Title:

Impact of oral cholera vaccines in cholera-endemic countries: a mathematical modeling study

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Summary:

Background: Impact evaluation of vaccination programs is necessary for making decisions to introduce oral cholera vaccines (OCVs) in cholera-endemic countries.

Methods: We analyzed data to forecast the future global burden of cholera. We developed a mathematical model of cholera transmission in three countries as examples: Nigeria, Uganda, and Indonesia. After fitting the model, we evaluated the impact of OCVs delivered in four vaccination strategies varying by target age group and frequency of vaccination over the period of 2015-2030.

Results: Data suggest that the global annual incidence of cholera will increase from 3 046 238 in 2015 to 3 787 385 in 2030 with the highest burden in Asia and Africa where overall population size is large and the proportion of population with access to improved sanitation facilities is low. We estimate that OCV will reduce the cumulative incidence of cholera by half in Indonesia and >80% in Nigeria and Uganda when delivered to 1+ year olds every three years at a coverage rate of 50%, although cholera may persist through higher coverage rates (i.e., >90%). The proportion of person-to-person transmission compared to water-to-person transmission is positively correlated with higher vaccination impact in all three countries.

Conclusions: Periodic OCV vaccination every three or five years can significantly reduce the global burden of cholera although cholera may persist even with high OCV coverage. Vaccination impact will likely vary depending on local epidemiological conditions including age distribution of cases and relative contribution of different transmission routes.

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Keywords: Oral cholera vaccine; Mathematical model; Water-to-person transmission

Key messages:

- The global burden of cholera may increase over the period of 2015-2030 with the highest burden in South Asia and Africa
- Oral cholera vaccines can significantly reduce the global burden of cholera although cholera may persist even with high vaccine coverage
- The proportion of person-to-person transmission compared to water-to-person transmission is positively correlated with higher vaccination impact

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Main document:

Introduction

Cholera is a serious public health problem in developing countries. One recent study estimates there are 1.3-4.0 million cholera cases and 21 000-143 000 deaths per year.[1] As of 2012, there are 69 cholera-endemic countries with annual cholera incidences ranging from 10 to 2 600 cases per 10 000 persons. In addition to being endemic to many countries, cholera can cause epidemics in populations with little or no natural immunity, often following natural disasters during which the quality of water and sanitation can be compromised. The cholera epidemic in Haiti following the catastrophic earthquake in 2010 provides a pertinent example, where 745,588 cases and 8,972 deaths were reported to Ministry of Health as of 10 August 2015.[2]

Because the etiological agent, *Vibrio cholerae*, is transmitted via the fecal oral route, improving water, sanitation, and hygiene (WASH) is the cornerstone of a cholera control strategy. [3] However, improving WASH in low income countries requires sustained health effort and financial resources over many years, while oral cholera vaccines (OCVs) can produce an immediate impact for residents residing in endemic or epidemic areas [4-6]. Two OCVs that contain killed cholera *Vibrio* whole cells have been prequalified by WHO and are available for purchase by United Nations (UN) agencies.[7] WHO recommends periodic mass vaccination campaigns of OCVs targeted to preschool- and school-aged children in endemic areas with a pre-emptive and reactive vaccination strategies for epidemics.[7]

However, OCVs have seldom been used for the control of cholera in either endemic or outbreak situations [3] and policy makers will likely require evidence of the feasibility and impact of vaccination programs before OCVs are widely used. Mass oral cholera vaccinations have been shown to be feasible in developing country settings including a Sudanese refugee camp in Uganda,[8] South Sudan,[9] during an outbreak in Guinea,[10-12] and endemic areas in Haiti, Bangladesh, and India.[5, 13-16] OCV vaccinations were shown to be successful at reducing cholera incidence during outbreak

in Vietnam[17] and Zanzibar,[18] and also in a cholera-endemic population in India,[4, 19, 20] Bangladesh,[5] and Haiti.[6]

In addition, modeling studies have demonstrated hypothetical benefits of OCV vaccination in simulated epidemics in Haiti,[13, 21-23] Zimbabwe,[24] and Bangladesh.[25-27] These studies provide insights into the impact of control measures in a relatively small area or over a short period of time. However, knowledge on the long-term impact of large-scale (e.g., national) vaccination programs would still be necessary to plan a large-scale introduction of the vaccine, which, for example, international organizations such as Gavi, the Vaccine Alliance can initiate. In this paper, we provide some possible estimates for the future global burden of cholera and the impact of OCV at the national level over the period of 2015-2030. We use mathematical models of cholera transmission to evaluate the impacts of OCV vaccination strategies in three example countries in Africa and Asia with high cholera burden. Vaccination strategies explored are similar to what Gavi explored in their vaccine investment strategy: vaccination of children aged 1-14 years or persons aged 1+ year and above every three or five years.[28]

Methods

The current and future global burden of cholera

One study estimates cholera causes 1.3-4.0 million cases including 21 000-143 000 deaths per year as of 2012. [1] The authors identified 69 cholera-endemic countries and categorized them into nine regions based on WHO region and mortality stratum: AFR-D, AFR-E, AMR-B, AMR-D, EMR-D, EUR-B, SEAR-B, SEAR-D, and WPR-B. They then estimated the cholera burden for each region. (A more detailed explanation appears in the Supplementary Material S0). These estimates are much higher than the number of cases reported to WHO, which varies from 190 130 to 589 854 by year from 2008 to 2012.[29-33] WHO acknowledges that many cholera cases are not recorded because of

limited surveillance and fear of trade and travel sanctions.[34] We therefore base the current global burden of cholera on these estimates.

To estimate the future burden, we assumed per capita cholera incidence will be stable in cholera-endemic countries. However, cholera incidence at the country level will change as do the population size and the proportion of population with access to improved sanitation facilities, without which people will be at risk of cholera in cholera-endemic countries. We estimated the proportion of the population at risk of cholera after 2015 by fitting a saturating exponential function to the data on the population with access to improved sanitation facilities (see Supplementary Material S1 for details).[35] By multiplying these estimated proportions with the UN projected population size (medium variant)[36], we calculated the expected size of the population at risk of cholera. We then calculated burden of cholera by multiplying the expected size of the population at risk of cholera with incidence per capita per year estimates, as is done in the previous study.[1]

The mathematical model of cholera transmission

The model tracks the size of the population uniquely characterized by a combination of infection status (i.e., susceptible, exposed, infectious, or recovered) and age (<1, 1-4, 5-14, or 15+ year olds). The model also tracks the concentration of vibrio cholera in the water to simulate the transmission via vibrio cholera in the water in addition to person-to-person transmission. Figure 1 shows a schematic of the model, omitting age groups for simplicity. The model is formulated by a system of ordinary differential equations (see Supplementary Material S2), with parameters shown in Table 1. The rate of new infections by person-to-person transmission is determined by the product of the size of the susceptible population, the proportion of the infectious population, and transmission rate per unit time, β^I . Rate of new infections via water-to-person route is determined according to Holling type II functional response with another transmission rate parameter, β^W [37] Transmission rates can have seasonality, which is modeled using a sine function (see Supplementary Material S2). Infected people acquire temporary immunity after recovery, as do vaccine recipients after receiving two doses of OCVs.

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205 We assess dynamics of cholera transmission and the impact of vaccination programs under a broad
206 range of parameter values to address their uncertainties (Table 1). Using Latin hypercube sampling,
207 we generated 200 samples, which we assume is large enough to cover the parameter space adequately,
208 for each of 10 parameters related to natural history of infection (δ , η , ϵ , γ , and ω) and the biology of
209 the vibrio cholera (μ^B , σ , κ , ϕ , and τ), where parameter values are based on previous studies and our
210 best guesses.[20, 25, 26, 30, 38-43]. In addition, we set the ratio r of the person-to-person (β^I) to
211 water-to-person (β^W) transmission rate at 100 000 as baseline. This is loosely based on the previous
212 study, where parameter estimates imply the ratio is about 200 000.[26] However, values of β^W and β^I
213 will likely be unidentifiable from real data that always comes with noise. [44] We examine the ratio of
214 β^I to β^W over a broad range (10^{-10} to 10^6). Our preliminary exploration of the model also showed that we
215 can fit the model to data with either β^I or β^W alone using most parameters sets, and if we try to
216 estimate both parameters simultaneously, the model is usually stuck in local minima, which limits our
217 chance to explore different combinations of β^I and β^W . We implemented a system of differential
218 equations in Java and integrated it using the 4th order Runge-Kutta method.

219

220 **Figure 1 Schematic for the flow of people across disease and vaccination status.** Newly infected
221 people undergo exposed (not infectious) and either asymptomatic or symptomatic states, and then
222 recover. Susceptible people may receive vaccine and are partially protected from infection. Vaccine-
223 induced and naturally acquired immunities decay over time. Death occurs in each subpopulation, but
224 is omitted in the figure for simplicity. Susceptible or vaccinated individuals may be infected by
225 infectious (symptomatic or asymptomatic) individuals or through vibrio in the water (shown as dashed
226 lines).

Model calibration

We simulate cholera transmission for three example countries with high, medium, and low cholera burden: Nigeria in AFR-D, Uganda in AFR-E, and Indonesia in SEAR-B. We calculated age-specific death rates by country from life expectancy at age 0, 1, 5, and 15 (see Supplementary Material S3), and then adjusted birth rates to match the size of the simulated population with the expected size of the population at risk of cholera. Then we calibrated the model again by adjusting four parameters, β^w (or β^I), χ_2 , χ_3 , and χ_4 such that the difference between the model and the data in incidence and age distribution of cholera cases is minimized (see Supplementary Material S3). [45-48] Hereafter, we mention only β^w instead of " β^w (or β^I)" for simplicity, but β^I is also varied as we vary β^w because $\beta^I = r\beta^w$. Using the parameter sets ($n=77$) that led to a good match between the model and the data for all three countries, we explored dynamics of disease transmission and the impact of vaccination programs in the model. For American regions where cholera was introduced relatively recently (e.g., cholera outbreak in Haiti since 2010) and per capita cholera incidence is particularly high, many studies have examined dynamic of cholera transmission and effectiveness of intervention strategies.[38, 39, 43, 49, 50] Similarly, other studies have examined the impact of OCVs in Bangladesh in SEAR-D.[25, 26]

245 **Table 1. Model parameters**

Symbol	Description	Baseline value	Range	Ref
ν^*	Per-capita birth rate (year^{-1})	country-specific	NA	Estimated
μ_i^*	Per-capita death rate for age group i (year^{-1})	country-specific	NA	[51]
μ^I	Case fatality ratio	country-specific	NA	[1]
α_i	Aging rate for age group i (year^{-1})	NA	NA	NA
$VE_s^\#$	Proportional reduction in susceptibility in vaccine recipients for <1, 1-4, 5-14, and 15+ year olds	NA, 0.56, 0.9, 0.98	NA	NA
β^I	Person-to-person transmission rate by a symptomatic patient (year^{-1})	NA	NA	Estimated
β^W	Water-to-person transmission rate (year^{-1})	NA	NA	Estimated
χ_i	Relative susceptibility for age group i	NA	NA	Estimated
r	Ratio β^I to β^W ($\beta^I = r\beta^W$)	10^5	$10\text{-}10^6$	[26]
δ	Proportion of infections asymptomatic	NA	0.5-0.95	[19, 52]
ω	Waning rate of immunity (year^{-1})	NA	1/2-1/20	[25, 30, 39, 52, 53]
$1/\epsilon$	Mean latent period (day)	NA	0.5-6	[25, 49]
$1/\gamma$	Mean infectious period (day)	NA	3-17	[25, 26, 38-44, 49]

σ	Contribution of cholera excreted by a symptomatic patient (cells/ml) (day ⁻¹)	NA	1-500	[26, 41]
μ^B	Death rate of <i>V. cholerae</i> in the water (day ⁻¹)	NA	1/2-1/200	[26, 32, 34, 38, 39, 43, 44, 49]
κ	Concentration of <i>V. cholerae</i> that yields 50% chance of catching cholera (cells/ml)	NA	10 ⁴ -10 ⁶	[26, 39]
η	Proportional reduction in β^I and σ in asymptomatic infection	NA	0.1-0.99	[25, 26, 38-40, 49]
ϕ	Amplitude of the transmission rate boosting function	NA	1-10	[25]
τ	Period of the transmission rate boosting function	NA	0.5,1,0 [†]	[45, 54, 55]

246 *Death rates for each age group are calculated based on life expectancy and birth rates were adjusted to match the size of the population at risk of cholera over
247 time (see Supplementary Material S3)

248 [#]Proportional reduction in susceptibility was adjusted to match direct vaccine effectiveness from simulation with the protective efficacy measures from a
249 clinical trial (see Methods and Supplementary Material S4)

250 [†]0 means that boosting function will be replaced with 1 and thus the transmission rate will remain constant over time with no seasonality.

Impact evaluation of vaccination strategies

We used the calibrated model to evaluate the effectiveness of the four vaccination programs: preschool- and school-aged children (i.e., 1-14 year olds) or 1+ year olds are vaccinated through mass vaccination campaigns every 3 or 5 years, as recommended by WHO.[7] We assume that the complete vaccination campaign using a two-dose OCVs takes six weeks regardless of the coverage rate and the region, loosely based on the previous mass vaccination campaigns in developing countries.[8, 12, 14, 15, 18, 56] We assume OCVs reduce the susceptibility of vaccine recipients (VE_s) by 50%, 80%, and 85% for individuals aged 1-4, 5-14, and 15+ years, respectively. This assumption is based on the protective efficacy estimates for each group at 2 and 5 years after the vaccination during an OCV clinical trial in Kolkata, India.[20, 52]

Results

The expected size of the population at risk of cholera increases from 1 348 194 910 in 2015 to 1 549 854 090 in 2030 and the cholera incidence increases from 3 046 238 in 2015 and 3 787 385 in 2030 globally (Figure 2 and see Table S1 in the Supplementary Material for details for each region and country). African and South Asian regions (AFR-D,-E, and SEAR-D) comprise 84.2% and 86.6% of global population at risk of cholera in 2015 and 2030, respectively. Cholera incidence in these three regions is responsible for 27.6% and 21.1% of global incidence in 2015 and 2030, respectively. This appears somewhat low considering the size of the population at risk of cholera and happens because of high incidence per capita in Haiti and Dominican Republic (AMR-B and -D). Cholera burden tends to decrease over time in low-mortality regions (AMR-B, EUR-B, SEAR-B, -D and WPR-B) whereas it increases in high-mortality regions (AFR-D, -E, AMR-D and EMR-D). Increase in cholera incidence in high-mortality regions arises because population growth counteracts the improvement in sanitation (see Figure S1 in the Supplementary Material for the trend of improved sanitation in each country).

Figure 2 Expected population at risk (a) and incidence of cholera (b) during 2015-2030

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278 Models produce good match with annual incidence and age distribution of cholera cases for three
 279 countries (Figure 3(a) and 3(b)), with four parameters (β^w and χ_i for $i=2,3,4$) adjusted (Figure 3(c) and
 280 3(d)). Difference in age distribution of cases between Indonesia and the other two countries (e.g.,
 281 incidence rate is lowest in 5-14 year olds for Indonesia) appears to lead to the differences in estimated
 282 relative susceptibility and transmission rates. Children aged 1-4 years have the highest susceptibility in
 283 Nigeria and also in Uganda with some variability across different parameter sets, whereas infants, whose
 284 susceptibility was set to be one, have the highest susceptibility in Indonesia (Figure 3(c)). Water-to-
 285 person transmission rates (β^w) are highest in Indonesia (Figure 3(d)), which is unexpected given the
 286 lowest annual incidence among the three countries, but the actual transmission rates should reflect the
 287 product of β^w and χ_i , which will result in lowest values in Indonesia because of its low values of χ_i . Indeed,
 288 basic reproduction numbers, which should reflect annual incidence and are defined as the one over the
 289 proportion of susceptibles at steady state, are highest in Uganda (mean: 1.18, 95% confidence interval:
 290 1.12-1.24), followed by Nigeria (mean: 1.07, 95% CI: 1.05-1.09), and Indonesia (mean: 1.02, 95% CI:
 291 1.02-1.03). Note the model is calibrated to annual incidence and proportion by age group and so the
 292 models with the same annual incidence may show different sub-year incidence patterns. For example,

incidence is stable during the entire year in some parameter sets whereas it is periodic with its maxima occurring once or twice a year in other parameter sets (Figure S3 in the Supplementary Material).

Figure 3 Models were calibrated to annual incidence and the proportion by age group of cholera cases in Nigeria, Uganda, and Indonesia. (a) and (b) show annual incidence and proportion by age group, respectively, from data (red stars) and from simulation of the model with 77 different parameter sets (box plots). (c) and (d) show estimated parameter values of relative susceptibility (χ_i) and water-to-person transmission rate (β^w), respectively. Dotted horizontal line in (c) refers to susceptibility of the infants (i.e., <1 year olds).

305

306 Simulation shows introducing a vaccination program reduces cholera incidence, where vaccines are given
307 to people aged 1 year and older every three years starting in 2016 (Figure 4(a)). Cholera incidence
308 following a vaccination program is maintained at low levels in all three countries with incidence being
309 lowest in Indonesia where per capita incidence without vaccination is also lowest. Figure 4(b) shows that
310 percent reduction in the number of cholera cases, or overall vaccine effectiveness in other literature,[25,
311 57] increases with increasing vaccine coverage rate in all three countries over the period of 2015-2030.
312 However, cholera persists even at very high vaccine coverage rate (e.g., 90 or 100%) in some parameter
313 sets in all three countries. Difference in percent reduction by country seems to arise because different age
314 groups have different susceptibility and will likely play different roles in determining the population level
315 of cholera. For example, infants are the most susceptible age group in Indonesia (Figure 3(c)) and thus
316 vaccinating 1+ year olds will likely have smaller impact in Indonesia than vaccinating the same
317 population in Uganda where infants have the lowest susceptibility. In Nigeria, susceptibility of infants is
318 higher than 5+ year olds, but lower than 1-4 year olds and thus the vaccination impact is between that in
319 Uganda and Indonesia. Vaccinating about a half of the population every three years over the period of
320 2015-2030 reduces cholera incidence about 90%, 95%, and 60% in Nigeria, Uganda, and Indonesia,
321 respectively. Figure 4(c) shows the number of cholera cases averted can vary from <1 to >50 case per
322 1000 vaccine doses depending on the vaccine coverage rate and country. The number of cases averted
323 shows the opposite pattern to the percentage reduction and decreases as the vaccine coverage rate
324 increases. This occurs mainly because the indirect preventive effect of a vaccine becomes redundant as
325 the number of vaccine recipients increases. Vaccinating fewer people (e.g., only children aged 1-14 years)
326 at the same frequency or vaccinating the same people at a lower frequency (e.g., every five years)
327 produces lower impact (see Figures S4 and S5 in the Supplementary Material). Figure 4(d) shows that just
328 a single round of vaccination can have significant impact over the years with the cases averted increasing
329 over time.

Figure 4. Impact of vaccination in Nigeria (white), Uganda (red), and Indonesia (green) over the period of 2015-2030. Results from the model with 77 different parameter sets from are shown as box plots with sample means being connected with dotted lines. Vaccines are given to 1+ year olds every three years. In (a), vaccination occurs in 2016, 2019, and 2022 at the coverage rate of 30%. For (b) and (c), vaccine coverage rate was varied from 10 to 100% by 10%.

Table 2 shows the number of cases and vaccine doses required under different vaccination strategies in three countries. Vaccinating children aged 1-14 years at the coverage rate of 70% every five years, which requires the minimum amount of vaccines among the four strategies, will likely prevent on average 2 877 934 (95% CI: 2 745 031 - 3 010 838 assuming normal distribution) cases in Nigeria, 1 228 190 (95% CI:

1 162 680 - 1 293 701) cases in Uganda, and 145 689 (95% CI: 127 815 - 163 564) cases in Indonesia over the period of 2016-2030.

Simulation results show person-to-person transmissions takes over 40% of the total transmission for all three countries (Figure 5(a)). Also, a linear model fitting suggests a possible positive relationship between the impact of vaccination (at the coverage rate of 70% for 1+ year olds as an example) and the fraction of person-to-person transmissions. This in turn implies a possible overestimation of vaccine impact if the fraction of person-to-person transmissions is lower in reality than our model assumes. Figures 5(b)-5(d) show simulation results in case where the ratio of β^I to β^W is chosen uniformly at random between 1 and 10^6 , with all the other parameters staying the same. The fraction of person-to-person transmissions and the reduction in the number of cholera cases by vaccination varies more widely than the case where the ratio of β^I to β^W is fixed (Figure 5(b)). Percent reduction across vaccine coverage rate and the number of cases averted per 1000 doses are smaller compared with when the ratio of β^I to β^W is fixed (Figure 5(c) and 5(d)).

355 **Table 2** Vaccination impact in three countries over the period of 2016 to 2030 at the coverage rate of 50% for the target population. Numbers are
356 given as mean (95% confidence interval).

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Vaccination strategy	Country					
	Nigeria		Uganda		Indonesia	
	Cumulative number of cholera cases	#Vaccine doses	Cumulative number of cholera cases	#Vaccine doses	Cumulative number of cholera cases	#Vaccine doses
No vaccination	4 756 222 (4 733 764 – 4 778 681)	NA	1 884 716 (1 855 144 – 1 914 288)	NA	612 508 (600 897 – 624 119)	NA
1+ yo, every 3 yrs	503 679 (433 896 – 573 462)	242 909 066 (232 387 460 – 253 430 672)	93 349 (73 981 - 112 716)	50 295 095 (48 219 064 – 52 371 127)	194 000 (177 647 – 210 354)	114 595 723 (107 495 242 - 121 696 204)
1+ yo, every 5 yrs	801 264 (696 282 – 906 246)	156 440 158 (151 508 814 – 161 371 501)	198 312 (154 615 – 242 008)	32 022 488 (30 952 280 – 33 092 696)	248 620 (230 510 – 266 729)	75 745 139 (72 134 470 – 79 355 808)

1-14 yo, every 3 yrs	1 442 727 (1 326 205 – 1 559 249)	116 517 794 (112 881 040 – 120 154 548)	469 140 (417 477 – 520 804)	21 990 179 (21 297 002 – 22 683 357)	423 114 (408 703 – 437 524)	6 192 691 (5 868 089 – 6 517 293)
1-14 yo, every 5 yrs	1 878 288 (1 742 024 – 2 014 551)	73 023 720 (71 523 910 – 74 523 530)	656 526 (592 489-720 562)	13 743 343 (13 439 430 – 14 047 255)	466 819 (453 479 – 480 159)	3 666 429 (3 525 790 – 3 807 067)

Figure 5. Impact of vaccination and fraction of person-to-person transmissions over the period of 2015-2030. Black, red, and green colors represent Nigeria, Uganda, and Indonesia, respectively. The ratio β^I to β^W is fixed at 10^5 in (a) and chosen uniformly at random between 1 and 10^6 in (b). The cumulative fraction of person-to-person transmissions is calculated over the period of 2016-2030 when there is no vaccination program. Reduction of cholera cases were calculated when vaccines are given to 1+ year olds every three years starting in 2016. Circles and lines represent results from the model with 77 parameter sets and linear regression, respectively.

Discussion

Our analyses indicate the global burden of cholera will increase over the next decade, provided cholera incidence at the country level is stable and people without access to improved sanitation facilities are at risk of cholera in cholera-endemic countries. This happens because population growth increases the size of the population at risk of cholera, despite the improvement in the sanitation status of countries.

Mathematical models of cholera transmission calibrated to Nigeria, Uganda, and Indonesia in high cholera burden regions of Africa and South Asia predict OCVs can produce immediate impacts on cholera burden regardless of whether vaccines are given just once or periodically. Model predictions agree with other modeling exercises and vaccination experience in reality. The estimates of basic reproduction number for Uganda (1.18, 95% confidence interval: 1.12-1.24) are similar to those for Zimbabwe (1.15, 95% confidence interval: 1.08-1.23), [58] which belong to the same cholera burden category of AFR-E. No cholera cases arose in vaccinated populations during a cholera epidemic which occurred the year after a vaccination campaign in refugee camps in Adjumani, Uganda.[59] In Hue, Vietnam, vaccinating residents aged two years and above every three or five years has eliminated cholera cases since 2003.[60] Other regions experienced reduced incidence of cholera cases in vaccinated populations, regardless of whether vaccines are given preemptively (Beira, Mozambique [56] and Zanzibar, Tanzania [18] and Dhaka, Bangladesh [5]) or reactively (Vietnam [17], Haiti [6]). The predicted number of cholera cases averted per 1000 two-dose regimen from our model analyses are in a similar range to predictions of previous model analyses [25, 49]. These estimates appear to be higher than the number of cases averted among vaccine recipients measured during a clinical trial that does not take indirect effect of the vaccine into consideration.[52]

This study has several limitations. First, we acknowledge per-capita incidence data from the previous study is a gross simplification [1]. Furthermore, the model assumes per-capita cholera incidence will be stable in cholera-endemic countries during the period of simulation (i.e., 15 years). These simplifications

warrant a cautious interpretation of simulation results. Second, the model does not account for heterogeneity, but assumes homogeneous mixing at the national level for all individuals at risk of cholera. In reality, cholera burden will vary across different sub-national areas and the vaccine coverage rate necessary to stop its transmission will also be different from the national average. Third, the model does not account for potential catastrophes such as earthquakes, tsunamis, or war that can compromise the quality of water sources and personal hygiene and thus spread cholera further, as has been shown among internally displaced persons and refugees in South Sudan [61] and during the 2010 Haiti earthquake.[62] Fourth, the model includes arbitrary parameters χ_i to explain age distribution of cholera cases. It is generally believed that the different cholera incidence rates by age are mainly due to history of exposure and subsequent immunity to the disease.[3] Because the likelihood of historic exposure to the pathogen will increase with age, cholera incidence rates will decrease with age accordingly. However, this immunity to the disease does not fully capture the observed variance in age distribution. There may be behavioral (e.g., age-specific mixing or risky behavior) or biological differences (e.g., strength of the immune system) that put young children at higher risk of (symptomatic) infection.

Our study shows the impact of OCV vaccination may vary by the proportion of transmissions that occur person-to-person vs. water-to-person routes: the higher the proportion of water-to-person transmissions, the lower the overall vaccine effectiveness. This has an important implication on the modeling exercise to predict the impact of OCV vaccination especially because the two transmission rates (person-to-person and water-to-person) are practically unidentifiable when they coexist.[44] This implies that previous modeling analyses may have overestimated the impact of vaccination if model assumptions led to unrealistically low water-to-person transmissions. One recent OCV clinical trial in urban Bangladesh shows that the overall effectiveness of OCV is around 37% when the vaccine coverage rate was about 65%.[5] This appears to be lower than predictions from our model analyses, which assumes low water-to-person transmissions, and other modeling studies,[25, 26, 63] where the fraction of water-to-person

transmission appears low [26] or is not modeled explicitly.[25] Although there are other differences that make a direct comparison between model predictions and results from clinical trials difficult including population migration, as indicated in the study, we believe careful attention on how two modes of transmissions are conceptualized in the model is warranted.

Along with previous modeling studies and clinical trials, our study predicts that OCVs may serve as an important tool to reduce the global burden of cholera. Periodic vaccination every three or five years can be an effective vaccination strategy and even a single round of mass vaccination can bring a significant impact in the long run. The impact of vaccination may vary by, among many other factors, how much transmission occurs via water-to-person or person-to-person route. A more sophisticated approach that can address this will be needed to better examine the impact of OCVs.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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