**Working Title:**

Characterizing the Drivers of Waning Herd Immunity: A Modeling Study of Oral Cholera Vaccines

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**INTRODUCTION**

Vaccines can provide recipients with direct protective effects by priming their immune systems before wild exposure to a pathogen. For contagious diseases, indirect protective effects of a vaccine campaign emerge when an individual (vaccinated or unvaccinated) has a lower rate of encountering the pathogen because some fraction of their contacts were vaccinated and are therefore less likely to carry the pathogen themselves.1,2. The extent of indirect protection therefore depends on both the degree to which each recipient benefits from the vaccine (ie, vaccine efficacy (VE)) and the fraction vaccinated (ie, vaccine coverage (VC)).

First recognized prior to the campaign to eradicate smallpox and later summarized mathematically,1, the common goal of vaccination is to achieve herd immunity. This phenomenon emerges when effective reproductive number (Re), defined as the expected number of infections per case, is reduced below one.

Over time, the direct effects of some vaccines wane and render the recipient once again susceptible to the disease. Likewise, waning of indirect protection in a particular population can result from the waning of direct effects, but also through population turnover with a net replacement of vaccinated individuals with unvaccinated individuals.

Although much attention is given to measuring the duration and magnitude of vaccine efficacy, many questions regarding the duration of herd immunity remain. In practice, vaccines can be a relatively quick stopgap to protect an at-risk population until longer-term solutions can be instituted, but there is a need to know how much time is “bought” by such a vaccination campaign. For routine rather than stopgap vaccination, the decision of when to boost or revaccinate will depend in part on the duration of herd immunity (DHI) following vaccination. Lastly, it remains to be seen how strongly, and in what direction, population mobility should be considered when prioritizing target populations for vaccination.

We study the model system of oral cholera vaccines (OCV) to address these questions. Due to reliable vaccine efficacy and high coverage through mass campaigns, cholera vaccines can generate powerful herd protection effects.3 The WHO manages an OCV stockpile to facilitate vaccine usage in three settings: high-endemicity “hot spots”, high-risk humanitarian crises, and outbreak response.4 While the principle concern for reactive vaccination in response to outbreaks may be the short-term (e.g., <6 month) OCV effectiveness,5 the value of pre-emptive vaccination, strongly depends on the duration of time we can expect to prevent a cholera outbreak.

These are not merely hypothetical concerns. In the Bentiu Persons of Concern (PoC) Camp in South Sudan, mass vaccination was performed in July 2014 and June 2015, yet the camp sustained an outbreak of 88 cases in July-November 2016.6 Furthermore, in two large OCV clinical trials, loss to follow up due to migration of participants was reported at only 10% over two years in Calcutta7 and up to 58% over two years in parts of Dhaka.8

In this paper, we use mathematical models to study the implications of vaccine waning and human mobility on herd immunity over time. 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. Finally, we provide a tool that can help guide decisions regarding the expected duration of herd immunity in a particular context.

**METHODS**

We developed a compartmental model framework of a population that is being targeted with vaccination. The population groups of principle interest for this study are individuals who are fully susceptible to disease (S) and those who were vaccinated *n*-months ago (Vn) (Figure CC). In order to account for the observation that vaccine direct effects do not tend to wane exponentially, we created an ensemble of *n* monthly stages (V­1, V2, ..., Vn), which collectively generate an Erlang-distribution for the duration of time in the V-ensemble.9,10 We set the mean time residing in any V­n­ compartment to 30.5 days; therefore, individuals move from compartment S to V1 for months [0,1) post-vaccination on average, to V2 for months [1,2) post-vaccination, etc.

We adapted monthly VE(t) estimates using data from Clemens et al.11 that were re-analyzed by Durham et al.12 We define VE(1) to be the VE for months [0,1) post-vaccination, VE(2) to be the VE for months [1,2) post-vaccination, etc. We parameterized the time-varying distribution VE(t) of WC and BS-WC vaccines using tables provided by Durham et al.12 and linear interpellations between 6-month estimates, bounded at zero and one. As the WC vaccine is more commonly used, especially through the WHO OCV Stockpile, we focus our main results on the WC vaccine and present results for the BS-WC vaccine in the supplement.

We assume individuals within the population are well-mixed. Individuals emigrate from the population at a rate that is equal for all compartments. Unless otherwise noted, the total system size is held constant by offsetting this emigration with an equal rate of immigration. Our main results conservatively assume that immigration is entirely into the S compartment, meaning incoming migrants bring neither vaccine-derived nor naturally acquired immunity into the population (see the supplement for alternative assumptions regarding immune migrants).

The system of ordinary differential equations generated by the model was solved using the *deSolve* package13 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>.

In order to provide benchmarks for mobility in populations that have received OCVs, we estimated migration rates from three settings. First, to represent a more stable population, we estimate a migration rate of from the observation that only 9% of an OCV study population in Calcutta had changed in the two years following vaccination in 2006.7 Secondly, to represent a highly mobile population, we estimate a migration rate of from the observation that 58% of a study population in Dhaka had relocated over two years.8 Thirdly, to represent a displacement camp with intermediate mobility, we estimate a migration rate of in the Bentiu Persons of Concern (PoC) Camp in South Sudan in the period from February to October 2016, during which IOM reports a rather stable population of 104,000 people and approximately 2,000 entries/exits per month [<http://www.iomsouthsudan.org/tracking/>]. See Supplemental Information for more details.

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

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

and is the total population size at time *t* and is constant unless otherwise noted. Due to the special behavior of deterministic models, when a simulation asymptotically approaches from below, we define DHI as the time until .

We use our measurement of to estimate the probability of the community sustaining an outbreak given the introduction of a single case. For this calculation, we assume a Poisson distribution of secondary infections and define an outbreak as at least 10 cases (see supplemental information for different outbreak thresholds).14 The closed-form solution for the probability of an outbreak of size () initiated by a single infectious case is defined by the Borell-Tanner distribution14,15:

We consider three vaccination strategies: (1) routine vaccination; (2) periodic mass vaccinations; and (3) mass vaccination followed by routine vaccination. Routine vaccination can be performed daily for a particular fraction of individuals who happen to be susceptible at the time (such as those entering the population through immigration or birth). Currently, a complete vaccine course of OCVs includes two doses administered approximately two weeks apart,4 but because the focus of this study is on the scale of years, not days, we assume mass vaccination campaigns elapse over a single day. Furthermore, we focus on the number of vaccine courses rather than the number of actual vaccines per course for generalizability across disease systems.

During simulations with disease transmission, we utilize compartments for individuals who are exposed but not yet infectious (E), infectious (I), and recovered and immune (R) (Figure CC). Mean transition rates between these compartments are defined as following: for the incubation period () [Azman 2013]; for the duration of infectiousness ();16,17 and for the duration of natural immunity ().18–20 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 .

**RESULTS**

In a static population (i.e., no births, deaths, or migration), vaccination can provide some herd protection as long as direct vaccine efficacy remains, which we estimate to be 4.2 years for the WC vaccine in our deterministic model framework (Figure AA, dotted line). The inclusion of migration can substantially decrease this duration. In a high-migration setting with an average duration of residence of 2 years, the duration of any herd protection decreases to 3.6 years following mass vaccination with the WC vaccine and 9.2 years even for a perfect vaccine (Figure AA, solid lines).

Rates of birth and death must be unreasonably large in order to compete with these two drivers of waning of herd protection. Even pessimistic estimates of a life expectancy of 40 years only result in a 2% decrease in the duration of herd protection as compared to setting rates of birth and death to zero (Supplemental Figure AA). Between the three primary forces causing herd immunity to wane, namely waning direct effects, migration, and births/deaths, we find that the first two are substantially more influential than the third. We therefore present results in the absence of birth and death rates for simplicity unless otherwise noted.

Of interest to policy-makers is not just the duration of any herd protection, but specifically the duration of herd immunity (DHI). Figure VC shows the strong positive dependence of DHI on high initial vaccine coverage and low R­0­­. DHI is also shortened in the presence of increasing migration and birth/death rates (Supplemental Information TBD).

Although deterministic models exhibit threshold-like behavior once the reproductive number exceeds one, an outbreak in reality is possible below the threshold and is not guaranteed above the threshold.2 Holding vaccine coverage at 100%, Figure BB shows that mass vaccination reduces, but not eliminates, the probability of an outbreak for a duration of time that depends critically on the vaccine efficacy profile and migration rate. DHI can be inferred from the time of crossing the horizontal grey line, which marks the 24.6% probability of an outbreak (10 cases) when the reproductive number is equal to one. For a setting with high transmission potential and high migration (red solid line), mass WC vaccination may not be able to achieve herd immunity, but can still drastically reduce by nearly 50 percentage points the probability of an outbreak given introduction. See Supplemental Information for dependence on other factors such as vaccine coverage, seasonality, and birth/death rates.

We considered several operational strategies for sustaining herd immunity through vaccination alone. We find that for a fixed vaccine allotment, “Mass then Maintain” strategies that complement a single mass vaccination campaign with routine vaccination can maintain herd immunity longer than either recurring mass vaccination or routine vaccination strategies alone. 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. We found that in a population with size , R0=1.5, and high population turnover, provision of up to vaccine courses can sustain herd immunity for 3.6 years through annual mass vaccination, 5.0 years through “Mass then Maintain”, and up to 4.0 years through routine vaccination (Figure FF).

{Preliminary:

We find that the difference between the strategies increases with R0 and migration rates, but the ranking of the strategies remains the same (Table TBD).

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In addition to its strong influence on the duration of herd immunity, one may also suspect that communities with higher migration rates are also more likely to have cholera imported. In order to optimize OCV impact, there is a tension between remote areas, where OCV protection is long-lasting but cholera introduction is more rare, and highly mobile communities, where the opposite is expected. Figure DD shows vaccine benefits may be maximized for communities with intermediate levels of connectedness, assuming the risk of cholera introduction is proportional to the rate of population turnover (e.g., the pathogen is introduced via migration). In the example of Figure DD, where R0=1.5 and the probability an incoming migrant is infectious is 1/N, the migration rate recorded in Bentiu 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. If one is 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.8

**DISCUSSION**

Our results show that even for a population that recently underwent a mass OCV campaign, there is a risk of cholera re-emergence in the near future, but the probability of an outbreak can be reduced by high vaccine coverage. Such re-emergence does not imply vaccine failure, but instead can result from population turnover, waning of direct effects, or pernicious seasonal forcing. Additionally, non-random mixing of populations can result in patches with outbreak potential within a population with an average Re below the threshold of one [cite HIV, measles]

Our results can help inform decision-makers about the time window they can expect a population to resist a cholera outbreak even if the pathogen were to be introduced. During this window, WASH interventions can be scaled-up to provide longer-term protection, or a data-driven routine re-vaccination schedule can be determined. Because a complete characterization of the parameter space

One practical implementation of “Mass then Maintain” can include a high-coverage mass campaign followed by routine vaccination of new members of the population (through birth or immigration). In Bentiu, this strategy organically resulted from the routine distribution of vaccine leftover from a mass vaccination campaign. However, for populations with moderate to low migration rates, other susceptible individuals (such as those missed during other campaigns or those vaccinated more than 5 years ago) must be vaccinated in order to maintain herd immunity. {Also consider [Lessler 2016 PLOSMed] for an example of serologically triggered vaccination. They point out that in high-incidence areas, triggers could come so often that frequent planned vaccinations could be more appropriate.}.

Current guidelines for the optimal use of the OCV stockpile recommend the consideration of “Areas with important population movements” [WHO 2013]. The role of mobility in connecting a heterogeneous transmission landscape was demonstrated by Azman et al [2014 Proc R Soc B], but here we show there are two competing effects of high mobility on the duration of herd immunity. First, 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. Second, settings with high migration rates will also experience faster waning of herd protection. Therefore, the expected benefit of mass vaccination has a shorter duration in high-mobility settings. Together, these 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. In sensitivity analyses using different parameter sets, we find that the probability of an outbreak is generally decreased most by vaccination in settings with migration rates between and {Preliminary Finding}. We find that the optimal migration rate shifts lower (i.e., preferring less mobile populations) in settings with a high average R0 and higher seasonal amplitude. Our primary results assume an outbreak is at least 10 cases. If this threshold is increased to 100 or 1,000 cases, the probabilities of “outbreaks” decreases, but the optimal migration rate is not affected. These findings assume cholera is only introduced through migration, that each imported infection is independent, that infectious cases are imported at the very beginning of their disease [cite], and that the count of secondary cases follows a Poisson distribution.

Regarding mass vaccination targeting, our results support intuition that communities with low migration rates may retain herd immunity for a long time after vaccination, but are unlikely to have cholera introduced and therefore the probability of a cholera outbreak is always low. Conversely, highly mobile communities are more likely to have cholera introduced, but population turnover can quickly cause herd immunity to wane.

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.

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. However, they demonstrate how our tool can be used to implement our findings in actual practice. For example, in our model Calcutta is characterized as a population with low turnover and a historical R0 of {something}. Given it’s {large?} population, our model indicates that the most theoretically appropriate course of action would be… {just one way to add your goal (2) from 11/30 email}

Cholera vaccine efficacy has been shown to vary by age of recipient, however for simplicity we do not model this age structure in the main results. If children are members of a mass vaccination campaign, we would expect herd immunity would wane more quickly, and especially so if children are disproportionate sources of transmission. Furthermore, routine vaccination may benefit from targeting individuals as they reach the age of five years, for example, instead of vaccinating closer to birth.

The model we have created here is not limited to cholera. Other infectious diseases, like meningitis and Yellow Fever, oth of which the WHO maintains stockpiles for, can be evaluated in a similar manner. Namely, in Calcutta, because yellow fever’s R0 is {x}, and accounting for the differences between the yellow fever vaccine and Shanchol, our model instead recommends that… {Corey, this feels like the most natural place to include a mention of other diseases to me. To include it earlier seems to derail the momentum you’re building and the interconnectedness of the other ideas. This feels like a separate point to me. However, it may also be too cheesy to say “and our model works for other things too! The sky is the limit” at the end of the paper}

**FIGURE CAPTIONS**

**Figure AA. Changes in the proportion of the population susceptible (X(t)) as a function of years since vaccination.** Population susceptibility following mass vaccination (100% coverage) of WC and a hypothetical vaccine with VE=1 increases more quickly in the presence of high migration rates (solid lines) as compared to low migration rates of (dashed lines) or no migration (dotted lines).

**Figure BB. Changes in the probability of an outbreak as a function of years since vaccination.** The probability of an outbreak, defined as at least 10 transmission events following a single introduction, increases with time since mass vaccination (100% coverage) of WC and a hypothetical vaccine with VE=1 for all time. Settings with basic reproductive numbers of 1 (blue), 1.5 (green), and 2 (red) have increasingly high asymptotic outbreak probabilities of 24.6% (horizontal grey line), 59.7%, and 79.7%, respectively. Settings with high migration rates for (solid lines) demonstrate substantially faster growth in the probability of an outbreak than settings with low migration rates of (dashed lines).

**Figure VC**. **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.

**Figure CC. Compartmental model framework.** For our main results, we assume a direct disease transmission process and a leaky vaccine action model. Individuals who are vaccinated progress through stages V1, V2, ...., V­­n at an average rate of 1 per month. The force of infection for individuals in a compartment Vi is reduced by a factor of (1-VE(i)).

**Figure DD. Vaccine targeting optimized in settings with intermediate rates of migration.** Vaccine impact is measured by the decrease in the N-year cumulative probability of an outbreak comparing a mass WC vaccination campaign with VC=1 versus no vaccination, and is shown to reach maxima (triangles) at intermediate levels of connectivity. The time horizon of interest since vaccination (colored lines) modifies these maxima. Vertical grey lines denote the estimated migration rates for Calcutta, Bentiu, 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. See Supplemental Information for alternative parameters sets.

**Figure FF. Vaccine strategies to maximize DHI.** (A) Recurring mass vaccination with 100% coverage of susceptibles every year (dashed line) or two years (dotted line) is shown to periodically achieve then lose herd immunity, as recorded by the faded horizontal lines below. (B) Mass vaccination of 80% followed by routine vaccination of 8 (green), 12 (teal), or 16 (purple) individuals per day is shown to maximize DHI. (C) Routine vaccination only. 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 = .

**SUPPLEMENTAL INFORMATION**

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 [cite].

Our primary results assume a “leaky” vaccine mode of action, but analysis using an “all or none” mode of action was repeated using a time-invariant VE estimate and creating paths from each vaccine compartment back to the S compartment so that the duration of time in the V­n ensemble is variable (????). More details on the methods and results from this model can be found in the supplementary information. In summary, the results presented in the main text were robust to the assumed mode of vaccine action.

Furthermore, our primary results assume a direct transmission route of cholera, while some models prefer transmission through an intermediary such as a water reservoir [cite]. Our results regarding the duration of herd protection are insensitive to assumptions regarding transmission route, as they deal with vaccine effects and changes to the population demographic via birth/death or migration.

**Supplemental Figure AA. Changes in the proportion of the population susceptible (X(t)) as a function of years since vaccination.** As per Figure BB, but with the addition of high birth/death rates (1/40 years) and the BS-Whole Cell vaccine profile.

**Supplemental Figure BB “Seasonal”. Changes in the probability of an outbreak as a function of years since vaccination**. As per Figure BB, except the transmission parameter follows an annual seasonality with sinusoidal amplitude of +/- 5%.

**Supplemental Figure VC**. **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.