of cumulative health impacts from 2018-2030 by vaccination deployment strategy for baseline model parameter**.

Vaccination deployment strategy	Cumulative cases averted	Cumulative deaths averted	Cumulative DALYS averted
Rate optimized	830,785 (803,370-859,980)	32,489 (32,021-33,672)	761,575 (747,642-777,378)
Rate-logistics optimized	620,010 (599,150-643,791)	24,381 (23,822-25,360)	583,844 (570,238-596,625)
Case optimized	698,046 (648,877-722,717)	27,936 (26,290-28,646)	656,765 (617,172-665,467)
Case-logistics optimized	619,125 (597,745-642,740)	24,305 (23,748-25,281)	581,299 (568,051-594,379)
Water optimized	274,258 (270,319-277,002)	10,678 (10,518-10,828)	255,108 (251,732-258,805)
Sanitation optimized	110,801 (103,735-114,110)	3,758 (3,498-3,845)	84,894 (79,237-86,839)
Watsan optimized	199,413 (187,610-203,934)	7,230 (6,787-7,432)	170,567 (160,447-175,348)
Untargeted	66,600 (65,733-67,702)	2,802 (2,779-2,848)	65,685 (65,197-66,335)

Supplemental Figures

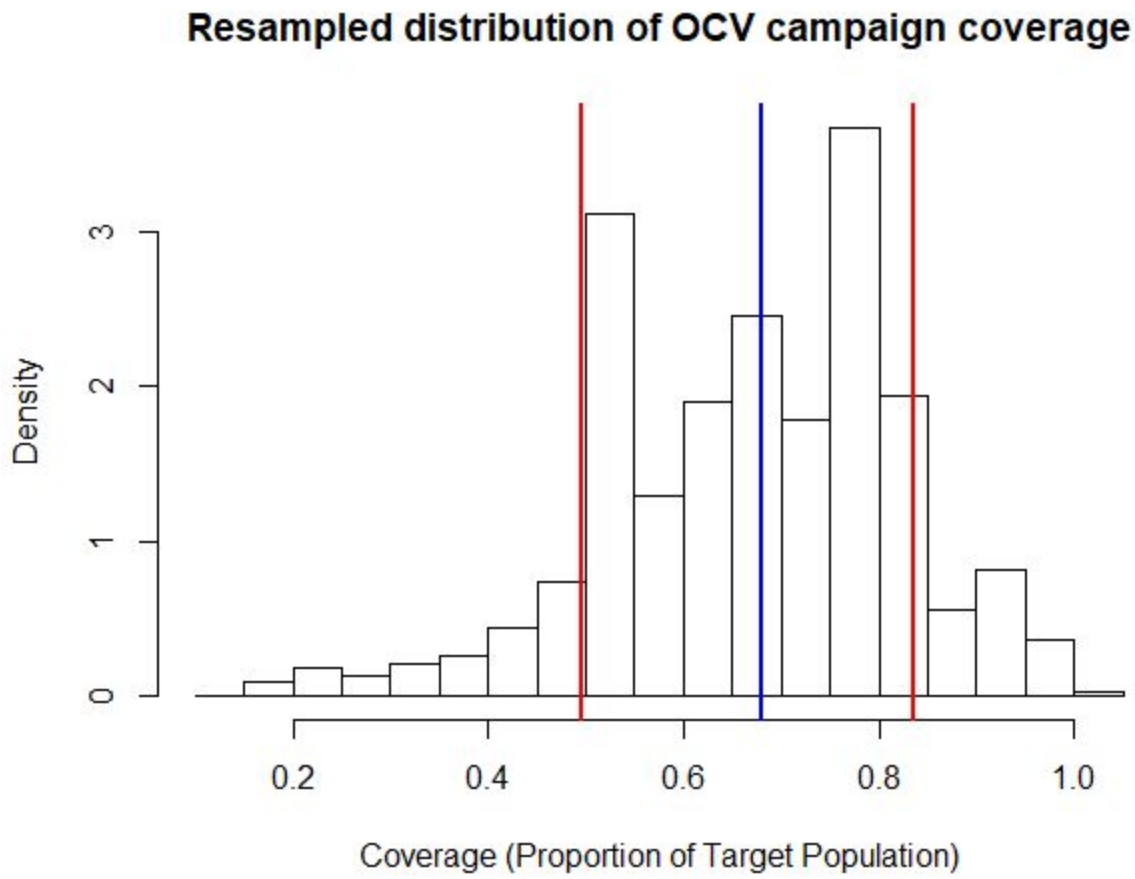

Figure S1. **Distribution of OCV campaign coverage**. We generated a distribution of OCV campaign coverage estimates by resampling estimates from published OCV coverage surveys. The median of the resampled distribution (0.68, blue line) was used for baseline model settings, while the 10th and 90th percentiles of the resampled distribution (0.50 and 0.84 respectively, red lines) were used for the low and high coverage sensitivity analyses.

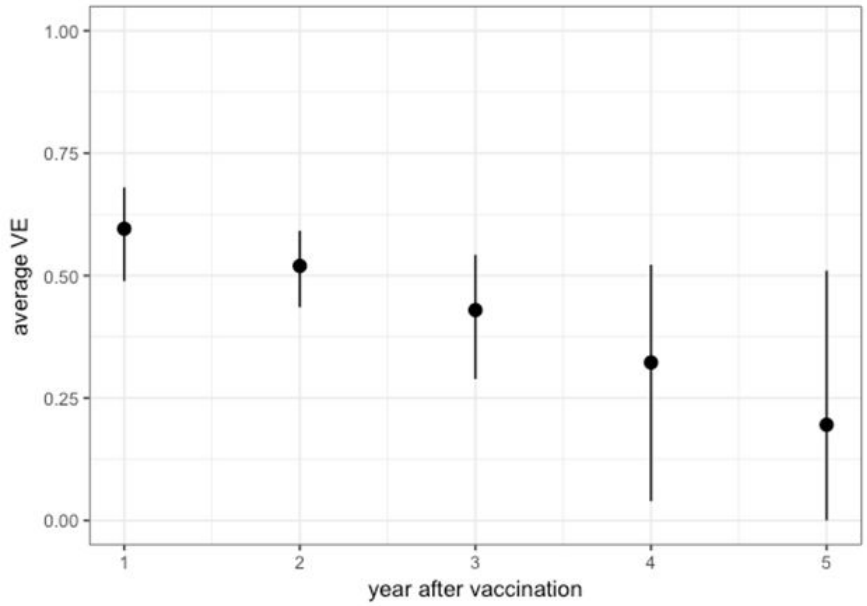

Figure S2. **Waning vaccine efficacy in years after vaccination**. The data displayed represents the median point estimate and 95% confidence intervals across data collected across seven vaccine efficacy studies. Median point estimates were used to parametrize the primary model, while the 2.5 and 97.5 percentiles were used to parametrize the low and high vaccine efficacy models, respectively.

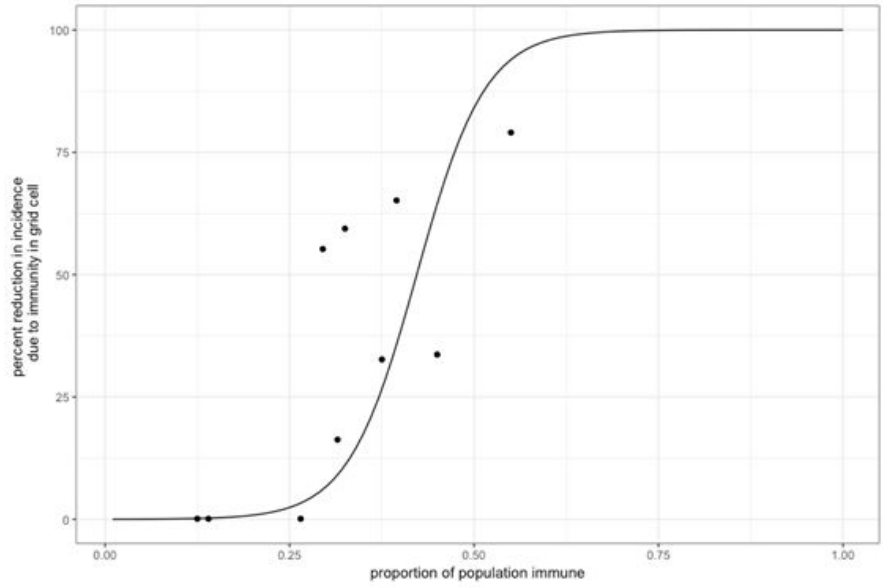

Figure S3. **Indirect protective effect of vaccination**. Each point represents the percent reduction in incidence due to cholera vaccination coverage (population immunity), as reported by a randomized controlled trial. The black line represents the logistic function fit to these data.

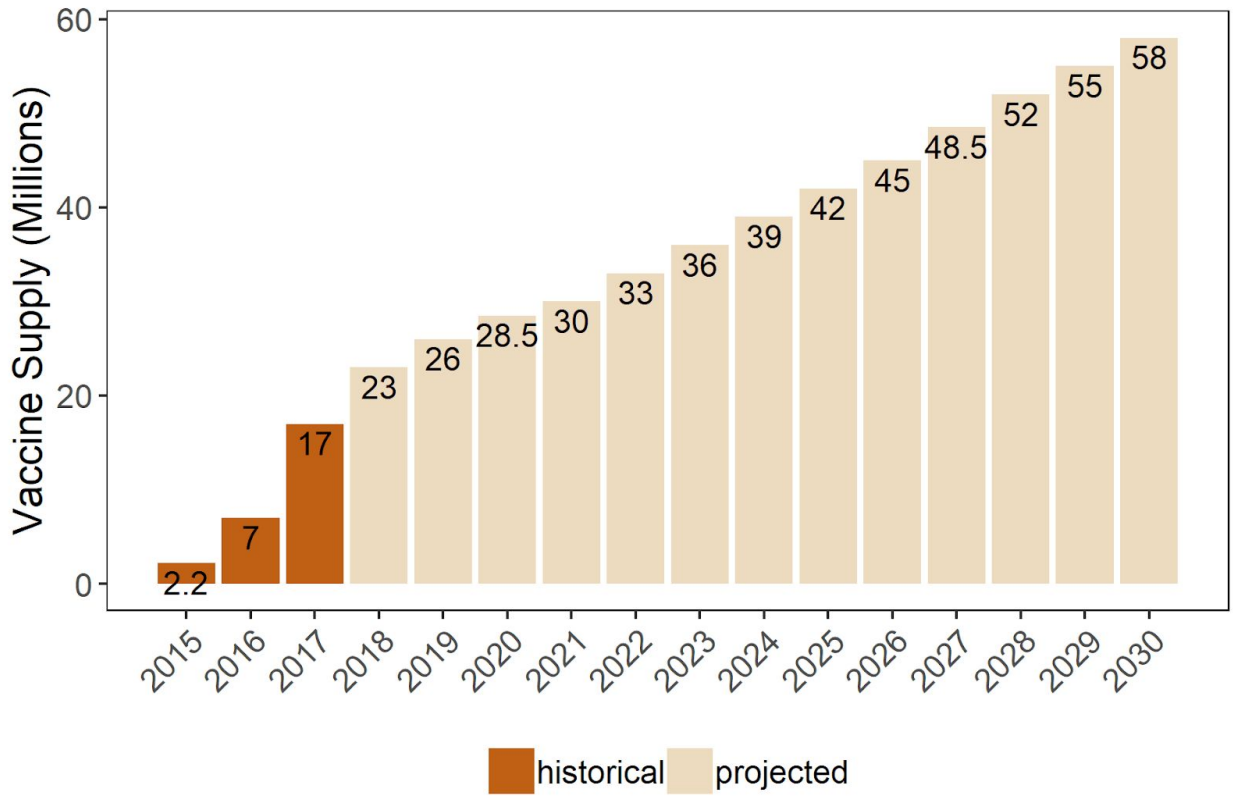

Figure S4. **The historical (2015-2017) and projected (2018-2030) cholera vaccine supply**. The projected vaccine supply per year (in millions) was used as a model input.

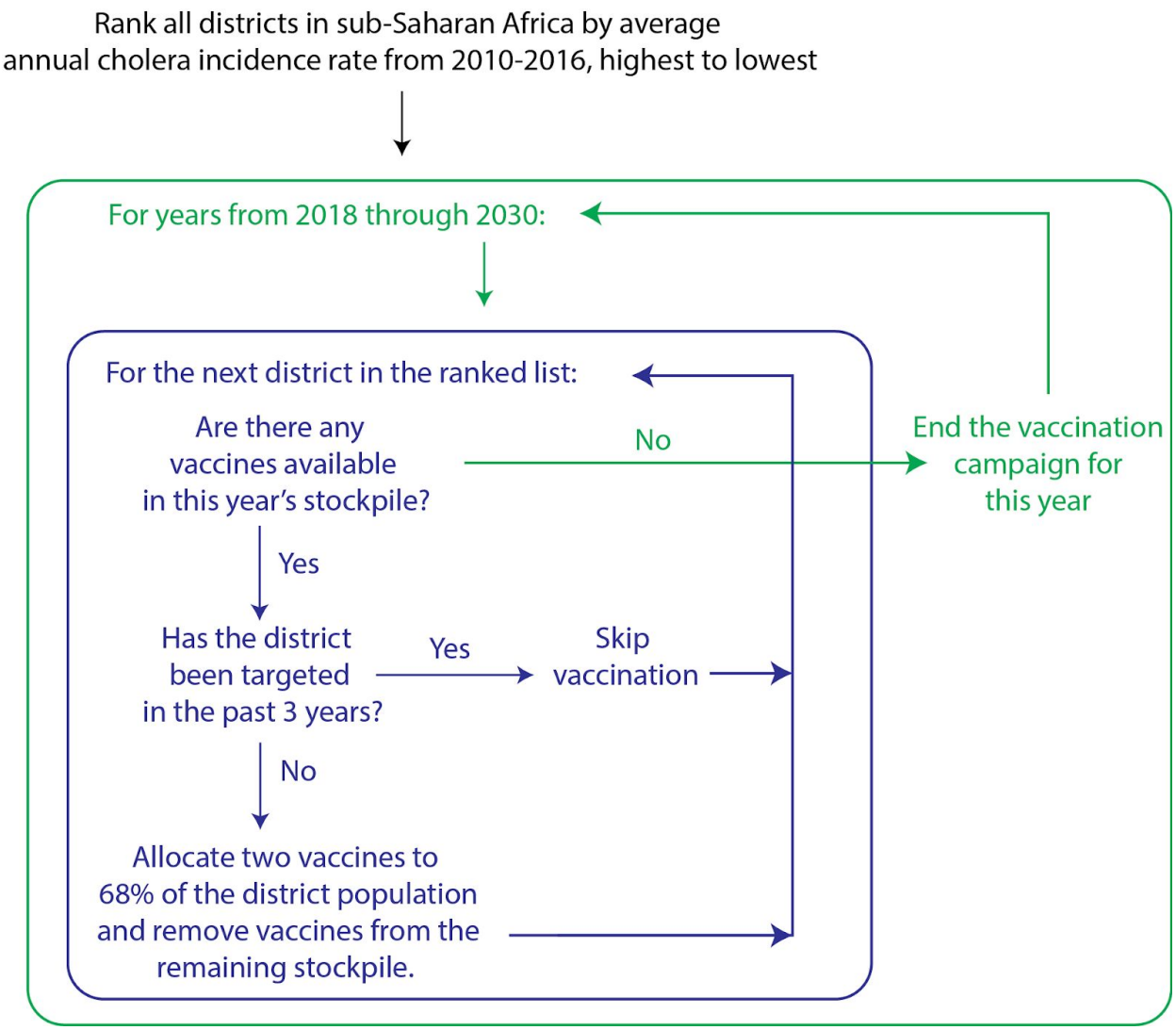

Figure S5. **Flowchart depicting the *rate optimized* vaccination deployment strategy with primary scenario parameters**.

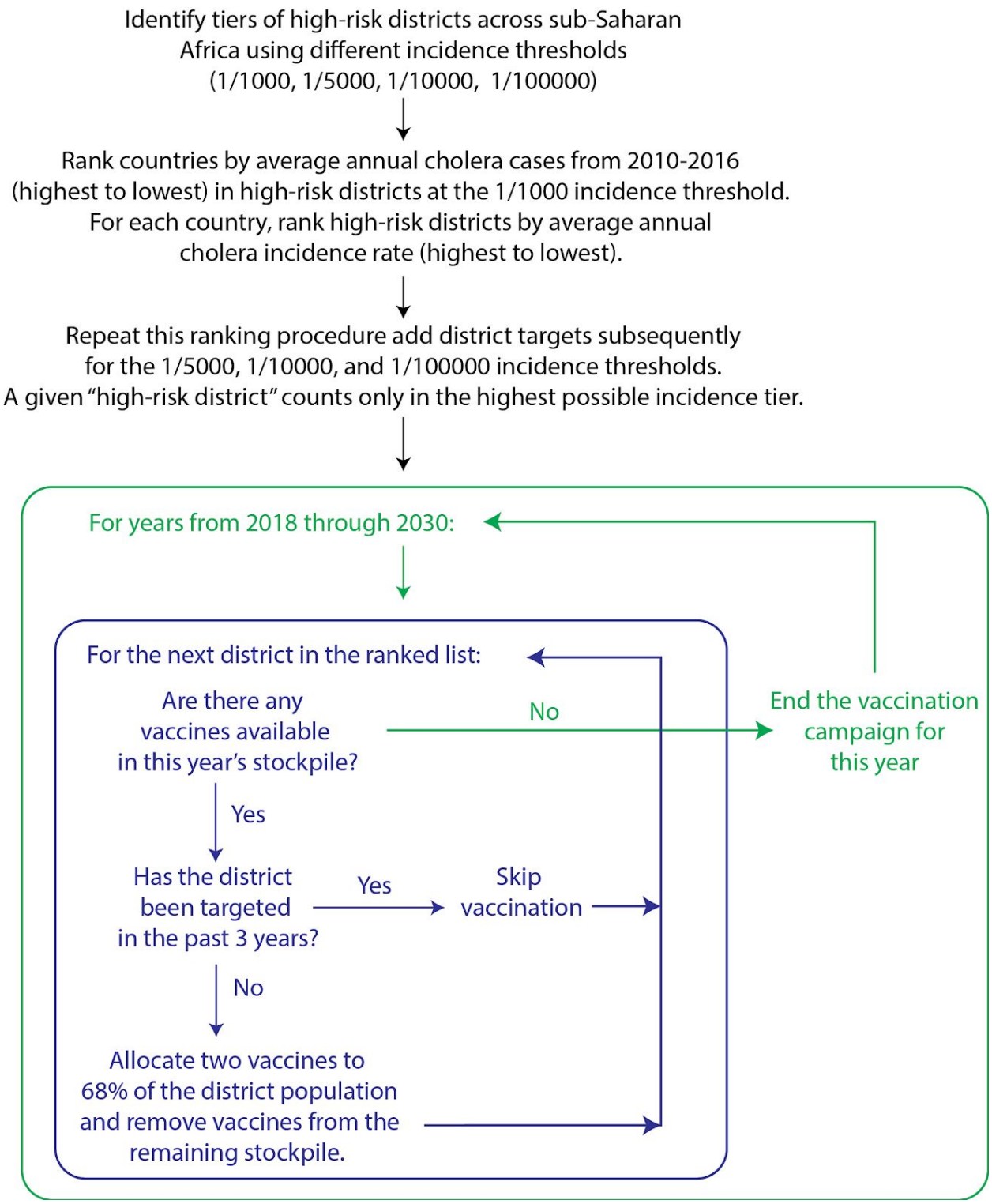

Figure S6. **Flowchart depicting the *rate-logistics optimized* vaccination deployment strategy with primary scenario parameters**.

Figure S7. **Inverse-variance weighted case fatality ratios by country**. We calculated the inverse-variance weighted case fatality ratios by country for all years of data available in the WHO Global Health Observatory database. For a given country, data could have been reported for any year within the range of 1970 through 2016. For countries with implied CFRs greater than 7% or those with no data available (colored in seafoam green), we used the mean of the weighted case fatality ratios below 7% (3.4%).

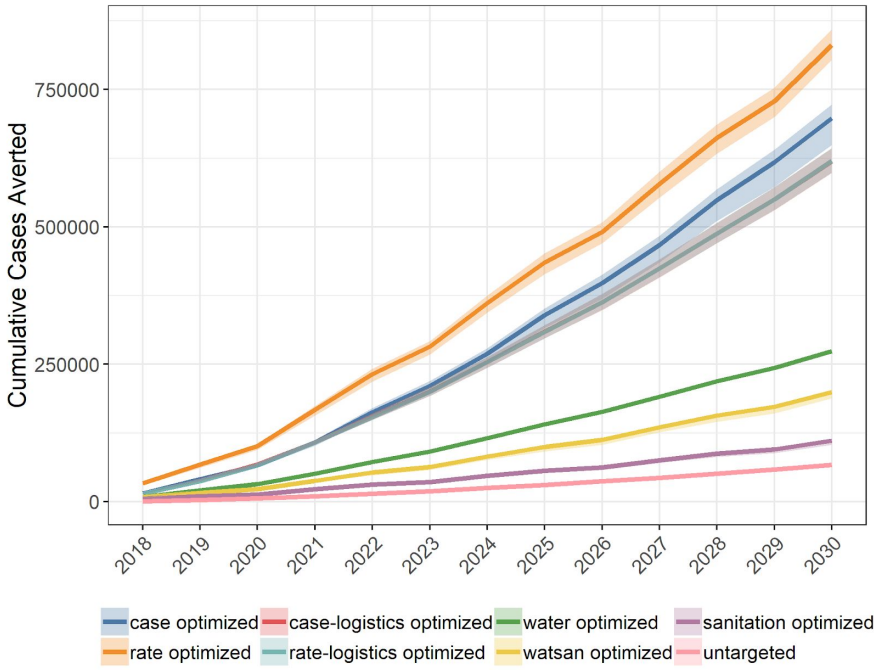

Figure S8. **Cumulative cases averted from mass oral cholera vaccination campaigns across all vaccination deployment strategies in sub-Saharan Africa from 2018 through 2030**.

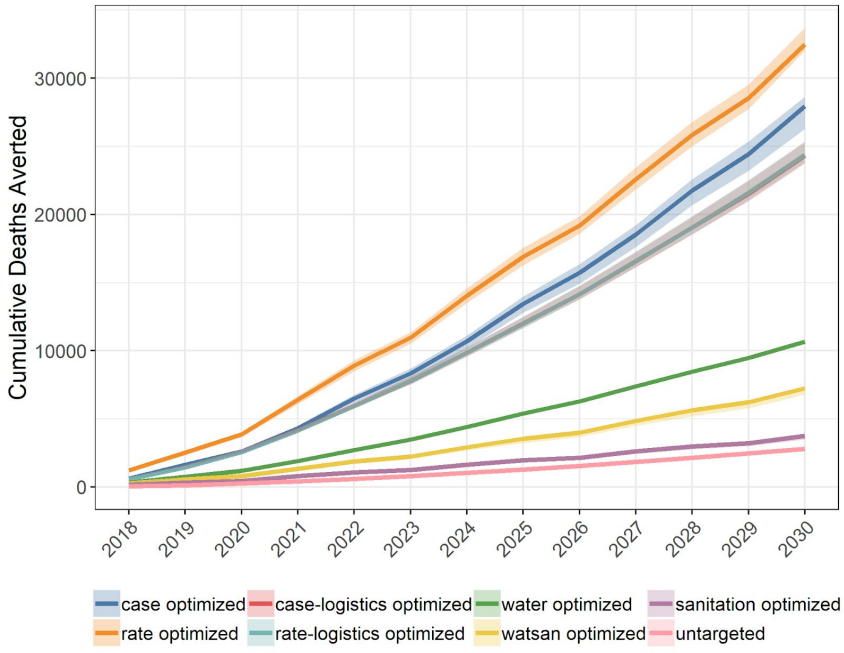

Figure S9. **Cumulative deaths averted from mass oral cholera vaccination campaigns across all vaccination deployment strategies in sub-Saharan Africa from 2018 through 2030**.

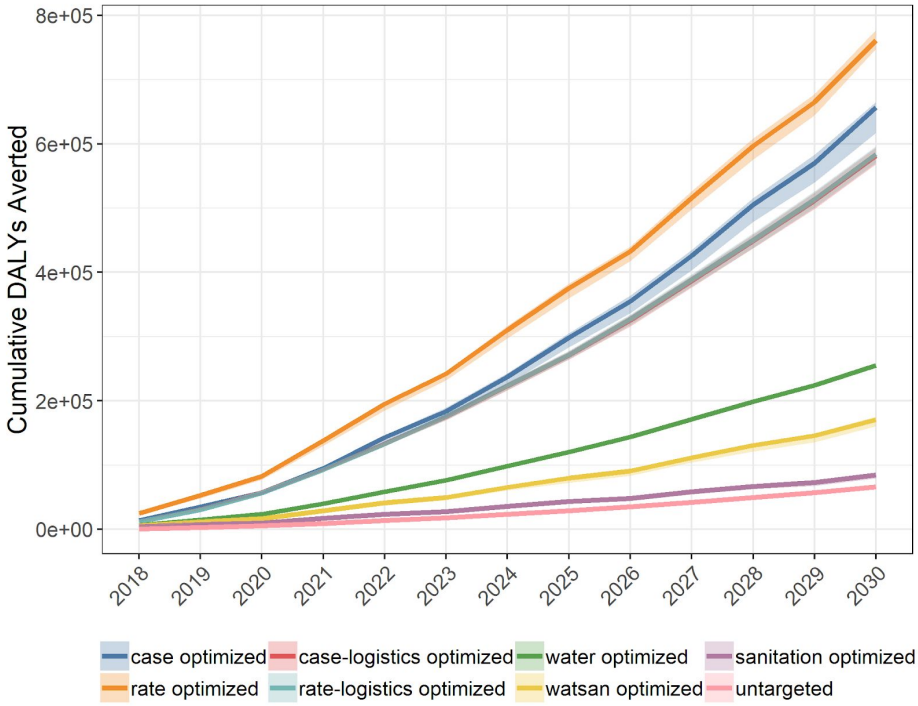

Figure S10. **Cumulative DALYs averted from mass oral cholera vaccination campaigns across all vaccination deployment strategies in sub-Saharan Africa from 2018 through 2030**.

References and Notes

1. Rebaudet S, Sudre B, Faucher B, Piarroux R. Environmental determinants of cholera outbreaks in inland Africa: a systematic review of main transmission foci and propagation routes. J Infect Dis. 2013;208 Suppl 1: S46–54.

2. Griffith DC, Kelly-Hope LA, Miller MA. Review of reported cholera outbreaks worldwide, 1995-2005. Am J Trop Med Hyg. 2006;75: 973–977.

3. Moore SM, Azman AS, Zaitchik BF, Mintz ED, Brunkard J, Legros D, et al. El Niño and the shifting geography of cholera in Africa. Proceedings of the National Academy of Sciences. 2017;114: 4436–4441.

4. WHA71.4 Cholera prevention and control [Internet]. World Health Assembly; 2018 May. Report No.: WHA71.4. Available: http://apps.who.int/gb/ebwha/pdf_files/WHA71/A71_R4-en.pdf

5. Deployments from the oral cholera vaccine stockpile, 2013–2017. Wkly Epidemiol Rec. 2017;92: 437–442.

6. Maurice M'bangombe, Lorenzo Pezzoli, Bruce Reeder, Storn Kabuluzi, Kelias Msyamboza, Humphreys Masuku, Bagrey Ngwira, Philippe Cavailler, Francesco Grandesso, Adriana Palomares, Namseon Beck, Allison Shaffer, Emily MacDonald, Mesfin Senbete, Justin Lessler, Sean M Moore & Andrew S Azman. Oral cholera vaccine in cholera prevention and control, Malawi. Bulletin of the World Health Organization. 2018;96: 428–435.

7. Bi Q, Ferreras E, Pezzoli L, Legros D, Ivers LC, Date K, et al. Protection against cholera from killed whole-cell oral cholera vaccines: a systematic review and meta-analysis. Lancet Infect Dis. 2017;17: 1080–1088.

8. Lessler J, Moore SM, Luquero FJ, McKay HS, Grais R, Henkens M, et al. Mapping the burden of cholera in sub-Saharan Africa and implications for control: an analysis of data across geographical scales. Lancet. 2018; doi:10.1016/S0140-6736(17)33050-7

9. Bi Q, Azman AS, Satter SM, Khan AI, Ahmed D, Riaj AA, et al. Micro-scale Spatial Clustering of Cholera Risk Factors in Urban Bangladesh. PLoS Negl Trop Dis. 2016;10: e0004400.

10. Kim J-H, Mogasale V, Burgess C, Wierzba TF. Impact of oral cholera vaccines in cholera-endemic countries: A mathematical modeling study. Vaccine. 2016;34: 2113–2120.

11. Tatem AJ. WorldPop, open data for spatial demography. Scientific Data. 2017;4: 170004.

12. Lam E, Al-Tamimi W, Russell SP, Butt MO-UI, Blanton C, Musani AS, et al. Oral Cholera Vaccine Coverage during an Outbreak and Humanitarian Crisis, Iraq, 2015. Emerg Infect Dis. 2017;23: 38–45.

13. Tohme RA, François J, Wannemuehler K, Iyengar P, Dismer A, Adrien P, et al. Oral Cholera Vaccine Coverage, Barriers to Vaccination, and Adverse Events following

Vaccination, Haiti, 2013. Emerg Infect Dis. 2015;21: 984–991.

14. Luquero FJ, Grout L, Ciglenecki I, Sakoba K, Traore B, Heile M, et al. First outbreak response using an oral cholera vaccine in Africa: vaccine coverage, acceptability and surveillance of adverse events, Guinea, 2012. PLoS Negl Trop Dis. 2013;7: e2465.

15. Uddin MJ, Wahed T, Saha NC, Kaukab SST, Khan IA, Khan AI, et al. Coverage and acceptability of cholera vaccine among high-risk population of urban Dhaka, Bangladesh. Vaccine. 2014;32: 5690–5695.

16. Abubakar A, Azman AS, Rumunu J, Ciglenecki I, Helderman T, West H, et al. The First Use of the Global Oral Cholera Vaccine Emergency Stockpile: Lessons from South Sudan. PLoS Med. 2015;12: e1001901.

17. Massing LA, Aboubakar S, Blake A, Page A-L, Cohuet S, Ngandwe A, et al. Highly targeted cholera vaccination campaigns in urban setting are feasible: The experience in Kalemie, Democratic Republic of Congo. PLoS Negl Trop Dis. 2018;12: e0006369.

18. Kar SK, Sah B, Patnaik B, Kim YH, Kerketta AS, Shin S, et al. Mass vaccination with a new, less expensive oral cholera vaccine using public health infrastructure in India: the Odisha model. PLoS Negl Trop Dis. 2014;8: e2629.

19. Khan IA, Saha A, Chowdhury F, Khan AI, Uddin MJ, Begum YA, et al. Coverage and cost of a large oral cholera vaccination program in a high-risk cholera endemic urban population in Dhaka, Bangladesh. Vaccine. 2013;31: 6058–6064.

20. Khatib AM, Ali M, von Seidlein L, Kim DR, Hashim R, Reyburn R, et al. Effectiveness of an oral cholera vaccine in Zanzibar: findings from a mass vaccination campaign and observational cohort study. Lancet Infect Dis. 2012;12: 837–844.

21. Ali M, Emch M, von Seidlein L, Yunus M, Sack DA, Rao M, et al. Herd immunity conferred by killed oral cholera vaccines in Bangladesh: a reanalysis. Lancet. 2005;366: 44–49.

22. Ali M, Sur D, You YA, Kanungo S, Sah B, Manna B, et al. Herd protection by a bivalent killed whole-cell oral cholera vaccine in the slums of Kolkata, India. Clin Infect Dis. 2013;56: 1123–1131.

23. Cholera vaccines: WHO position paper – August 2017. Wkly Epidemiol Rec. 2017;92: 477–498.

24. Pullan RL, Freeman MC, Gething PW, Brooker SJ. Geographical inequalities in use of improved drinking water supply and sanitation across Sub-Saharan Africa: mapping and spatial analysis of cross-sectional survey data. PLoS Med. 2014;11: e1001626.

25. Ilboudo PG, Le Gargasson J-B. Delivery cost analysis of a reactive mass cholera vaccination campaign: a case study of Shanchol™ vaccine use in Lake Chilwa, Malawi. BMC Infect Dis. 2017;17: 779.

26. Ciglenecki I, Sakoba K, Luquero FJ, Heile M, Itama C, Mengel M, et al. Feasibility of mass vaccination campaign with oral cholera vaccines in response to an outbreak in Guinea.

PLoS Med. 2013;10: e1001512.

27. Cavailler P, Lucas M, Perroud V, McChesney M, Ampuero S, Guérin PJ, et al. Feasibility of a mass vaccination campaign using a two-dose oral cholera vaccine in an urban cholera-endemic setting in Mozambique. Vaccine. 2006;24: 4890–4895.

28. Schaetti C, Weiss MG, Ali SM, Chaignat C-L, Khatib AM, Reyburn R, et al. Costs of illness due to cholera, costs of immunization and cost-effectiveness of an oral cholera mass vaccination campaign in Zanzibar. PLoS Negl Trop Dis. 2012;6: e1844.

29. Edejer TT-T, World Health Organization. Making Choices in Health: WHO Guide to Cost-effectiveness Analysis. World Health Organization; 2003.

30. Bank W, World Bank. World Development Indicators 2017 [Internet]. 2017. doi:10.1596/26447

31. Hsiao A, Hall AH, Mogasale V, Quentin W. The health economics of cholera: A systematic review. Vaccine. 2018;36: 4404–4424.

32. Freeman MC, Garn JV, Sclar GD, Boisson S, Medlicott K, Alexander KT, et al. The impact of sanitation on infectious disease and nutritional status: A systematic review and meta-analysis. Int J Hyg Environ Health. 2017;220: 928–949.

33. Wolf J, Hunter PR, Freeman MC, Cumming O, Clasen T, Bartram J, et al. Impact of drinking water, sanitation and handwashing with soap on childhood diarrhoeal disease: updated meta-analysis and meta-regression. Trop Med Int Health. 2018;23: 508–525.

34. Nygren BL, Blackstock AJ, Mintz ED. Cholera at the crossroads: the association between endemic cholera and national access to improved water sources and sanitation. Am J Trop Med Hyg. 2014;91: 1023–1028.

35. JMP Methodology 2017 Update and SDG Baselines [Internet]. World Health Organization/UNICEF; 2018 Mar. Available: https://washdata.org/sites/default/files/documents/reports/2018-04/JMP-2017-update-methodology.pdf

36. Cumming O, Curtis V. Implications of WASH Benefits trials for water and sanitation [Internet]. The Lancet Global Health. 2018. pp. e613–e614. doi:10.1016/s2214-109x(18)30192-x

37. World Health Organization. Progress on Drinking Water, Sanitation and Hygiene: 2017 Update and SDG Baselines. 2017.

38. World Health Organization. Global Health Observatory [Internet]. Cholera cases and deahts. 2017. Available: http://apps.who.int/gho/data/node.home

39. United Nations Secretariat, Department of Economic and Social Affairs, Population Division. World Population Prospects, 2017 Revision [Internet]. Life expectancy at birth for both sexes. 2017. Available: https://esa.un.org/unpd/wpp/

40. Azman AS, Rumunu J, Abubakar A, West H, Ciglenecki I, Helderman T, et al.

Population-Level Effect of Cholera Vaccine on Displaced Populations, South Sudan, 2014. Emerg Infect Dis. 2016;22: 1067–1070.

41. Ferreras E, Chizema-Kawesha E, Blake A, Chewe O, Mwaba J, Zulu G, et al. Single-Dose Cholera Vaccine in Response to an Outbreak in Zambia. N Engl J Med. 2018;378: 577–579.

42. Luquero FJ, Grout L, Ciglenecki I, Sakoba K, Traore B, Heile M, et al. Use of Vibrio cholerae vaccine in an outbreak in Guinea. N Engl J Med. 2014;370: 2111–2120.

43. Institute for Health Metrics and Evaluation, Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016. Disability Weights. 2017.

44. Semá Baltazar C, Baltazar CS, Rafael F, Langa JPM, Chicumbe S, Cavailler P, et al. Oral cholera vaccine coverage during a preventive door-to-door mass vaccination campaign in Nampula, Mozambique. PLoS One. 2018;13: e0198592.