**Title A:**

The Impact of Human Mobility and Imperfect Vaccines on Waning Herd Immunity to Cholera

**Title B:**

Prolonging Herd Immunity to Cholera via Vaccination: Accounting for Human Mobility and Vaccine Waning

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To Do

**Abstract**

**Background**

Oral cholera vaccination is being considered as an approach to preventing outbreaks in at-risk settings and controlling cholera in endemic settings. However, vaccine-derived herd immunity may be short-lived, rendering the population susceptible to outbreaks in the absence of complementary interventions or revaccination. Rational control strategies must account for the complex interaction between several drivers of waning herd immunity, including human mobility and population turnover, as well as imperfect or waning vaccine efficacy.

**Methods and Findings**

We use mathematical models to simulate routine and mass oral cholera vaccination in a population with varying degrees of migration, transmission intensity, and vaccine coverage. We show that migration and waning vaccine efficacy strongly influence the duration of population-level, herd immunity while birth/death processes have minimal impacts. As compared to either periodic mass vaccination or routine vaccination alone, a community could be protected longer by a blended “Mass and Maintain” strategy. We show that vaccination may be best targeted at populations with intermediate degrees of mobility as compared to communities with very high or very low population turnover. We analyze the 2014 and 2015 vaccination campaigns in the Bentiu Protection of Civilians Camp in South Sudan, and estimate that the camp population was over 80% susceptible at the beginning of an outbreak, despite two high-coverage vaccination campaigns in the two previous years.

**Conclusions**

Oral cholera vaccines can be powerful tools for quickly protecting a population for a period of time that depends critically on vaccine coverage, vaccine efficacy over time, and the rate of population turnover through human mobility. Due to waning herd immunity, epidemics in vaccinated communities are possible but become less likely through complementary interventions or data-driven revaccination strategies.

**Introduction**

Vaccination campaigns with sufficiently high efficacy and coverage can ideally achieve herd immunity in the population, an emergent state in which sustained transmission becomes unlikely.[1–3] Herd immunity is not permanent, however, and can wane over time via short-lived vaccine efficacy and an influx of susceptible, unvaccinated individuals. Due to a reliable efficacy profile and high attainable coverage, the killed oral cholera vaccine (kOCV) can generate powerful herd protection effects.[4,5] The World Health Organization (WHO) recently created a kOCV stockpile to facilitate vaccine usage in three settings: (1) humanitarian crises at high risk of cholera importation; (2) high-endemicity “hot spots”; and (3) outbreak response.[6] As the stockpile approaches its fifth year, evaluation of its management must address uncertainties in sustainability and long-term strategy, particularly regarding the duration of herd immunity (DHI) in these three settings.

Regarding the first setting, kOCVs can be a quick stopgap measure to protect cholera-prone dynamic populations such as refugee camps,[7] but it remains unclear how much time is “bought” by vaccination before longer-term solutions such as water, sanitation, and hygiene promotion are necessary. Second, feasibility and economic analyses of vaccination in endemic settings are strongly influenced by the frequency of revaccination.[8] Third, it remains to be seen how strongly, and in what direction, population mobility should be considered when prioritizing target populations for vaccination.

These are not merely hypothetical concerns. Beginning in October 2016, the Bentiu Protection of Civilians (PoC) Camp in South Sudan sustained a cholera outbreak despite high-coverage mass vaccination campaigns in both 2014 and 2015.[9,10] Consequently, questions have emerged about the utility of vaccination and the expected risk of outbreaks, particularly in dynamic populations where cholera often breaks out.[11] Modeling studies of other diseases (e.g., [12–16]) suggest a suite of factors which may have contributed to the camp’s susceptibility to an outbreak, including waning vaccine efficacy, the influx of susceptible displaced people, an extremely high birth rate, and resettlement of vaccinated individuals. However, the relative contributions of these factors and their implications for vaccination strategy in the future are not clear.

Here we examine the implications of vaccine waning and human mobility on herd immunity over time, providing new insights related to the risk of outbreaks in vaccinated populations. Using mathematical models, we compare how well several common vaccination strategies sustain herd immunity and we demonstrate the non-monotonic relationship between migration rate and the projected impact of pre-emptive vaccination. We analyze the 2016 outbreak in Bentiu, and show that despite repeated vaccination, the population was over 80% susceptible just before the epidemic. Our results suggest that the optimal vaccination strategy will depend on the interaction between vaccine characteristics and population dynamics, and that a “Mass and Maintain” vaccination approach is likely to provide the longest duration of herd immunity in many cases.

**Methods**

*Model*

We developed mathematical models of a well-mixed population that is being targeted with vaccination. The population compartments of principal interest for this study are individuals who are fully susceptible to disease, , and those who were vaccinated *n*-months ago, (Fig 1). To account for the observation that kOCV direct effects do not tend to wane exponentially,[17] we created an ensemble of *n* monthly stages (), which collectively generate an Erlang-distribution for the duration of time in the -ensemble.[18,19] We set the mean time residing in any ­ compartment to 30.5 days; therefore, susceptible individuals move after vaccination to compartment for an average of one month, then to for an average of one month, and so forth until month *n* = 48, after which efficacy is assumed to be zero and therefore individuals return to a state of full susceptibility, .

The system of ordinary differential equations generated by the model was solved using the *deSolve* package[20] in the statistical software program R (version 3.2.4). All code used to generate this paper can be found at <https://github.com/peakcm/cholera>.

*Vaccination Strategies*

Vaccination is implemented according to two approaches: mass and routine. We model mass vaccination as a large fraction (e.g., ) of individuals moving into the compartment on a particular day, possibly recurrently (e.g., annually). Routine vaccination moves a substantially smaller fraction of individuals (e.g., ) into the compartment every day. In each approach, vaccine priority is given first to susceptible individuals, , then those who were vaccinated the longest time ago (i.e., , then , and so on until reaching the allotted number of vaccines for that day). In addition to mass vaccination and routine vaccination, we test a blended “Mass and Maintain” strategy in which one-time mass vaccination at the beginning of follow-up precedes routine vaccination. See supplemental materials for mathematical details on modeling mass vaccination transition rates.

Currently, a complete kOCV course of includes two doses administered approximately two weeks apart.[6] However, because the timescale of interest for this study is measured in years, not days, we assume mass vaccination campaigns elapse over one day and provide protection instantaneously. Furthermore, for generalizability across disease systems, we focus on the number of vaccine courses rather than the number of actual vaccines per course.

We parameterized the time-varying vaccine efficacy, , of kOCV (whole-cell with B-subunit) using estimates from a large clinical trial in Bangladesh.[17,21] To provide monthly estimates of vaccine efficacy, , we linearly interpolated between 6-month point estimates with efficacy after the 4th year assumed to be zero, as the reported mean efficacy becomes negative.

*Human mobility*

We assume individuals emigrate from the population at a rate that is equal for all compartments. The total population size, , is held constant by offsetting emigration with an equal rate of immigration, unless otherwise noted. Our main results assume that incoming migrants bring neither vaccine-derived nor naturally-acquired immunity into the population.

We estimated migration rates from three example settings where kOCVs have been used, including: (1) a ‘stable’ urban population; (2) a highly mobile urban population; and (3) a displaced person setting with intermediate mobility. First, to represent a stable urban population, we estimate a migration rate of (i.e., an average residence time of 20 years) from the observation that only 9% of an OCV study population in Calcutta, India, changed in the two years following vaccination in 2006.[22] Secondly, to represent a highly mobile urban population, we estimate a migration rate of from the observation that 58% of a study population in Dhaka, Bangladesh, had relocated over two years.[23] Thirdly, to represent a displacement camp with intermediate mobility, we estimate a resettlement rate of in the Bentiu PoC Camp in South Sudan in the period from February to October 2016, during which the International Organization on Migration (IOM) reports a rather stable population of 104,000 people and approximately 2,000 monthly individuals both entering the camp and resettling from the camp [<http://www.iomsouthsudan.org/tracking/>].

*Outcome Measurements*

We define the duration of herd immunity (DHI) as the number of years following a vaccination campaign with an effective reproductive number, , below one. We calculate

[1]

where is the proportion of the population susceptible at time *t*,

[2] .

Due to the special behavior of deterministic models, when a simulation asymptotically approaches from below, we define DHI as the time until .

Using the time-dependent effective reproductive number, , we estimate the probability of the community sustaining an outbreak given the introduction of a single case. When , final epidemic size tends to follow a bimodal distribution with a probability of sporadic die-out and a probability of a large epidemic. Using a recent method for computing epidemic final size distributions,[24] we find the threshold of 10 cases is a reasonable cutoff size such that a large outbreak is henceforth very likely for sizeable values of (Fig S1). We therefore define an outbreak as more than 10 cases and, by assuming a Poisson distribution of secondary infections (mean = ), we can calculate the probability of an outbreak of more than cases initiated by a single infectious case using the Borel-Tanner distribution:[25,26]

[3] .

*Mobility-informed vaccination targeting*

To assess the role of mobility on the optimal pre-emptive targeting of kOCVs, we simulate a setting with migration rates ranging from zero, representing a closed population, to a very high value of (i.e., an average residence time of one year). Since we focus here on an at-risk population in a non-endemic setting, our outcome of interest is the cumulative probability of sustaining a cholera outbreak that was seeded by an imported case, which equals one minus the probability of having no outbreaks greater than cases:

[4]

where D is the duration of follow-up time in days, is the minimum outbreak size, and is the expected number of infected individuals who migrate into the population in one day. is calculated by:

[5]

where is the probability an incoming migrant is infected, is the size of the targeted population, is the daily migration rate, and therefore the daily number of incoming migrants equals . We assume each imported case has an independent probability of starting an outbreak of more than cases given the effective reproductive number on that day .

We measure the difference between the cumulative outbreak probability, , over days in the absence of vaccination as compared to the first days following mass vaccination. A larger difference suggests a more impactful vaccination intervention. For our main results, we focus on a setting with moderate transmissibility () and set the probability, that a migrant is infected equal to , which simplifies Equation 5 to (see supplementary materials).

*Bentiu PoC Camp Case Study*

We examine these drivers of waning herd immunity in a well-described outbreak in the Bentiu PoC Camp in South Sudan. We estimate the camp population size between February 2014 and December 2016 using reports from IOM (Fig S2)[<http://www.iomsouthsudan.org/tracking/>]. Of the three million persons targeted for health resources in broader South Sudan, including the Bentiu PoC Camp, UNFPA expects 335 deliveries per day, which equates to birth rate of approximately .[27] We assumed this to be our demographic turnover rate as a conservatively high estimate.

We estimated population susceptibility over time, , in six scenarios (Table 1). In the “observed” scenario, we used empirical measures of four key drivers of waning herd immunity, specifically: the birth/death rate of ; an empirical distribution of efficacy over time, ; a camp resettlement rate of (i.e., an average camp residence time of 4.3 years) which is balanced by an equal rate of entries for a net-zero impact on; and a dynamic population size, , driven by net growth or shrinkage through camp entries or exits. We compare this scenario with counterfactual scenarios that eliminate at least one of these drivers and will therefore increase DHI. We constructed a composite counterfactual scenario in which: the birth/death rate was set to zero; vaccine efficacy was held constant at its maximum value (70.3%) for all time since vaccination; the camp resettlement rate was set to zero; and the population size was held constant at approximately the level observed during the outbreak (100,000). To isolate the impact of each driver of waning herd immunity, we run simulations where one driver is set to the “observed” condition while the other three drivers are set to their counterfactual condition to remove their influence (Table 1).

To assess the relative importance of each driver of waning herd immunity in this case study, we calculate a measure of attributable percent. For a scenario that isolates one driver, we measure the proportion susceptible () on October 16, 2016, the start of the observed outbreak. To compare scenarios, we calculate the difference between estimates of the proportion susceptible at the start of the outbreak under scenario with estimates in the composite counterfactual scenario,

Finally, we calculate the percent of waning herd immunity attributable to each driver

.

Lastly, in order to estimate the probability of an outbreak given introduction of a cholera case using the population susceptibility over time, , we must estimate the basic reproductive number, . Following frameworks[28,29] recently applied to cholera in South Sudan,[30]we retrospectively estimate the time-varying reproductive number using daily case reports, which we extract from Cholera Situation Reports from the South Sudan Ministry of Health,[31] and an expected generation interval distribution, which we assume to follow a discretized gamma distribution with median of 5 days.[30] This method assumes uniform mixing, no imported cases after the first case, and no missing data. Maximum likelihood estimation procedures were implemented in the statistical software program R using the *R0* package.[32]**RESULTS**

*Dynamics of population susceptibility and herd immunity*

Following mass vaccination with 100% coverage, population susceptibility, , quickly increases over time in the presence of high migration rates and short-lived vaccine efficacy (Fig 2A, solid line). Even with a hypothetical perfect vaccine which retains VE=1 indefinitely, high migration rates can drive population susceptibility near 100% within 9-10 years (Fig 2B, solid line). Between three primary drivers causing herd immunity to wane, namely migration, waning efficacy, and demographic turnover through births and deaths, we find that the first two are substantially more influential than the third. As compared to rates of birth and death set to zero, even pessimistic estimates of a life expectancy of 40 years result in negligible differences in (Fig S3).

Following kOCV vaccination with 100% coverage in a population with high migration, we estimate the vaccine-derived DHI to be approximately 0.47 years when , 0.98 years when , and 3.90 years when (Fig 2C, solid lines). These durations increase to 1.06 years, 1.89 years, and 4.70 years, respectively, in the presence of low migration rates instead (Fig 2C, dashed lines). As expected, DHI is reduced when vaccine coverage is less than 100%, and, depending on both the coverage and , herd immunity is sometimes unattainable (Fig S4).

Achieving herd immunity is a key theoretical threshold, but in reality an outbreak is possible below the threshold and is not guaranteed above the threshold.[33] Mass vaccination reduces, but not eliminates, the probability that an imported case sparks an outbreak for a duration of time that depends critically on the migration rate and how vaccine efficacy wanes over time (Fig 2E-F). For example, even though herd immunity is lost within just 0.47 years in a high migration setting when (Fig 2C, solid red line), the outbreak probability is kept below 50% for twice as long (Fig 2E, solid red line).

*Optimizing revaccination with “Mass and Maintain” strategies*

We considered several operational strategies for sustaining herd immunity through vaccination alone. In a hypothetical population of size with and a high rate of migration (), mass vaccination every year or every two years with 100% coverage of susceptibles can render herd immunity for 3.5 or 2.8 years, respectively, before depleting a fixed vaccine allotment of full courses (Fig 3A). If these vaccines are instead allotted on a daily basis through routine vaccination, DHI can be extended to 4.4 years (Fig 3B). We find that a blended “Mass and Maintain” strategy that complements a single mass vaccination campaign with subsequent routine vaccination can maintain herd immunity longer than either strategy alone (Fig 3C), both for this example and for a wide range of settings with various migration rates and values (Table S1). The intuition behind this complementary strategy is that recurring mass campaigns have diminishing returns per vaccine once herd immunity is achieved; meanwhile routine vaccination alone requires a long period of time to build-up herd immunity.

*Optimizing pre-emptive mass vaccination by targeting intermediate mobility settings*

In addition to the importance of migration on DHI, one may posit that communities with higher migration rates are also more likely to have cholera imported. In order to optimize pre-emptive kOCV impact in at-risk settings, there is a tradeoff between targeting low-mobility communities, where herd immunity may last for a long time but cholera introduction is rare, and high-mobility communities, where the opposite is expected. We find that communities with intermediate levels of migration may experience the largest vaccine-derived decrease in the probability of an outbreak sparked by an imported case (Fig 4). For example, the migration rate recorded in the Bentiu PoC Camp in mid-2016 is near the optimal condition for maximizing the impact of a single mass vaccination campaign in the 4-6 year time horizon, assuming . If one is more interested in shorter time horizons since vaccination, the migration rate that maximizes vaccine impact favors mobile communities, similar to the high population turnover observed in Dhaka in the study by Qadri et al.[23] Sensitivity analyses suggest that intermediate mobility rates (e.g., between those observed in Dhaka and Calcutta) generally maximize vaccine impact, but the optimal migration rate is slower in settings that have a larger population size (), a higher transmission potential (), or where a higher fraction of incoming migrants are infected (e.g., due to high-burden neighbors) (Fig S5). Conversely, settings with small population size, low transmission potential, and whose migrants have a small probability of being infectious require very high migration rates in order to garner much baseline risk of cholera importation and outbreak.

*Bentiu PoC Camp Case Study*

The Bentiu PoC Camp grew from 4,291 occupants in February 2014 to a peak of 140,101 in December 2015 and then converged to approximately 104,000 in May 2016 (Fig 5A). Assuming a cholera-naïve population before vaccination, we estimate the population fraction susceptible reached a low of 0.37 after the second mass vaccination campaign before increasing to 0.81 on October 16, 2016, at which time the first cholera case of the outbreak was detected (Fig 5B). By December 1, 2016, we estimate that only 40.5% of camp residents had ever been vaccinated, which closely matches a WHO/IOM survey performed that month that reported kOCV coverage of 40%.[31]

Using case reports and assuming a fixed generation interval distribution, we estimate the mean effective reproductive number, , exceeded unity for nearly two months, with a maximum likelihood estimate of 1.45 (1.18-1.75) (Fig S7). Using Equation 1 and the population fraction susceptible of 0.81 above, we estimate the basic reproductive number, , was approximately 1.80 in this setting in the absence of vaccination. These findings are within the range of estimates derived from South Sudan in 2014.[30] Assuming this pre-vaccination estimate of , we find that after vaccination the probability of an outbreak first exceeded 0.50 in May, 2016, and reached 0.57 when the outbreak began in October (Fig 5C, black line). Using a “Mass and Maintain” strategy including vaccination of 100% of individuals migrating into the camp after the second mass vaccination campaign, we estimate the proportion susceptible on October 16, 2016 would have been 0.52 instead of 0.81, thereby still retaining herd immunity at the time () (Fig S6).

The drivers of waning herd immunity in this population, from strongest to weakest, were short-lived vaccine efficacy, population growth, camp resettlement rate, and lastly births and deaths (Table 1). In the counterfactual scenario lacking these drivers, we would expect the proportion susceptible on October 16, 2016 to be as low as , which would render herd immunity even if approached nearly 3.

**DISCUSSION**

Vaccination can rapidly protect a population at risk of a cholera outbreak, but the duration of vaccine-derived herd immunity depends critically on vaccine coverage, waning vaccine efficacy, and the? population mobility that drives a net influx of susceptible people. In our case study of the Bentiu PoC Camp, we find that these drivers are sufficient to explain the vulnerability of this population to an outbreak despite two recent high-coverage vaccine campaigns. Therefore, disease re-emergence does not imply vaccine failure and can be avoided by data-driven revaccination strategies or by scaling-up long-term solutions while under the temporary cover of vaccination. Our results provide key time windows during a population can expect to resist a cholera outbreak even if the pathogen were to be introduced. We developed an interactive tool to facilitate implementation of these results for a user-defined setting (<https://coreypeak.shinyapps.io/herd_protection_estimator/>).

One practical implementation of the “Mass and Maintain” vaccination strategy in a camp setting can include a one-time mass vaccination campaign followed by routine vaccination of new members of the population, such as births and new entries. In an urban or open population, such as Dhaka or Calcutta, routine identification of new members becomes more challenging, but performance of the WHO Expanded Programme on Immunization in cholera endemic regions like Bangladesh are promising.[34] Recent work has also shown serological triggers for periodic mass vaccination can be an effective alternative method to maintain herd immunity to measles.[35]. For cholera specifically, there is a need for more research into cross-sectional markers of immunity which can inform risk profiling, revaccination timing, and, if stratified by age, the impact of mass vaccination.[36]

Current guidelines for the optimal use of the kOCV stockpile recommend targeting “areas with important population movements.”[37] Mobility is recognized as an important driver of the performance of vaccination strategies to control ongoing cholera outbreaks.[38] Here, we focus on pre-emptive vaccination of at-risk communities to show the competing effects of high mobility on expected vaccine impact. In order to operationalize the finding that vaccination may be most impactful for populations with intermediate degrees of mobility, data on migration rates from sources such as censuses or mobile phone call data records must be collected to define “intermediate” mobility for a given context.[39]

Our results depend on several simplifying assumptions. By modeling a well-mixed population, we are assuming no heterogeneity in contact patterns or local reproductive numbers. In reality, we expect diseases, especially those like cholera with environmental transmission dynamics, to exhibit substantial spatial heterogeneity in transmission intensity. These differences become crucial if, as we may expect, migration occurs at higher rates into sub-regions with higher transmission potential due to confounders like poverty and temporary housing. In that case, we would expect DHI to decrease, the probability of an outbreak to increase, and the routine vaccination of migrants to become even more crucial.

Our model assumes a leaky mode of vaccine action, whereby vaccination reduces the disease susceptibility of each recipient. Our calculation of proportion susceptible, , is robust to other assumptions regarding the method by which vaccine effects wane, namely: time-dependent failure in “take,” corresponding to an all or nothing response; and time-dependent failure in “degree,” corresponding to a leaky vaccine response (Fig S8).[40] Our parameterization of a waning leaky vaccine aligns with prevailing interpretations[17] of the clinical trial data,[21] but alternative possible explanations for changes in over time in an RCT are difficult to rule-out, such as frailty, loss to follow up, and random variability.[41]

The migration rates estimated from Dhaka, Bentiu, and Calcutta are intended for benchmarking purposes and do not imply that migration rates are either constant or generalizable to the whole city or region. Indeed, we would expect to retain herd immunity longer after vaccination for a given migration rate if the rate was calculated in a population which included a stable sub-group of permanent residents and a small, highly mobile sub-group of temporary residents.

Cholera vaccine efficacy has been shown to vary by age of recipient,[17,21] however for simplicity and lack of detailed data we do not model this age structure. If children respond poorly to kOCV and are members of a mass vaccination campaign, we would expect herd immunity to wane more quickly, and especially so if children are disproportionate sources of transmission. Furthermore, over the course of an outbreak, we may expect the relative contributions of different age groups to differ, which can have important consequences on vaccine impact and targeting.[42] For simplicity, we focus on pre-emptive vaccination of a generalized population without previous exposure to cholera.

The model we present is not limited to cholera or other diseases with only short-duration or leaky vaccines (e.g., the typhoid capsular polysaccharide vaccine [43]). The phenomenon of waning herd immunity also has strong implications on disease control strategies that include mass vaccination or “mop up” vaccination, such as measles[44] and yellow fever.[45] For yellow fever in particular, fractional vaccine doses have been used to extend vaccine supply under the assumption that vaccine efficacy of fractional doses lasts at least one year.[46] Following the mass vaccination of 25 million people in Angola and the Democratic Republic of the Congo, routine vaccination may be the most efficient way to henceforth sustain herd immunity in these populations, should this be the goal. Human mobility and waning herd immunity are key considerations for when these urban populations should be revaccinated.

Herd immunity is a key target for the control of vaccine-preventable diseases and can be monitored over time using information on the vaccine efficacy and population turnover rates. We show this information is essential for optimizing revaccination strategies, targeting vaccine stockpiles, and explaining re-emergence of outbreaks in recently vaccinated populations.

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**Author Contributions**

Conceived and designed the experiments: CMP ALR ASA COB. Performed the experiments: CMP ALR. Analyzed the data: CMP. Wrote the first draft of the manuscript: CMP. Contributed to the writing of the manuscript: CMP ALR ASA COB. Agree with the manuscript’s results and conclusions: CMP ALR ASA COB. All authors have read, and confirm that they meet, ICMJE criteria for authorship.

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**Competing Interests**

The authors have declared that no competing interests exist.

**Abbreviations**

DHI, duration of herd immunity; kOCV, killed oral cholera vaccine.

**Table 1. Magnitude of potential drivers of waning herd immunity in Bentiu PoC Camp**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Scenario** | **Vaccine Efficacy** | **Population Size** | **Birth &**  **Death Rate** | **Resettle-ment Rate** | **Percent Susceptible on Oct 16, 2016** |  | **Attributable Percent** |
| **Composite Counterfactual** | 70.3% | 100,000 | 0 | 0 | 34.4% | -- | -- |
| **Only waning** | Empirical | 100,000 | 0 | 0 | 58.2% | 23.8% | 34.9% |
| **Only changes** | 70.3% | Empirical | 0 | 0 | 56.6% | 22.2% | 32.6% |
| **Only Births & Deaths** | 70.3% | 100,000 |  | 0 | 38.1% | 3.7% | 5.4% |
| **Only Resettlement** | 70.3% | 100,000 | 0 |  | 52.9% | 18.5% | 27.1% |
| **Observed** | Empirical | Empirical |  |  | 80.8% | 46.3% | **--** |

**FIGURE CAPTIONS**

**Fig 1. Mathematical model framework.**

Susceptible individuals () can become vaccinated () and proceed through each monthly vaccine compartments (). Individuals enter the system through birth and immigration (top arrow) and leave the system through death and emigration (grey arrows). The force of infection for individuals in a compartment is reduced by a factor of according to a leaky model of vaccine action. Disease progression compartments for exposed but not yet infectious (E), infectious (I), and recovered (R) are shown, but are not explicitly modeled due to the focus of this study on vaccine-derived herd immunity.

**Fig 2. Dynamics of population susceptibility and herd immunity.**

Dynamics following mass vaccination (100% coverage) with kOCV (left column) or a hypothetical vaccine with VE=1 indefinitely (right column). (**A-B**) Population susceptibility increases over time in the presence of migration rates of (solid line), (dashed line), and zero (dotted). (**C-D**) The effective reproductive number changes over time with X(t) differently for settings with basic reproductive numbers of 2 (red), 1.5 (green), and 1 (blue). (**E-F**) The probability that a single case sparks and outbreak of more than 10 cases. Birth and death rates are set to zero in each simulation.

**Fig 3. Revaccination strategies to maximize DHI.**

(**A**) Recurring mass vaccination events (arrows) with 100% coverage of susceptible people every year (dashed line) or two years (dotted line) is shown to periodically achieve then lose herd immunity, designated by the horizontal line at . Faded horizontal bars show times with herd immunity under each strategy and the total DHI is annotated to the right of each. (**B**) Routine vaccination of 8 (green), 12 (teal), or 16 (purple) individuals per day achieve herd immunity in a population of 10,000 for 0, 4.4, and 4.3 years, respectively. (**C**) A “Mass and Maintain” strategy with one-time vaccination at 75% coverage followed by routine vaccination with 8, 12, or 16 doses can render herd immunity for 1.6, 5.2, and 4.3 years, respectively. The following are held constant for all simulations: population size = 10,000; maximum vaccine courses = 30,000; ; migration rate = ; and birth and death rates = .

**Fig 4. Vaccine targeting optimized in settings with intermediate rates of migration.**

Vaccine impact, as measured by the difference in the cumulative probability of an outbreak comparing a mass kOCV campaign (coverage 100%) versus no vaccination, is shown to reach maxima (triangles) at intermediate levels of mobility (x axis). The time since vaccination (colored lines) modifies these maxima. Grey dashed lines denote the estimated migration rates for Calcutta, Bentiu PoC Camp, and Dhaka. In this example, and the average probability that a migrant is infected is , where is the population size.

**Fig 5. Bentiu PoC Camp case study.**

(**A**) Reported population size of the Bentiu PoC Camp (blue line), individuals vaccinated assuming two-dose coverage (green bars), and monthly case counts from October to January (inset grey bars). IOM began reporting entries and exits in December 2015, which are represented by the faint green and red ribbons around the blue line. (**B**) The proportion susceptible over time (green line) decreases due to mass vaccination events and increases over time since vaccination. (**C**) The probability that a single case sparks an outbreak of more than 10 cases increases with and R0, as represented by line color: R0=1 (blue); 1.5 (green); 1.8 (black); and 2 (red).

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**SUPPLEMENTAL INFORMATION**

**Table S1. Sensitivity analysis of revaccination strategy optimization**

|  |  |  |  |
| --- | --- | --- | --- |
| R0 | Migration Rate  (years-1) | Optimal Strategy | DHI  (years) |
| 1.25 | 0 | Mass and Maintain | 18.3 |
| 1.50 | 0 | Mass and Maintain | 10.0 |
| 2.00 | 0 | Mass and Maintain | 5.1 |
| 2.50 | 0 | Mass and Maintain | 3.0 |
| 1.25 |  | Mass and Maintain | 17.9 |
| 1.50 |  | Mass and Maintain | 8.8 |
| 2.00 |  | Mass and Maintain | 4.8 |
| 2.50 |  | Mass and Maintain | 3.2 |
| 1.25 |  | Mass and Maintain | 12.2 |
| 1.50 |  | Mass and Maintain | 5.8 |
| 2.00 |  | Mass and Maintain | 4.1 |
| 2.50 |  | Mass and Maintain | 2.6 |
| 1.25 |  | Mass and Maintain | 9.1 |
| 1.50 |  | Mass and Maintain | 4.7 |
| 2.00 |  | Mass and Maintain | 3.5 |
| 2.50 |  | Mass and Maintain | 1.4 |
| 1.25 |  | Mass and Maintain | 4.8 |
| 1.50 |  | Mass and Maintain | 2.2 |
| 2.00 |  | Mass and Maintain | 1.5 |
| 2.50 |  | Mass and Maintain | 1.3 |

Comparison of the performance of Routine, Mass, and Mass and Maintain vaccination strategies with respect to DHI in a population of size 10,000, a vaccine supply of 30,000 courses, and the following operational parameters: routine vaccination of between 2 and 16 courses per day; mass vaccination coverage between 0 and 100% of susceptible individuals; and mass vaccination frequency between annual and every 3 years.

**Table S2. Review of attack rates in select large recent epidemics.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Country | Year | Cases Reported1 | Population2  (thousands) | Attack Rate  (per thousand) | | Daily Proportion Infectious3 |
| Annual | Weekly Average |
| Zimbabwe | 2008 | 60,055 | 13,495 | 4.45 | 0.09 | 0.00005 |
| 2009 | 68,151 | 13,721 | 4.97 | 0.10 | 0.00005 |
| Haiti | 2010 | 179,379 | 10,000 | 17.93 | 0.34 | 0.00017 |
| 2011 | 340,311 | 10,145 | 33.54 | 0.65 | 0.00033 |
| 2012 | 112,076 | 10,289 | 10.89 | 0.21 | 0.00011 |
| 2013 | 58,809 | 10,431 | 5.64 | 0.11 | 0.00006 |
| 2014 | 27,753 | 10,572 | 2.62 | 0.05 | 0.00003 |
| 2015 | 36,045 | 10,711 | 3.37 | 0.06 | 0.00003 |
| Crude Average | | | | 10.43 | 0.20 | 0.00010 |

1 http://gamapserver.who.int/gho/interactive\_charts/cholera/atlas.html

2 <https://esa.un.org/unpd/wpp/>

3 Assuming an average duration of infectiousness of 3.5 days,[47] half the weekly average cases would be infectious on a given day.

**Fig S1. Final epidemic size distribution and choice of cutoff.**

The final epidemic size distribution in a population of 1000 is monotonically decreasing when equals 0.9 (red) and follows a bimodal distribution when equals 1.2 (yellow), 1.5 (green), 1.8 (blue), and 2.5 (black). The inset shows a cutoff of 10 cases can discriminate large and small outbreaks with high sensitivity, but specificity can be low with low values of .

**Fig S2. Bentiu PoC Camp population estimates over time.**

In order to simulate the Bentiu PoC Camp, we separated the IOM population estimates (black line) into four segments (separated by vertical dashed lines). During the first segment from February 2014 to June 2014, we assumed linear population growth (blue line). During the second segment from June 2014 to December 2015, we simulated exponential growth at a rate of . During the third segment from December 2015 to May 2015, we assumed exponential decay at a rate of . During the fourth and final segment beginning May 2015, we assumed population size was constant. The use of exponential and constant segments allowed for population size to change dynamically within a compartmental model framework, and provided population estimates that were visually reasonable. Our model simulations began on June 15, when vaccination first occurred.

**Figure S3. Changes in the proportion of the population susceptible () as a function of years since vaccination in the presence of non-zero birth rates.**

As per Fig 2A-B, but with the addition of high birth/death rates () and the Whole Cell vaccine profile (without the B-subunit). Even conservatively fast rates of birth and death ( are slow compared to the rates of vaccine efficacy waning and high ( or low () migration, and therefore have little impact.

**Fig S4**. **Duration of herd immunity (DHI) as a function of vaccine coverage and basic reproductive number.**

For both the whole cell and whole cell (with B-subunit) kOCVs, DHI is maximized in settings with high vaccine coverage and low basic reproductive numbers. Migration rates are set to zero. Uncolored regions never obtain herd immunity.

**Fig S5. Vaccine targeting sensitivity to and the fraction of migrants infected, .**

With increases in or the fraction of migrants infected, , the optimal migration rate decreases from the fastest tested rate, (red), to the slowest tested rate, (blue). Contour lines denote average residence time in years from case studies in Dhaka (2), Bentiu (4.3), and Calcutta (20). For each simulation, the population size, , is set to 10,000.

**Fig S6. Time-dependent proportion susceptibility, X(t), in the Bentiu PoC Camp in the presence of a Mass and Maintain vaccination strategy.**

As per Fig 5B, with an additional dashed line indicating a counterfactual scenario whereby vaccines were administered to 100% of the estimated 55,628 new entries to the camp after the second mass vaccination campaign. With this strategy, population susceptibility on October 16, 2016 is 0.52 (dashed line), as compared to 0.81 in the absence of the Mass and Maintain strategy (solid green line).

**Fig S7. Time-dependent reproductive number () and daily cholera case counts in Bentiu PoC Camp between October, 2016, and January, 2017.**

Using the daily case counts (grey bars) and a generation interval with median of 5 days and following a gamma distribution with shape=0.5 and rate=0.1 as per ref [30], we report a mean time-dependent reproductive number (red line) above unity for nearly two months. 95% confidence intervals are shown in pink.

**Fig S8. Calculation of is robust to vaccine efficacy waning due to time-dependent failures in “take” or “degree.”**

Vaccine efficacy waning that is due to a time-dependent failure in “take” (i.e., an “All or Nothing” vaccine waning) (left panel) retains a constant (dashed lines) while the number of individuals in the ensemble decreases over time (dotted lines) from 75% to 0% using a theoretical example vaccine. For a time-dependent failure in “degree (i.e., a leaky vaccine waning) (right panel), individuals remain in the ensemble, but vaccine efficacy wanes from 75% to 0%. The proportion susceptible over time, calculated by Equation 5 is identical for both modes of action (solid lines).

**Fig S9. Demonstration of logarithmic adjustment for transition rates.**

As the desired fraction of individuals to be vaccinated in a single day increases (x axis), the vaccination transition rate with the logarithmic adjustment (see supplementary materials) moves the accurate fraction of the population into the compartment (solid line) while a transition rate that is simply equal to just the number of vaccines to be used (dashed line) does not move enough individuals into .

**Supplemental Text:**

*Vaccination transition rate calculation*

In the simplest case whereby vaccination occurs at the onset of the study, we initialize the model with compartment equal to the number of vaccine recipients and subtract these from the compartment. This approach suffices for one-time mass vaccination, but we must explicitly model vaccination transition rates for recurrent mass vaccination and routine vaccine. Assuming vaccines are available for use on a given day, the transition rate () from to is calculated by:

When the number of vaccines allocated on a given day is much smaller than the number of susceptible individuals eligible to receive vaccination (e.g., ), then the logarithmic adjustment term will approach and therefore the transition rate will approximately equal the number of vaccine courses available (i.e., ) (Fig S9, dashed line).

However, when a substantial fraction of the population is to receive mass vaccination on a single day (e.g., ), the number of vaccine courses available, , increasingly becomes a poor estimate for the transition rate, , needed to move the appropriate number of individuals into . Therefore, the logarithmic adjustment term inflates the transition rate and allows the deterministic solver to move the desired number of individuals into (Fig S9, solid line). For computational tractability, we assume the vaccine campaign coverage, , does not exceed 99%.

When the number of available vaccines, , exceeds the number of individuals in the compartment, vaccines are then given first to those who were vaccinated the longest time ago (i.e., first, then , and so on).

*Vaccination Targeting in Intermediate Mobility Settings*

In order to calculate the expected impact of vaccination on reducing the probability of an outbreak sparked by an imported case, we must assume individuals migrating into the population are infected with cholera with a certain probability (). As described in Methods and Materials, we set equal to for our main results, which simplifies Equation 5 to For main text Figure 4, we consider a population of size 10,000 and therefore . This value for is consistent with a rough estimate of the average fraction of the population infectious on a given day during large recent epidemics in Zimbabwe (2008-2009) and Haiti (2010-2015) (Table S2).

We present a sensitivity analysis of the optimal migration rate with values of between 0.00001 and 0.001 (an order of magnitude larger and smaller than the main result presented) and ranging from 0.75 to 3. We find when R0 and are large, representing a setting that has high transmission potential and a high influx of migration from cholera-affected neighbors, the impact of vaccination over a 4-year time horizon is optimized when migration is slow (i.e., the average residence time increases) (Fig S5, blue). Conversely, high migration rates will tend to optimize the impact of vaccination in settings where transmission potential is low and a small proportion of migrants are infected (Fig S5, red). Because the population size, , and the fraction of migrants infected, , are coupled in Equation 5, the variables behave similarly and therefore the optimal migration rate tends to decrease as the population size increases.

*Interactive Online Supplement*

The interactive online supplement (found at: ,<https://coreypeak.shinyapps.io/herd_protection_estimator/>) includes additional features as follows.

To account for seasonal forcing, the transmission parameter () is allowed to vary with each day (t) according to a sinusoidal function where *f* is the magnitude of seasonal forcing and is a frameshift parameter accounting for the time of initial vaccination campaign (τ=0 if vaccination occurs at the peak transmission season, τ=π if vaccination occurs at the trough of transmission season). Therefore, we assume an annual cycle, but note that some regions such as Dhaka may exhibit biannual cycles.[48]

During simulations with disease transmission, we utilize compartments for individuals who are exposed but not yet infectious (), infectious (), and recovered and immune () (Fig 1). Mean transition rates between these compartments are defined as following: for the incubation period ();[49] for the duration of infectiousness ();[38,47] and for the duration of natural immunity ().[50–52] Infection of susceptible individuals () is driven by a density-dependent force of infection such that R0 = . The force of infection on vaccinated individuals () is scaled by .