

1 **Impact of a multi-pronged cholera intervention in an endemic setting**

2 Short title: Short-term impact of OCV and WASH in a cholera endemic area

3 Alexandre Blake¹, Adam Walder², Ephraim Hanks², Placide Okitayembo Welo³, Francisco Luquero⁴, Didier
4 Bompangue^{3,5}, Nita Bharti¹

5 Corresponding author: Alexandre Blake, agb163@psu.edu

6

7 1: Biology Department, Center for Infectious Disease Dynamics, Penn State University, University Park,
8 Pennsylvania, United States of America

9 2: Statistics Department, Center for Infectious Disease Dynamics, Penn State University, University Park,
10 Pennsylvania, United States of America

11 3: Programme National d'Elimination du Choléra et de lutte contre les autres Maladies Diarrhéiques,
12 Kinshasa, Democratic Republic of the Congo

13 4: Epicentre, Paris, France

14 5: Department of Ecology and Control of Infectious Diseases, Faculty of Medicine, University of Kinshasa,
15 Kinshasa, Democratic Republic of the Congo

16

17 **Abstract**

18 Cholera is a bacterial water-borne diarrheal disease transmitted via the fecal-oral route that causes high
19 morbidity in sub-Saharan Africa and Asia. It is preventable with vaccination, and Water, Sanitation, and
20 Hygiene (WASH) improvements. However, the impact of vaccination in endemic settings remains
21 unclear. Cholera is endemic in the city of Kalemie, on the shore of Lake Tanganyika, in the Democratic

22 Republic of Congo, where both seasonal mobility and the lake, a potential environmental reservoir, may
23 promote transmission. Kalemie received a vaccination campaign and WASH improvements in 2013-
24 2016. We assessed the impact of this intervention to inform future control strategies in endemic
25 settings.

26 We fit compartmental models considering seasonal mobility and environmentally-based transmission.
27 We estimated the number of cases the intervention avoided, and the relative contributions of the
28 elements promoting local cholera transmission.

29 We estimated the intervention avoided 5,259 cases (95% credible interval: 1,576.6-11,337.8) over 118
30 weeks. Transmission did not rely on seasonal mobility and was primarily environmentally-driven.

31 Removing environmental exposure or contamination could control local transmission.

32 Repeated environmental exposure could maintain high population immunity and decrease the impact of
33 vaccination in similar endemic areas. Addressing environmental exposure and contamination should be
34 the primary target of interventions in such settings.

35

36 **Author summary**

37 Cholera is a major global health concern that causes high morbidity. It is a bacterial water-borne disease
38 that can be transmitted via the fecal-oral route or the ingestion of contaminated water. Hence, both
39 population mobility and environmental exposure can promote cholera persistence. The primary tools to
40 prevent cholera include vaccination and Water, Sanitation, and Hygiene (WASH) improvements. The
41 effectiveness of these interventions is well understood in epidemic settings, but their impact in endemic
42 settings is unclear. Achieving cholera elimination requires disentangling the contributors to
43 transmission, specifically population mobility and aquatic reservoirs, and assessing the impact of
44 interventions performed in endemic settings.

45 This study focuses on Kalemie, a cholera endemic city in the Democratic Republic of Congo, on shore of
46 a lake that serves as a potential environmental reservoir. It quantifies the short-term impact of an
47 intervention that used targeted vaccination and WASH. The study shows that the impact of vaccination
48 was dampened by very high background immunity due to constant environmental exposure. This
49 suggests that WASH improvements should be the primary intervention in such settings despite the time-
50 and resource-intensive nature of implementation.

51

52 **Introduction**

53 Cholera is a bacterial water-borne diarrheal disease transmitted through the fecal-oral route. Since the
54 beginning of the 7th cholera pandemic, cholera has been endemic in sub-Saharan Africa (SSA) (1) which
55 now experiences the highest morbidity and mortality globally (2), excluding major epidemic events that
56 occurred in Haiti and Yemen. Typical cholera symptoms include vomiting and diarrhea with rice-water
57 stools, potentially leading to severe dehydration. Individual symptoms can range from asymptomatic
58 infections, to mild infections with symptoms that are hardly distinguishable from other diarrheal
59 diseases, to the typical severe watery diarrhea (3). The case fatality rate (CFR) can reach 70% among
60 severe cases without appropriate treatment, mainly rehydration (4). As many as 80% of infections can
61 be asymptomatic in endemic areas (4), resulting in underestimates of cholera burden.

62 Cholera's causal agent, *Vibrio cholerae* (*V. cholerae*), specifically serogroups O1 and O139, survives in
63 aquatic environments and is present in the excreta (stools and vomit) of infected individuals. Infection is
64 acquired by ingesting a sufficient bacterial load from the environment (indirect transmission), or contact
65 with infectious excreta (direct transmission). *V. cholerae* abundance in aquatic reservoirs varies through
66 interactions with biotic and abiotic factors. Elements of aquatic flora and fauna are associated with *V.*
67 *cholerae* abundance (5). Concomitantly, environmental parameters including water temperature and

68 salinity also influence the *V. cholerae* life cycle in its aquatic reservoir (6,7). Viable *V. cholerae* can persist
69 in the environment in suboptimal conditions for over 15 months in a non-culturable state (5), from
70 which it can revert to a culturable state in favorable conditions. Inappropriate waste management can
71 introduce *V. cholerae* in natural or manmade water reservoirs (8,9) and trigger outbreaks through
72 consumption of contaminated water. An outbreak can then be fueled by both direct and indirect
73 transmission as the increased prevalence of the infection can result in contamination of additional water
74 reservoirs. The dominant transmission routes can be hard to disentangle but their identification is
75 critical to control cholera.

76 The Global Task Force on Cholera Control (GTFCC) has set a road map to eliminate cholera in 20 endemic
77 countries by 2030 (10), defining SSA as an important target. Generally, diseases or pathogens are
78 considered endemic in an area when they display persistent local transmission for an extended period of
79 time. For cholera, the World Health Organization (WHO) defines an area as endemic when local
80 transmission caused confirmed cases in the previous three years (10). This definition encompasses a
81 wide variety of transmission patterns, which could cause the same intervention to have different
82 impacts in different endemic areas. In non-endemic areas, the environmental contribution to cholera
83 transmission is often low, but in endemic areas the relative contribution of direct and indirect
84 transmission routes is often unknown. The benefits expected from cholera interventions, as traditionally
85 implemented in outbreak response, become less clear in endemic settings because they do not
86 necessarily target the dominant transmission route.

87 Cholera transmission can be prevented by improving water and sanitation infrastructures and with
88 vaccination. Water, sanitation, and hygiene (WASH) improvements have historically been the primary
89 prevention tool. WASH improvements are resource- and time-intensive to implement (11). They are
90 extremely effective; waste management and water infrastructures have largely prevented cholera
91 transmission in high income countries (12). Large scale WASH improvements are necessary to control

92 cholera (13), however resource scarcities limit such improvements in the countries carrying most of the
93 global burden: SSA nations have some of the poorest access to clean water and improved toilets in the
94 world (14). In comparison, implementing a vaccination campaign is fast and can reduce cholera
95 transmission quickly. The empirical results of the reactive use of oral cholera vaccines (OCV) in 2012 in
96 Guinea and theoretical results from modeling studies demonstrated the utility of vaccination as a tool to
97 control cholera (15,16). A quick vaccine rollout leads to a rapid increase in population immunity that can
98 mitigate cholera transmission, but it is a short term solution because the acquired protection declines
99 after about 2-3 years (17). The increasing stockpile of OCV allowed for more frequent use of vaccines in
100 outbreak response and its novel use in endemic areas (18,19).

101 Both OCV and WASH improvements are important components of the multisectoral interventions
102 required to control cholera in areas with high burden (10,19). While the benefit of OCV is
103 straightforward in epidemic settings (20,21), it might be narrow in an endemic setting. The impact of
104 OCV on transmission correlates with the increase in population immunity but immunity may always be
105 high if cholera exposure is frequent and widespread, which can be the case in endemic settings.
106 Quantifying the impact of interventions using OCV in endemic settings could provide valuable
107 information to inform control strategies and achieve the ambitious goals set by the GTFCC.

108 The Democratic Republic of Congo (DRC) has consistently carried one of the highest cholera burdens in
109 the African Great Lakes region (2). Cholera is endemic in the Congolese city of Kalemie, in Tanganyika
110 Province, which lies on the shore of Lake Tanganyika (Figure 1A and Figure 1B). The area displays annual
111 peaks of cholera cases, typically during rainy seasons (Figure 1C), and reports suspected cholera cases all
112 year. Lake Tanganyika could act as an environmental reservoir providing frequent exposure. In parallel,
113 the local population is highly mobile with 24.7% of the residents of Tanganyika Province reporting
114 travelling at least once in the previous 12 months for a duration of at least 1 month (22). The strong
115 fishing activity, with fishermen moving seasonally and experiencing exposure to the lake and low

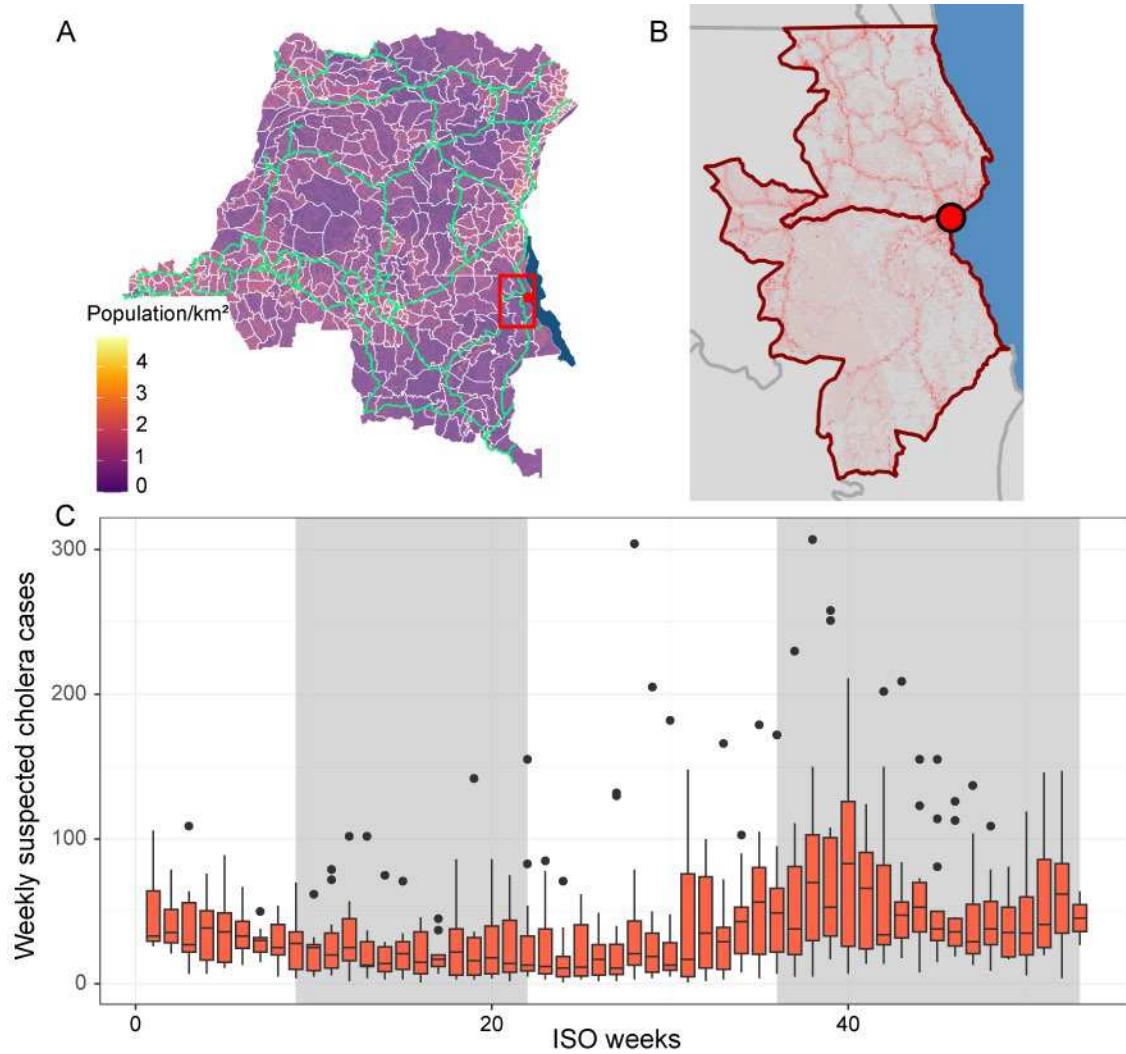
116 sanitation conditions, may be a potential source of reintroduction (23). Such mobility could also
117 promote cholera persistence through metapopulation dynamics.

118 The city of Kalemie received a cholera intervention in 2013-2016 that included both an OCV campaign
119 and limited WASH improvements. The health system in DRC is organized around nested geographical
120 units: Provinces, health zones (HZ), and health areas (HA). Public health interventions are often
121 organized and implemented at least at HZ level. The city of Kalemie spreads across two HZ, Kalemie and
122 Nyemba (Figure 1B). The vaccination campaign targeted HA that were in Kalemie city, where attack
123 rates had historically been the highest as of November 2013. The vaccination campaign originally
124 targeted about 120,000 people in four HA with two doses of Shanchol™, but was interrupted after three
125 days due to security issues. It resumed in July 2014 and the expiration of vaccine doses led to reducing
126 the target population to about 52,000 people in two HA. Ultimately, 81.2% of the target population
127 received at least one dose (24). The WASH component of the intervention focused on improving access
128 to clean water. Although it was not acting on every dimension of WASH, we simply refer to it as “WASH
129 intervention” below. Doctors Without Borders (*Médecins Sans Frontières*, MSF) extended access to tap
130 water in the northern part of the city by laying pipes, building water reservoirs, distributing water filters,
131 and setting up public drinking fountains in collaboration with *Solidarites International*. In addition, sand
132 filters were installed on paths where people draw water from the lake, and chlorination activities were
133 performed during outbreaks. The WASH intervention incurred delays in the aftermath of the security
134 issue that delayed the OCV intervention. Its first milestone, extending access to tap water was achieved
135 in October 2014 and the remaining components were completed incrementally until early 2016.

136 We fit a group of deterministic compartmental models that included interhuman cholera transmission
137 with and without environmental contribution and seasonal migration. We used the model with the best
138 fit to assess the short-term impact of this multi-pronged intervention in the city of Kalemie while

139 considering the potential influence of environmental drivers and their contributions to local
140 transmission.

141



142

143 **Figure 1:** Overview of the location and the seasonality of cholera cases in the study area. (A) Map of the DRC with
144 population density (log transformed), boundaries of health zones in white, major roads in light green, a red box around
145 the health zones of Kalemie and Nyemba. (B) Detail of red box from A, red circle on Kalemie city, Lake Tanganyika
146 in blue. Low population density in grey, high in red. Health zones of Kalemie and Nyemba outlined in dark red. (C)
147 Weekly number of reported suspected cholera cases (based on the International Organization for Standardization (ISO)

148 system) in the health zones of Kalemie and Nyemba from 2002 to 2014 (25), typical rainy season weeks shaded in
149 grey.

150

151 **Methods**

152 We fit a group of Susceptible-Infected-Recovered-Susceptible models with a compartment, B, for the
153 bacterial population in the environmental reservoir (SIRB), Lake Tanganyika (26). We explored the
154 influence of seasonal migration on cholera transmission by fitting models with different structures: with
155 both susceptible and infected (in bold in equations 1, 2, 5, and 6 below), or only susceptible individuals
156 migrating, or no migration.

157 We fit the SIRB models to the reported suspected cholera cases presenting at the only cholera
158 treatment center in the city of Kalemie from November 2013 to February 2016. For this period of time
159 only, detailed surveillance data were gathered in an electronic register with support from MSF as part of
160 a study to assess the impact of the intervention. Only residents of the city of Kalemie were included in
161 the analysis.

162 The structure of the full model is as follows:

$$163 \frac{dS}{dt} = \delta R - \beta_h \frac{SI}{N} - \beta_e \frac{B}{\kappa+B} (1 + \lambda_e f(rain_t)) S - \eta S + \mathbf{f}_S(\mathbf{rad}_t) \quad (1)$$

$$164 \frac{dI}{dt} = \beta_h \frac{SI}{N} + \beta_e \frac{B}{\kappa+B} (1 + \lambda_e f(rain_t)) S - \gamma I + \mathbf{f}_I(\mathbf{rad}_t) \quad (2)$$

$$165 \frac{dR}{dt} = \gamma I - \delta R + \eta S \quad (3)$$

$$166 \frac{dB}{dt} = \mu (1 + \lambda_c f(rain_t)) I - B(\varepsilon - \varphi_t) \quad (4)$$

167 with

$$168 \mathbf{f}_S(\mathbf{rad}_t) = \alpha_1 \mathbf{rad}_t \quad (5)$$

169 $f_I(rad_t) = \alpha_I rad_t$ (6)

170 $ratio_{S/I} = \frac{\alpha_1}{\alpha_I}$ (7)

171 $\varphi_t = e^{\alpha_2 + \alpha_3 sst_t + \alpha_4 chlor_t}$ (8)

172 $\eta = (\sigma_1 VC_{1t} + \sigma_2 VC_{2t})\theta$ (9)

173 $f(rain_t) = \frac{rain_t}{max(rain_t)}$ (10)

174 Susceptible individuals become infected through exposure to the environmental reservoir, β_e , or
175 through interhuman transmission, β_h . The WASH intervention decreased the environmental exposure
176 rate β_e to $\beta_e - \beta_{WASH}$ by the end of the study period. β_e was assumed to decrease linearly from β_e to $\beta_e -$
177 β_{WASH} from the time the first component of the WASH improvements was completed (ISO week 40 in
178 2014). The model did not allow the environmental contamination to vary because the intervention did
179 not target waste management. The infection probability from an exposure to the environment followed
180 a dose-effect relationship, with the half saturation constant κ . Infected individuals transitioned to the
181 recovered compartment at rate γ . Susceptible individuals could gain immunity through vaccination, η , 1
182 week after receiving the vaccine (15). This was included through a step function of the number of people
183 who received 1 or 2 doses (VC_{1t} and VC_{2t}) of ShancholTM. We estimated the number of vaccinated
184 individuals from vaccine coverage estimates from a survey performed by MSF (24) and the associated
185 population size estimates (see Supplementary information (SI)). We considered a range of values for
186 vaccine effectiveness for one and two dose regimens (σ_1 and σ_2), including estimates from studies done
187 in the aftermath of reactive vaccination campaigns performed in Zambia and Guinea (15,27) (see SI).
188 Our models assumed an all-or-nothing effect of vaccination, implying optimistic estimates of its impact,
189 but we also fit an alternative model structure with a leaky vaccine as sensitivity analysis (see SI).
190 Considering the wide age range of the target population (everyone older than 1 year), we assumed that

191 the proportions of susceptible, infected, and recovered among the vaccinated individuals were the same
192 as the general population when the doses were distributed. Immunity waned at rate δ , returning
193 immune individuals to the susceptible compartment. We did not include booster effects on immune
194 individuals receiving vaccine. Booster effects are unlikely to be detected in the study period of 118
195 weeks (most doses were distributed on the 32nd and 35th week), because the study period is shorter
196 than the average period of immunity, whether acquired through infection or vaccination (28,29). We
197 also assumed that vaccination had no impact on those who were infected at the time of vaccination. We
198 added a penalty term (Θ) to account for the spatially targeted nature of the vaccination campaign,
199 which focused on HA in the city of Kalemie with historically high attack rates, where residents had
200 experienced more cholera exposure, further decreasing the proportion of susceptibles. We considered a
201 range of possible values for Θ (between 0.7 and 1) (see SI).

202 Population size was allowed to vary through seasonal migration ($f_S(rad_t)$ and $f_I(rad_t)$), which can
203 influence local cholera transmission through regular reintroductions from areas with ongoing
204 transmission. We included migration by quantifying the seasonal variation of contemporaneous
205 anthropogenic nighttime radiance, extracted from Visible Infrared Imaging Radiometer Suite (VIIRS) data
206 (30) (see SI). We assumed that the net migration flow varied linearly with the first derivative of the
207 nighttime radiance data in the area (rad_t) (31). We first fit a generalized additive model with a cyclical
208 spline to the radiance data and then extracted its first derivative (see SI). We did not consider the
209 mobility of immune individuals, because they do not actively contribute to transmission. We considered
210 a range of values for the ratio of susceptible and infectious individuals among the mobile population
211 ($ratio_{S/I}$) (between 10 and 100) (see SI). We explored alternative model structures allowing only
212 susceptible individuals to be mobile ($f_I(rad_t) = 0$) or removing seasonal mobility ($f_S(rad_t) = 0$ and
213 $f_I(rad_t) = 0$) (see SI).

214 We considered the influence of water temperature, with lake surface temperature (SST_t), and
215 phytoplankton, with chlorophyll-a ($chlor_t$), as environmental drivers on aquatic bacterial growth (5). We
216 extracted these values from Moderate Resolution Imaging Spectroradiometer data (32) (see SI).
217 Precipitation ($rain_t$) could also increase exposure to environmental reservoir and its contamination with
218 infectious human excreta by respectively contaminating drinking water sources (33) ($\lambda_{ef}(rain_t)$) and
219 flooding defecation sites ($\lambda_{cf}(rain_t)$). We extracted precipitation estimates from meteorological
220 forcing data (34).
221 The bacterial population in the environment increased with contamination of the lake from the excreta
222 of infected individuals (μ), and a time dependent bacterial growth rate (φ_t) that varied with SST_t and
223 $chlor_t$. Conversely, it decreased through constant bacterial decay (ε).
224 The models did not include births, deaths, or the age structure of the host population because of the
225 short study period of 118 weeks. Based on case management and a CFR of 0.3% during this 118 week-
226 period (5 deaths reported among the 1634 resident suspected cholera cases), we did not include cholera
227 specific mortality.
228 We used a negative binomial process to link the predicted number of weekly incident cases (C_t) and the
229 weekly reported suspected cases (A_t): $A_t \sim NegBinom(C_t r, C_t \psi)$, with r , a combination of reporting
230 rate and the portion of true cases captured by the suspected case definition (see SI), assumed constant,
231 and $C_t \psi$, an overdispersion parameter scaling with the predicted number of new cases. The negative
232 binomial distribution can handle overdispersion and its scaling overdispersion parameter allows
233 variance estimates to better scale with fast and large variations of the incidence.
234 Using different assumptions regarding $ratio_{S/I}$, σ_1 , σ_2 , and θ , we fit a group of 96 models: 64 variations
235 of the full model, 16 variations of the model with only susceptible individuals migrating, and 16
236 variations of the model without seasonal migration (see SI). We assessed model fit with the widely

237 applicable information criteria (WAIC) (35) and selected the best performing model presented here with
238 the lowest WAIC or with fewer parameters for similar WAIC. We also performed a sensitivity analysis of
239 the best performing model by removing the possibility for bacterial growth ($\varphi_t = 0$) or the
240 environmental compartment and indirect transmission ($\beta_e = 0$) (see SI).

241 We estimated the parameters β_h , β_e , β_{WASH} , α_1 , α_2 , α_3 , α_4 , λ_e , λ_c , δ , μ , ε , r , and ψ , and the initial
242 conditions S_0 , I_0 , B_0 through Markov chain Monte Carlo sampling using the Metropolis-Hastings
243 algorithm. All the estimates presented are the mean values over the posterior distribution and their 95%
244 credible interval (95% CrI) using the highest density interval.

245 We assessed the short-term impact of each arm of the intervention separately and both arms together
246 by estimating the number of additional cases in their absence. We fixed η to 0 while keeping β_{WASH}
247 unchanged, simulating WASH improvements without vaccination, did not allow β_e to decrease
248 ($\beta_{WASH}=0$) while keeping η unchanged, simulating vaccination without WASH improvements, and then
249 fixed both η and β_{WASH} to 0, simulating no vaccination and no WASH improvements. We sampled
250 10,000 sets of parameters from the posterior distribution and calculated the number of additional cases
251 in each of the alternative scenarios compared to the intervention as it happened.

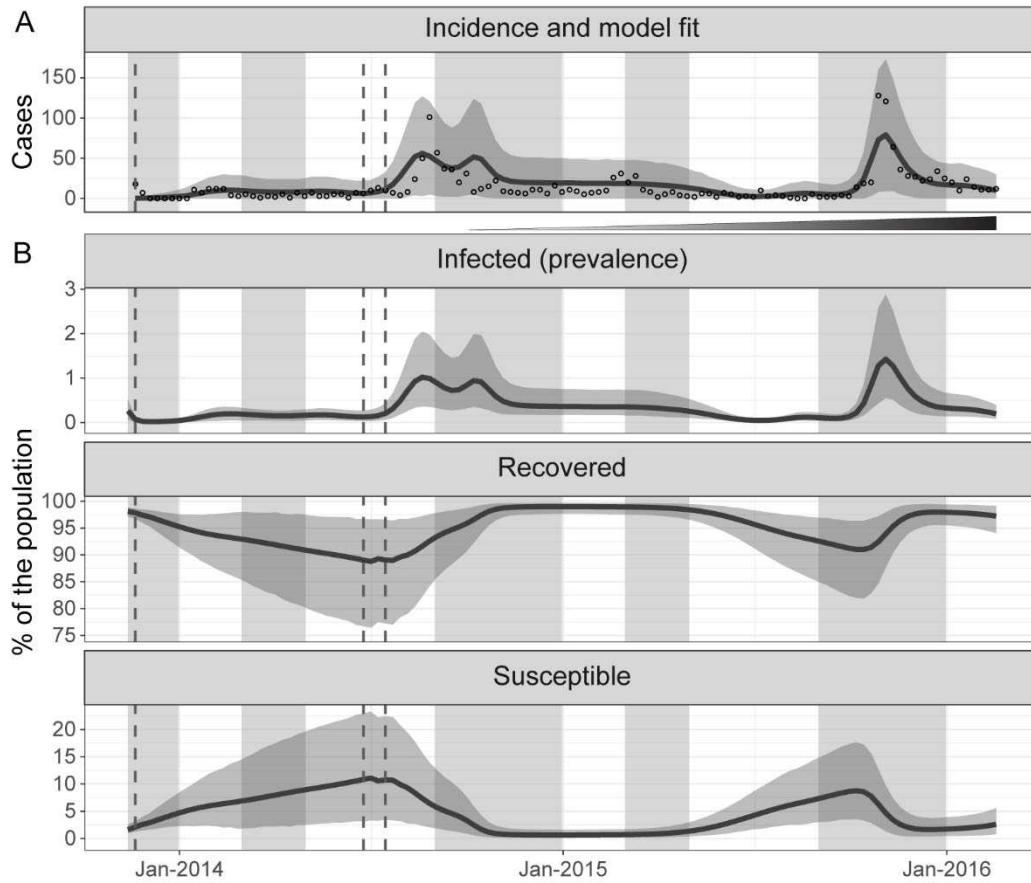
252 We explored alternative vaccination strategies by varying the timing and the size of the target
253 population, between 50,000 to 200,000 (19.0-76.1% of the population of the city of Kalemie), assuming
254 one campaign during the 118-week period with a two-dose regimen (without WASH). The maximum
255 target population size considered is within the MSF vaccination capacity observed in other settings (27).

256 We estimated the number of cases avoided for each scenario by calculating the reduction in cholera
257 cases compared to no intervention for each of 10,000 set of parameters sampled from the posterior
258 distribution. We considered 84 combinations of alternative timing and target population size. We
259 sampled 500 sets of parameters for each combination, computational intensity prohibited more.

260 We investigated the relative contributions of environmental exposure and contamination to
261 transmission assuming no intervention by simulating scenarios with no environmental exposure ($\beta_e=0$),
262 or no environmental contamination ($\mu=0$) and calculating the number of additional cases compared to
263 having them both (β_e , and μ unchanged) for each of 10,000 sets of parameters sampled from the
264 posterior distribution.

265 **Results**

266 Models with no seasonal migration had a comparable fit to the ones with only susceptible individuals
267 migrating or seasonal migration of both susceptible and infected individuals (see SI). This suggested that
268 mobility had minimal influence on the observed cholera dynamics. We selected the model with the
269 lowest WAIC among the ones without seasonal migration, which had fewer parameters. It reproduced
270 the reported weekly cholera cases well, with 98.3% (116/118) of the observed data in the model
271 prediction's envelope of the 95% CrI of weekly reported suspected cases (Figure 2A). The model
272 suggested high local immunity, fluctuating between 88.8% and 99.9% (Figure 2B). This high immunity
273 would be the likely consequence of annual outbreaks and persistent environmental exposure, which we
274 explain further below. Based on our model, the targeted vaccinations occurred when population
275 immunity was high: 97.8% (95% CrI: 96.7-98.6) in November 2013, 89. 0% (95% CrI: 76.7-96.7) in July
276 2014, and 89.1% (95% CrI: 77.2-96.6) during the catch-up in August 2014.



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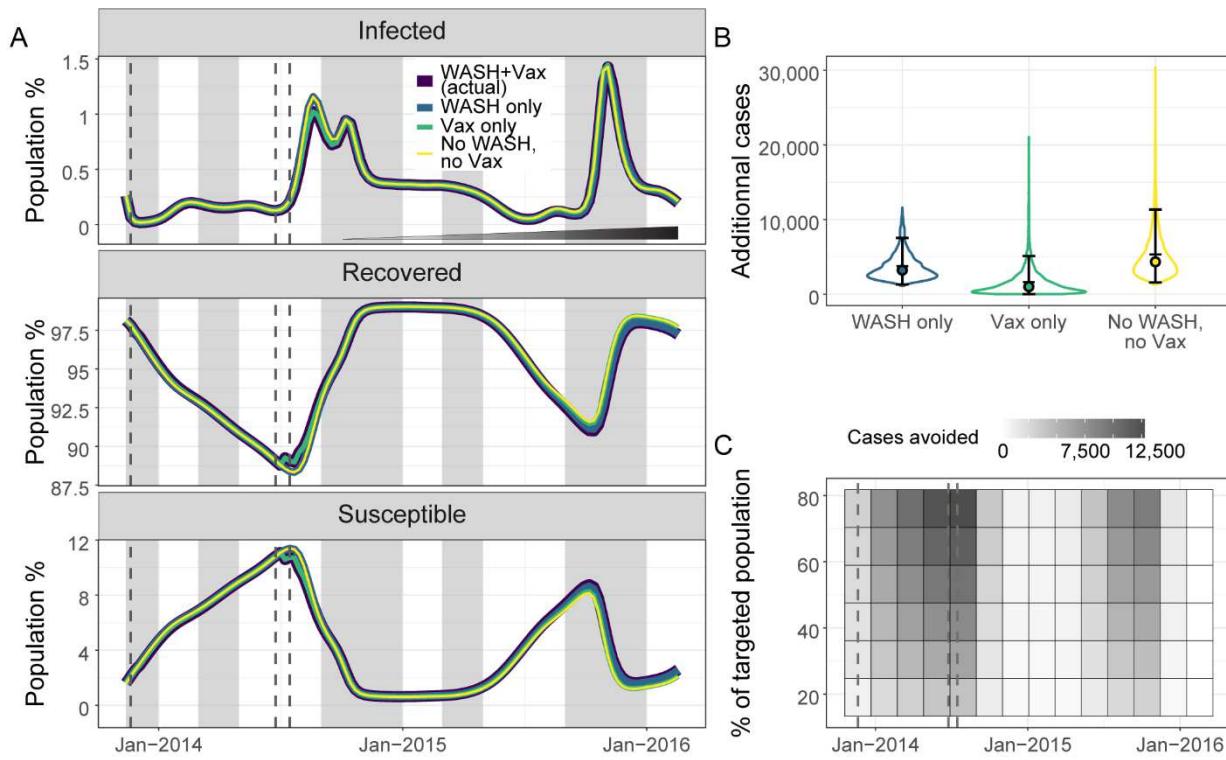
278 **Figure 2:** Incident cases, model fit, and variation of the percentage of infected, recovered, and susceptible over time.

279 (A) Weekly reported suspected cholera cases residing in the city of Kalemie (empty circles) from November 2013 to
280 February 2016 and mean model prediction of the reported weekly cholera cases (dark line) and its 95% credible
281 interval (grey envelope) (B) Mean model prediction of the percent of the population infected (prevalence), recovered,
282 and susceptible (dark lines) and their 95% credible interval (grey envelopes) from November 2013 to February 2016.
283 Typical rainy seasons are shaded in grey, the timing of the distribution of vaccine doses in vertical dashed grey lines,
284 and the incremental implementation of the improvements in water and sanitation is indicated by the widening and
285 darkening triangle between A and B.

286

287 Both the scenarios omitting vaccination (WASH only, and no WASH and no vaccination) visibly lacked a
288 reduction in the susceptible proportion of the population in July 2014 (Figure 3A, bottom panel). Over

289 this 118 week period, we estimated: 3,702 (mean: 3,702.3, 95% CrI: 1,302.5-7,542.0) additional cases
290 when removing vaccination alone (scenario with WASH only), 1,585 (mean: 1,585.5, 95% CrI: 1,321.9-
291 5,108.8) cases avoided by WASH alone (scenario with vaccination only), and 5,259 (mean: 5,258.6, 95%
292 CrI: 1,576.6-11,337.8) cases avoided by implementing both vaccination and WASH (scenario with no
293 vaccination and no WASH improvements) (Figure 3B).

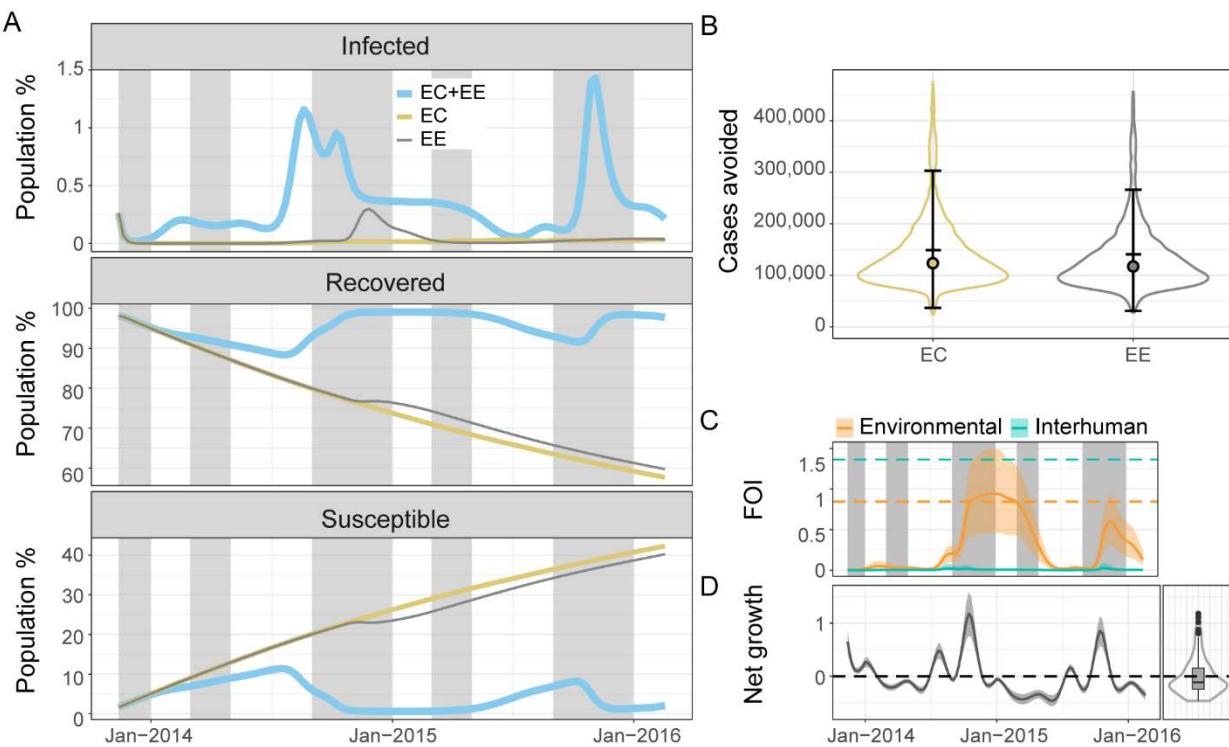


294 **Figure 3:** Estimated impact of the components of the intervention and impact of alternative vaccination strategies.
295 (A) Mean model predictions of the percentage of infected, recovered, and susceptible in the population considering:
296 the intervention as it happened of WASH and vaccination (dark blue), WASH only (blue), vaccination only (green),
297 and no intervention of either WASH or vaccination (yellow) from November 2013 to February 2016. The incremental
298 implementation of the improvements in water and sanitation is indicated by the widening and darkening triangle in
299 the top panel. Typical rainy seasons are shaded in grey and the timing of the distribution of vaccine doses is shown in
300 dashed grey lines. (B) Violin plots of numbers of additional cholera cases at the end of the study period with WASH
301 only (blue), vaccination only (green), or no intervention (no WASH and no vaccination) (yellow) compared to the
302 intervention as it happened of WASH and vaccination. The error bars, the filled circles, and the horizontal bars indicate

304 the 95% credible interval, the medians, and the means respectively. (C) Heatmap of the mean number of cases avoided
305 by changing the timing and the coverage of a vaccination campaign compared to a scenario without intervention. The
306 timing of the distribution of vaccine doses for the intervention as it happened is indicated by dashed grey lines.

307

308 Our model suggested that vaccination campaigns with small target population sizes would have a limited
309 impact in populations with high immunity (Figure 3C). However, the timing of a pulse of vaccination
310 could substantially influence the impact of vaccination campaigns. Specifically, timing the vaccination to
311 occur at the lowest point of population immunity and before an outbreak began increased its impact.
312 The best performing vaccination scenario (darkest cell of the heatmap in Figure 3C) avoided 12,777
313 cases (mean: 12,776.7, 95%CrI: 4,681.0-7-26,019.5) over 118 weeks for 200,000 vaccinated people.
314 However, the high level of local immunity would result in vaccinating a large proportion of immune
315 individuals, reducing the impact of the vaccination.



316

317 **Figure 4:** Contributions of the environmental reservoir in cholera transmission. (A) Mean model predictions of the
318 percentage of infected, recovered, and susceptible individuals in the population with environmental contamination
319 and exposure (EC+EE) (light blue), environmental contamination only (no environmental exposure) (EC) (beige), and
320 environmental exposure only (no environmental contamination) (EE) (grey) from November 2013 to February 2016.
321 Typical rainy seasons are shaded in grey. (B) Violin plots of numbers of cholera cases avoided by the end of the study
322 period with only EC (beige), or only EE (grey) compared to a scenario with EC and EE. The error bars, the filled
323 circles, and the horizontal bars indicate the 95% credible interval, the medians, and the means respectively. All the
324 scenarios considered in A and B assume that no intervention occurred. (C) Mean prediction of the variation of the
325 environmental (light orange line) and interhuman (light green line) components of the force of infection and their 95%
326 credible interval (light orange and light green envelopes) from November 2013 to February 2016. The light orange
327 and light green dashed lines indicate the mean values of the environmental exposure rate (β_e) and interhuman
328 transmission rate (β_h), respectively. (D) Left: Mean prediction of the variation of the environmental net bacterial
329 growth ($\varphi_t - \varepsilon$) (dark line) and its 95% credible interval (grey envelope) from November 2013 to February 2016.
330 Right: Violin plot and boxplot of the distribution of the mean prediction of the net bacterial growth rate from
331 November 2013 to February 2016. The dashed black line indicates 0: values below 0 show net decay and values above
332 0 show net growth.

333

334 We estimated that removing environmental exposure or contamination would have a critical impact on
335 cholera dynamics. These strategies avoided 142,518 cases (mean: 142,518.3, 95% CrI: 36,670.0-
336 303,068.3) and 134,373 cases (mean: 134,372.8, 95% CrI: 30,921.5-266,103.8), respectively. In each of
337 these scenarios local cholera transmission was virtually interrupted (Figure 4A and B). Environmental
338 contamination appeared necessary to maintain a bacterial load sufficient to support environmentally-
339 driven transmission because the fluctuation of *V. cholerae* population averaged towards net decay
340 (Figure 4D, right).

341 The high immunity inferred by the model was maintained through annual flare-ups and constant
342 environmental exposure. The environmental component of the force of infection ($\Phi_e = \beta_e \frac{B}{\kappa+B} (1 +$
343 $\lambda_e f(rain_t))$) was consistently greater than the interhuman transmission component ($\Phi_h = \frac{\beta_h I}{N}$) despite
344 β_h being greater than β_e (Figure 4C). Φ_h remained low because epidemic flare-ups did not lead to a high
345 prevalence of infection, the way they would in a mostly susceptible population. Conversely, Φ_e strongly
346 increased with pulses of net bacterial growth due to environmental drivers, despite an overall trend
347 favoring net decay (Figure 4D left and right).

348

349 **Discussion**

350 Based on our model, the impact of the intervention performed in Kalemie was modest when measured
351 by cases avoided, preventing an estimated 5,259 cases (mean: 5,258.6, 95% CrI: 1,576.6-11,337.8) for
352 both intervention arms combined. The reduction of the target population size following the interruption
353 of planned vaccination activities, the limited scale and the incremental implementation of the WASH
354 improvements, and the high level of population immunity likely all contributed to mitigating the impact
355 of the intervention.

356 Benefiting from vaccination in endemic cholera settings, as defined by WHO, requires an understanding
357 of dominant local transmission routes. Our model suggests that the impact of vaccination is small in
358 settings where an environmental reservoir provides constant exposure and maintains high immunity,
359 despite an optimistic assumption of an all-or-nothing vaccine. However, endemicity is more nuanced
360 than the current WHO definition suggests and OCV could still play an important role in some endemic
361 settings. The inability to identify and target the susceptible individuals would lead to vaccinating a
362 majority of immune individuals in this situation. Achieving very high vaccine coverage would immunize a
363 greater number of susceptible individuals, but at the cost of giving many additional doses to immune

364 individuals. This cost could be reduced by targeting the age group most represented among susceptibles
365 or by guiding vaccination with serosurveys. The age profile of the suspected cholera cases residing in
366 Kalemie (median age of 15 years, and interquartile range (IQR) of 3-34 years) during this period would
367 support restricting the maximum age of the target population to increase the impact of the vaccination
368 campaign. However, defining a meaningful age group target would require high resolution historical
369 epidemiological data, and those would only provide information on symptomatic cases, a portion of
370 infected cases. Similarly, guiding vaccination efforts with serosurveys to target susceptibles would incur
371 a substantial additional cost in addition to the difficulty of applying a binary interpretation to serosurvey
372 results.

373 Our estimates of average immunity duration ($1/\delta = 3.7$ years, 95% CrI: 1.8- 8.0 years) and the cumulative
374 incidence converted into an average yearly incidence rate (24.1%, 95% CrI: 11.7-47.5) are consistent
375 with current knowledge of post-infection immunity and other incidence rate estimates in another well
376 studied cholera endemic area, Bangladesh. Challenge studies have demonstrated that immunity lasts at
377 least 3 years after natural infection (36). National incidence rate in late 2015 in Bangladesh was
378 estimated at 17.3% based on a representative survey and analyses of vibriocidal titres (37).

379 Our model suggests that a well-timed large-scale vaccination could improve the impact of vaccination in
380 the city of Kalemie, potentially avoiding an average of 12,777 cases (95% CrI: 4,681.0-26,019.5) for
381 200,000 vaccinated individuals. However, this requires implementing a large vaccination campaign with
382 precise timing. It would be logistically challenging and costly to implement vaccination campaigns of this
383 scale with very precise timing, dictated by the need to vaccinate when immunity is at its lowest and
384 before environmental drivers trigger a pulse of force of infection. This approach would still achieve only
385 short term and small-scale benefits. On the other hand, our findings suggest that WASH improvements
386 on a scale large enough to prevent environmental exposure and contamination for the whole population
387 could have a dramatic long-term impact. Although we estimated that the WASH improvements in

388 Kalemie prevented a modest number of cases, this is likely partially due to the short period of time
389 considered to assess the impact of this part of the intervention. The main components of this WASH
390 intervention consisted of extending the pipe network and building a water reservoir, and they were
391 completed incrementally during the 118-week period. While extending access to the pipe network is an
392 important step, it does not guarantee reliable and consistent access to chlorinated tap water (38). The
393 magnitude of the improvements required to ensure both access to safe water and efficient waste
394 management, not only in Kalemie but throughout the cholera-affected nation of DRC, appears immense
395 but necessary to control cholera. Implementing WASH improvements should be considered a priority
396 not only to control cholera, but also to prevent the transmission of other water-borne and fecal-oral
397 pathogens that contribute to the disease burden in DRC (39). This approach will also help achieve the 6th
398 goal of the Sustainable Development Goals (40), to ensure availability and sustainable management of
399 water and sanitation for all, in a country where WASH improvements are critically needed (14).
400 Kalemie is not unique regarding a potentially strong environmental driver of cholera transmission.
401 Substantial environmental contributions for cholera cases have been reported in Haiti and Zimbabwe,
402 areas where the basic reproduction number was estimated to rely mostly on its environmental
403 component (16). Environmental drivers are also important drivers in other endemic settings like
404 Bangladesh and India, although they act differently: flooding in the early and late phase of the monsoon
405 is strongly associated with higher cholera incidence (41), while the peak of the monsoon is associated
406 with a cholera lull due the “dilution” of *V. cholerae* in its reservoir (42). Although mobility does not
407 appear to be necessary for local cholera persistence in the city of Kalemie, movement could make
408 Kalemie a source of cholera that can seed outbreaks in surrounding areas that lack an environmental
409 source and where exposure is less frequent. The older ages of the suspected cholera cases residing
410 outside of Kalemie (median age of 24.5 years, and IQR: 5.75-39.25 years) are consistent with lower
411 exposure rates and source-sink dynamics.

412 Our estimates supporting a major role of environmentally driven transmission in Kalemie's local cholera
413 dynamics appear plausible. Sensitivity analysis showed that removing the environmental component or
414 bacterial growth of the model significantly decreased its ability to fit the observed data (see SI).
415 Confirming our estimates of population immunity and the dominant source of bacterial infection would
416 require serological data and substantial microbiological monitoring of the lake water in the area.
417 Evidence of environmental presence of toxigenic *V. cholerae* is scarce in the area. Extensive water
418 sampling in Lake Tanganyika from October 22nd to 26th 2018 did not detect toxigenic *V. cholerae* (43).
419 However, it was detected in ten environmental samples, in fish and water, also collected from Lake
420 Tanganyika from October 2018 to March 2019 and there is some evidence of increased positive samples
421 during rainy seasons in other environmental sampling studies (44–46).
422 We estimated that the natural variation of the *V. cholerae* population in the lake leans in favor of net
423 decay. Previous modeling studies assumed bacterial growth rates to consistently be in favor of net
424 decay, whether they varied over time or not (47,48). More recent studies considered the possibility for
425 complex bacterial growth patterns but were entirely theoretical (49). Our model allowed environmental
426 bacterial abundance to vary based on environmental inputs, leading to temporary switches to net
427 bacterial growth. These were important in creating pulses of high environmentally-driven force of
428 infection. Improving the quality of consumed water (reducing environmental exposure) had a large
429 impact in our simulations and removing environmental contamination had an impact almost as large.
430 The overall trend toward net bacterial decay in our model highlights that regularly replenishing local
431 bacterial population through environmental contamination is potentially a critical component of local
432 persistence. This emphasizes the potential compounded benefits of comprehensive improvements to
433 sanitary infrastructures and access to clean water.
434 We did not consider cholera-induced mortality because of the low number of cholera-induced deaths in
435 this population and the local experience in managing cholera infections. However, there is evidence that

436 a substantial portion of cholera mortality occurs in the community (50), so we cannot rule out that some
437 cholera-induced mortality is not captured in the reported data. The lack of data on mortality in the
438 community prevented us from estimating the number of deaths avoided by the intervention. Our model
439 did not consider the booster effect of vaccination on already immune individuals. This could have led us
440 to slightly underestimate the duration of immunity but it is unlikely to have substantial impact on our
441 estimates considering the short study period (118 weeks) compared to our estimated average immunity
442 period (3.7 years). We also assumed that immunity wanes at similar rates for susceptible individuals
443 who were successfully vaccinated and following natural infection, but vaccine-induced immunity likely
444 wanes faster (51). This would have little impact on our estimates considering the small proportion of
445 susceptible individuals in the population when doses were distributed in our model as well as short
446 study period (52).

447 We included the potential impact of the WASH intervention in a simplistic way, assuming a linear
448 variation of the environmental transmission rate. In the absence of more detailed information, this
449 method required the fewest additional assumptions. To estimate environmental drivers, we used
450 measurements of chlorophyll-a and surface water temperature in the lake in addition to the influence of
451 rain. The interactions between *V. cholerae* and other elements of its aquatic reservoir are only vaguely
452 understood (5,53). We cannot assess how accurately we captured the main fluctuations of the
453 environmental bacterial population in the absence of thorough environmental sampling in the area.
454 However, we considered only environmental drivers that have been associated with *V. cholerae*
455 environmental abundance or exposure to the environmental reservoir. Phytoplankton growth, indirectly
456 measured through chlorophyll-a, has been associated with cholera outbreaks in several studies, and
457 specifically cyanobacteria are a credible reservoir for *V. cholerae* (5,54). Water temperature influences
458 phytoplankton growth (5), and the consequence of rainfall on environmental exposure and
459 environmental contamination to/from *V. cholerae* is credible in this setting along a lake with low access

460 to water and sanitation infrastructures (33). We explicitly included a direct proxy of human presence,
461 anthropogenic nighttime radiance, in the models considering seasonal mobility. Nighttime radiance is a
462 reliable indicator of human presence and has been used to infer population mobility in both high and
463 low-income countries (31,55,56). We are confident that we robustly captured the seasonal migration
464 and the environmental components in our model, though there might be limitations in the
465 spatiotemporal resolution and availability of remote sensing data, particularly for chlorophyll-a.

466 Impact assessments of cholera interventions are scarce in endemic settings, particularly beyond
467 estimates of vaccine effectiveness and vaccine coverage. Studies like this one are crucial to guide
468 cholera elimination. OCV and WASH improvements are core components of the toolbox to control or
469 eliminate cholera. However, the value of OCV for reactive vaccination in epidemic settings has not been
470 clear in areas with various patterns of endemicities. The assumption that most of the target population
471 is susceptible becomes less accurate as transmission is increasingly environmentally driven. Reducing
472 cholera transmission in endemic areas will require a location-specific understanding of the transmission
473 routes to tailor a strategy; a “one size fits all” approach is unlikely to achieve satisfying results.
474 Geographically-coordinated strategies that target location-specific transmission dynamics might also be
475 necessary to achieve regional cholera control.

476

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479

480 **Data accessibility**

481 The code necessary to reproduce the analysis and the figures is available on

482 https://github.com/bhartilab/cholera_kalemie

483 The data on weekly aggregated number of suspected cholera cases is owned by MSF-Epicentre and can

484 be requested by contacting Klaudia Porten (Klaudia.PORTEN@epicentre.msf.org).

485

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492

493 **Ethical considerations**

494 The Ethical Review Board of the University of Lubumbashi approved the study protocol to assess the

495 impact of the vaccination campaign (study protocol ethical number: UNILU/CEM/028/2013) and its

496 extension (study protocol ethical number: UNILU/CEM/050/2015). Individuals provided informed

497 consent to be part of the vaccine coverage survey. Pennsylvania State University's Institutional Review

498 Board determined the post-intervention handling and analyses of these anonymized data was not

499 Human Research (STUDY00015621).

500

501 **Authors' contributions**

502 FL, PEW, and DB designed the study to assess the impact of the intervention. AB and FL were involved in
503 managing the data collection of the strengthened surveillance and checking data quality. AB, AW, EH,
504 and NB developed the analytical plan of the additional analysis presented in this manuscript, and AB and
505 AW did the analysis. AB and NB drafted the manuscript, and AW,PEW, DB, FL, and EH critically revised it.
506 All authors gave final approval for publication and agree to be held accountable for the work performed
507 therein.

508

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