**Title:**

Cholera Epidemics in Vaccinated Populations: the Impact of Human Mobility and Imperfect Vaccines on Waning Herd Immunity

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To Do

**Abstract**

**Background**

Vaccination has gained consideration recently as an approach to prevent cholera outbreaks in at-risk settings and control cholera in endemic settings. However, vaccine-derived herd immunity may be short-lived and render a 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, population turnover, and imperfect or short-lived 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 herd immunity while birth/death processes have minimal impacts. We find that a blended “Mass and Maintain” strategy can protect a community longer than either periodic mass vaccination or routine vaccination alone. To prevent a cholera outbreak sparked by an imported case, vaccination may be best targeted at populations with intermediate degrees of mobility as compared to communities with very high or very low population turnover. Using our best estimates of population size, rates of turnover, and the 2014 and 2015 vaccination campaigns in the Bentiu Protection of Civilians Camp in South Sudan, we estimate the camp population was 80.8% susceptible on October 16, 2016 – the day of the first case reported from the ongoing outbreak.

**Conclusions**

Oral cholera vaccines can be powerful tools for quickly protecting a population for a certain period of time that depends critically on vaccine efficacy 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 rational revaccination strategies.

**Introduction**

A common goal of routine and mass vaccination campaigns is to achieve a state of herd immunity,[1–3] which occurs when direct and indirect vaccine protection reduce the expected number of infections per case below one (i.e., the effective reproductive number Re < 1). Vaccine-derived herd immunity emerges when vaccine coverage and vaccine efficacy are sufficiently high; conversely, herd immunity can be lost over time through the loss of efficacy (e.g., for short-lived vaccine direct effects) or coverage (e.g., through a net 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) manages a kOCV stockpile to facilitate vaccine usage in three settings: (1) high-risk humanitarian crises; (2) high-endemicity “hot spots”; and (3) outbreak response.[6] As the stockpile approaches its fifth year and key finding cycles, such as the GAVI Alliance 2018 vaccine investment strategy,[7] uncertainties in sustainability and long-term strategy must be addressed, particularly regarding the duration of herd immunity (DHI) in these three settings.

First, kOCVs can be a quick stopgap measure to protect cholera-prone dynamic populations such as refugee camps,[ref] but there is a need to know how much time is “bought” by vaccination before implementing longer-term solutions such as water, sanitation, and hygiene promotion. Second, economic and feasibility analyses of routine vaccination are strongly influenced by the frequency of revaccination [ref] – a topic that is poorly understood for kOCVs. 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. In the Bentiu Protection of Civilians (PoC) Camp in South Sudan, mass vaccination campaigns with high coverage were performed in July 2014 and June 2015. However, the camp sustained an outbreak starting in October 2016, raising questions about the utility of vaccination and the expected risk of outbreaks particularly in dynamic populations where cholera tends to breakout.[8] Previous modeling studies of other diseases (e.g., [9–13]) suggest a suite of factors 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 whether they are sufficient to explain the outbreak remains to be seen.

In this paper, we use mathematical models to study 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. We compare how well several common vaccination strategies sustain herd immunity and demonstrate the non-monotonic relationship between migration rate and the projected impact of mass vaccination.

**Methods**

*Model*

We developed a compartmental model framework 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,[14] we created an ensemble of *n* monthly stages (), which collectively generate an Erlang-distribution for the duration of time in the -ensemble.[15,16] 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, at which point 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[17] 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 strategy, 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 Text for mathematical details on the transition rates.

Currently, a complete vaccine course of kOCVs 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, we focus on the number of vaccine courses rather than the number of actual vaccines per course for generalizability across disease systems.

We parameterized the time-varying vaccine efficacy, , of kOCV (whole-cell with B-subunit) using estimates from a large clinical trial in Bangladesh.[14,18] 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. Therefore, 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 changed in the two years following vaccination in 2006.[19] 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 had relocated over two years.[20] 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 time 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 epidemic final size distributions,[21] we find the threshold of 10 cases is a reasonable cutoff size such that a large outbreak is henceforth very likely (Fig S TBD). Therefore, we define an outbreak as more than 10 cases and, by assuming a Poisson distribution of secondary infections (mean = ), we can calculate the probability of a small outbreak of more than cases initiated by a single infectious case using the Borel-Tanner distribution:[22,23]

[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 of more than cases that was seeded by an imported case, calculated by:

[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 population size, and is the daily migration rate. Essentially, 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 . The probability of sustaining an outbreak greater than cases by day is therefore equal to one minus the probability of having no outbreaks greater than cases.

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 (R0=1.5) and set the probability, that a migrant is infected equal to , which simplifies Equation 5 to

*Bentiu PoC Camp Case Study*

To demonstrate the value of characterizing waning herd immunity, we focus on the recent experiences with vaccination, population changes, and an 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 S1)[<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 .[24] 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 conservatively high birth/death rate of described above; 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 “observed” 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[25,26] recently applied to cholera in South Sudan,[27]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,[28] and an expected generation interval distribution, which we assume to follow a discretized gamma distribution with median of 5 days.[27] This method assumes uniform mixing, no imported cases, and no missing data. Maximum likelihood estimation procedures were implemented with the *R0* package[29] in the statistical software program R**.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 return population susceptibility near 100% within 9-10 years (Fig 2B, solid line). Between the three primary forces 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 S2).

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 R0=2, 0.98 years when R0=1.5, and 3.90 years when R0=1 (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 R0, herd immunity is sometimes unattainable (Fig S3).

Achieving herd immunity is a key threshold for epidemiologists, but in reality an outbreak is possible below the threshold and is not guaranteed above the threshold.[30] Mass vaccination reduces, but not eliminates, the probability that an imported case sparks an outbreak for a duration of time that depends critically on how the vaccine efficacy wanes over time and migration rate (Fig 2E-F). For example, in a setting where R0=2, the probability an imported case sparks an outbreak of more than 10 cases approaches 0.80 in the absence of vaccination. Even though herd immunity is lost within just 0.47 years in a high migration setting when R0=2 (Fig 2C, solid red line), the outbreak probability only exceeds 0.50 one year after vaccination with 100% coverage (Fig 2E, solid red line).

*Optimizing revaccination with “Mass and Maintain” strategies*

We considered several operational strategies for sustaining herd immunity through vaccination alone. Assuming a fixed vaccine allotment of full courses to a population of size with R0=1.5 and a high rate of migration (), mass vaccination every year or every two years with 75% coverage can render herd immunity for 3.5 or 2.8 years, respectively (Fig 3A). If vaccines are instead allotted on a daily basis through routine vaccination, herd immunity can be achieved for up to 4.4 years (Fig 3B). We find that a blended “Mass and Maintain” strategy that complements a single mass vaccination campaign with routine vaccination can maintain herd immunity longer than either strategy alone (Fig 3C). 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 strong influence 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 OCV impact in at-risk settings, there is a tradeoff between targeting remote communities, where herd immunity may last for a long time due to low immigration but cholera introduction is rare, and highly mobile 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 introduced via migration (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 R0=1.5. 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.[20]

*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). Large kOCV campaigns were performed in July 2014 (66,529 doses) and June 2015 (146,720 doses).[31,32] Assuming a cholera-naïve population before vaccination, we estimate the population fraction susceptible increased from a low of 0.37 after the second mass vaccination campaign to 0.81 on October 16, 2016, when the first cholera case of the outbreak was detected (Fig 5B). 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 0.66 instead of 0.81 (Fig S4).

Using case reports and assuming a fixed generation interval distribution, we estimate the mean effective reproductive number, Re(t), exceeded unity for nearly two months, with a maximum likelihood estimate of 1.45 (1.18-1.75) (Fig S5). Using Equation 1 and the population fraction susceptible of 0.81 above, we estimate the basic reproductive number, R0, 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.[27] If we assume =1.80, then the probability of an outbreak after vaccination in June 2015 first exceeded 0.50 in May, 2016, and reached 0.57 when the outbreak began in October (Fig 5C). By December 1, 2016, we estimate that only 40.5% of camp residents had ever been vaccinated, which closely matches a WHO/IOM survey that month showing kOCV coverage of 40%.[28]

The drivers of waning herd immunity in this population, from strongest to weakest, were waning , population growth , the population resettlement rate, and lastly births/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.

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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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% | 35.9% |
| **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 Net-Zero Resettlement** | 70.3% | 100,000 | 0 |  | 52.9% | 18.5% | 27.1% |
| **Observed** | Empirical | Empirical |  |  | 80.8% | 46.3% | **--** |

**DISCUSSION**

We demonstrate that even for a population that recently underwent a mass OCV campaign, there may still be a chance of cholera re-emergence in the near future, but this risk can be reduced by high vaccine coverage. A re-emergence event does not imply vaccine failure, but instead can result from waning direct effects or population turnover via migration or birth and death.

We present estimated time windows during which policy-makers can expect a population to resist a cholera outbreak even if the pathogen were to be introduced. During such a time, complementary interventions can be scaled-up to provide longer-term protection or a rational revaccination strategy can be determined. 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, as seen through forty-plus years with the WHO Expanded Programme on Immunization (EPI).[33] Recent work has also shown serological triggers for periodic mass vaccination can be an effective and efficient method to maintain herd immunity.[34] The authors find that in high-incidence areas (or when VE is moderate or low), serological triggers could come so often that frequent planned vaccinations may be more appropriate. Indeed, in our example with imperfect kOCVs, at least annual mass vaccination may be needed to maintain herd immunity. 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.[35]

Current guidelines for the optimal use of the OCV stockpile recommend targeting “areas with important population movements.”[36] Mobility is recognized as an important driver of the performance of vaccination strategies to control ongoing cholera outbreaks.[37] Here, we focus on pre-emptive vaccination of at-risk communities to show the competing effects of high mobility on expected vaccine impact. On one hand, we expect settings with high migration rates to experience more frequent introduction of cholera, all else being equal. Therefore, the expected probability of an outbreak in a population with higher migration is larger. On the other hand, settings with high migration rates will also experience faster waning of herd protection, with the key assumption that those entering the population have a lower degree of vaccine-derived or natural immunity. The population-level protection conferred by vaccination will have a shorter duration in high-mobility settings. Together, these competing forces would suggest that a setting with intermediate degree of mobility would have a moderate risk of cholera introduction but also a moderate duration of protection afforded by vaccination. In order to operationalize this finding, 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.[38] We find that the optimal migration rate shifts lower (i.e., preferring less mobile populations) in settings with a high average R0.

Our primary results assume an outbreak is at least 10 cases. If this threshold is increased, the probabilities of “outbreaks” decreases, but the optimal migration rate is not affected. These findings focus only on cholera outbreaks introduced through migration and assume that each imported infection is independent, that infectious cases are imported at the very beginning of their disease experience, and that the count of secondary cases follows a Poisson distribution.[22]

Our results depend on several simplifying assumptions. By assuming a well-mixed population, we are assuming no heterogeneity in contact patterns or local reproductive numbers. In reality, we expect diseases, especially ones with environmental transmission characteristics like cholera, to exhibit substantial spatial heterogeneity in transmission intensity. In sub-regions with high transmission potential, outbreaks may be more likely to occur, but likewise other areas of the region with lower potential will have a probability of outbreaks lower than the mean effective reproductive number would here suggest. These differences become crucial if, as we may expect, migration may occur at higher rates in settings with higher transmission potential due to confounders like poverty and temporary infrastructures. In that case, we would expect the routine vaccination of migrants to be even more crucial.

Our model assumes a leaky mode of vaccine action, whereby vaccination reduces the disease susceptibility of each recipient to a non-zero level. However, our calculation of proportion susceptible, X(t), is robust to other assumptions regarding vaccine action, including all or nothing, whereby vaccination reduces disease susceptibility by 100% for some recipients and 0% for others (Fig S6). Our parameterization of a leaky, waning vaccine aligns with prevailing interpretations[14] of the clinical trial data,[18] as opposed to alternative possible explanations for changes in VE(t) over time in an RCT, such as frailty, loss to follow up, random variability, etc.[39]

The migration rates estimated from the three settings are intended for benchmarking and not to imply that these rates are constant, or generalizable, for the whole population. Indeed, if within a single population there existed a stable group of permanent residents and a high mobile group of temporary residents, we may expect to retain herd immunity for a long time after vaccination for a given average residence time. The mobility rates we present exemplify the wide range of human mobility and its possible impact on OCV decision-making.

Cholera vaccine efficacy has been shown to vary by age of recipient,[14,18] however for simplicity we do not model this age structure in the main results. If children are members of a mass vaccination campaign and respond poorly to OCV, we would expect herd immunity would 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.[40] For simplicity, we focus on pre-emptive vaccination of a 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 such as the typhoid capsular polysaccharide vaccine.[41] We find the “Mass then Maintain” strategy continues to outperform routine vaccination or periodic mass vaccination even when there is a perfect vaccine (i.e., VE=1 indefinitely) (Fig S7). We also find that intermediate levels of migration continue to maximize vaccine impact for a perfect vaccine, but the optimal migration rate increases with vaccine performance (Fig S7). These findings support the use of mass vaccination to quickly introduce a new vaccine that henceforth is to become a member of the routine immunization program, as was done when the Salk inactivated polio vaccine was licensed in the 1950’s and was distributed *en masse* before becoming a routine childhood vaccine.[3]

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[42] and yellow fever.[43] For yellow fever in particular, fractional vaccine doses have been used to extend vaccine supply under the assumption that VE of fractional doses lasts at least one year.[44] 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 VE(t) profile and population turnover rates. We show this information is essential for optimizing revaccination strategies, targeting vaccine stockpiles, and explaining re-emergence of outbreaks in a previously vaccinated population.

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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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**FIGURE CAPTIONS**

**Fig 1. Compartmental model framework.**

Individuals in a well-mixed population include explicit compartments for susceptible () and vaccinated (). Individuals enter and leave the system through birth, death, and migration (grey dashed arrows) and progress between stages in the population (black arrows). The force of infection for individuals in a compartment Vi is reduced by a factor of . 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. We show a direct disease transmission process and a leaky vaccine action model.

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

Following mass vaccination (100% coverage) with kOCV (left column) or hypothetical vaccine with VE=1 indefinitely (right column), population susceptibility is shown to increase over time more quickly in the presence of high migration rates (Panels **A-B**). Consequently, the effective reproductive number (**C-D**) and the probability that a single case sparks and outbreak of at least 10 cases (**E-F**) also increase over time since vaccination. Birth and death rates are set to zero in each simulation.

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

(**A**) Recurring mass vaccination with 100% coverage every year (dashed line) or two years (dotted line) is shown to periodically achieve then lose herd immunity, designated by the horizontal line at Re=1. (**B**) Routine vaccination of 8 (green), 12 (teal), or 16 (purple) individuals per day in a population of 10,000. (**C**) An example “Mass and Maintain” strategy with one-time vaccination at 75% coverage followed by routine vaccination. The following are held constant for all simulations: population size = 10,000; maximum vaccine courses = 30,000; R0 = 1.5; migration rate = ; and birth and death rates = . Faded horizontal bars show times with herd immunity under each strategy and the total duration is annotated to the right of each.

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

Vaccine impact, as measured by the decrease 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. The time since vaccination (colored lines) modifies these maxima. Vertical grey lines denote the estimated migration rates for Calcutta, Bentiu PoC Camp, and Dhaka as described in Methods. In this example, R0 is set to 1.5 and the average probability that a migrant is infected is 1/N, where N is the community size.

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

(**A**) Estimated population size (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 and are represented by the faint green and red ribbons around the blue line. (**B**) The proportion susceptible over time decreases due to mass vaccination events, and increases quickly during periods of population growth due to influx of new camp residents assumed to be susceptible. (**C**) The probability that a single case sparks an outbreak of more than 10 cases increases with and R0, as represented by line color: blue, R0=1; green, 1.5; black, 1.75; and red, 2.

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**SUPPLEMENTAL INFORMATION**

**Fig S1. 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 (vertical dashed lines). During the first segment from February 2014 to June 2014, we assumed linear 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 functions allowed for population size to change dynamically within a compartmental model framework, and provided population estimates that were visually reasonable. Our deterministic simulations began on June 15, when vaccination first occurred.

**Figure S2. Changes in the proportion of the population susceptible () as a function of years since vaccination.**

As per Fig 2, but with the addition of high birth/death rates () and the BS-Whole Cell vaccine profile.

**Fig S3**. **Duration of Herd Immunity (DHI) as a function of vaccine coverage and basic reproductive number.**

DHI is maximized in settings with high vaccine coverage and low basic reproductive numbers. Due to a longer duration of moderate VE but shorter duration of any VE, the WC vaccine possesses a wider parameter space of long DHI (blue), but an earlier fade to low or no DHI (red or white) as compared to the BS-WC vaccine. Migration rates are set to zero. Uncolored regions never obtain herd immunity.

**Fig S4. Time-dependent proportion susceptibility, X(t), in the Bentiu PoC Camp in the presence of a Mass and Maintain vaccination strategy.**

As per Fig 5C, with an additional dashed line indicating a counterfactual scenario whereby 100% of migrants arriving at the camp following the second mass vaccination campaign received vaccination themselves upon arrival. Population susceptibility on October 16, 2016 is measured at 0.66, as compared to 0.82 in the absence of the Mass and Maintain strategy (solid green line).

**Fig S5. Time-dependent reproductive number () and daily cholera case counts in Bentiu PoC Camp between October and November 2016.**

Using the daily case counts (black bars) and a generation interval with mean of 5 days and following a gamma distribution with shape=0.5 and rate=0.1 as per ref [27]., we report a time-dependent reproductive number (red line) approaching 3 in the early stages of the Bentiu PoC Camp outbreak, with 95% confidence bounds excluding 1 (pink region).

**Fig S6. Calculation of robust to leaky or all or nothing modes of vaccine action.**

For a simple exponentially waning vaccine direct effect, an All or Nothing vaccine mode of action (left panel) retains a constant (dashed line) while the number of individuals in the compartment decreases over time (dotted line). For the Leaky vaccine (right panel), individuals stay in the compartment, but wanes. Regardless, the proportion susceptible(solid line) follows the same profile for both vaccine modes of action.

**Fig S7**. **Vaccine targeting optimized in settings with intermediate rates of migration.**

As per Fig 4, except for a perfect vaccine (VE=1 indefinitely).

**Fig S8. Demonstration of Logarithmic adjustment for transition rates.**

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

**Fig S TBD.** **Revaccination strategies to maximize DHI assuming a non-waning vaccine.**

As per Fig 3, except the vaccine now retains the maximum efficacy estimated for Shanchol (0.583) for all time. Mass then Maintain strategies again maximize DHI for a fixed vaccine supply.

**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 especially for 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 term will approach and therefore the transition rate will approximately equal the number of vaccine courses available (i.e., ) (Fig S8, 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 term inflates the transition rate and allows the deterministic solver to move the desired number of individuals into (Fig S8, solid line). For computational tractability, we assume the coverage, , does not exceed 99%.

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

*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 [ref].

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 ();[45] for the duration of infectiousness ();[46,47] and for the duration of natural immunity ().[48–50] 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 .