**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 system 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 [Fix 1971, Fine 1993]. 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).

First recognized during the campaign to eradicate smallpox [cite] and later summarized mathematically [cite], 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 herd immunity remain. For instance, 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 during when prioritizing target populations for vaccination.

We study the model system of oral cholera vaccines to address these questions. Due to reliable vaccine efficacy and high coverage through mass campaigns, cholera vaccines can generate powerful herd protection effects [Ali 2005].

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. 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), thereby generating an Erlang-distribution for the duration of time in the V-ensemble [Lloyd 2001, Krylova 2013]. 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 1990] that were re-analyzed by [Durham 1998] and 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 of vaccine efficacy of WC and BS-WC vaccines using tables provided by [Durham 1998] and linear interpellations between 6-month estimates, bounded at zero and one. As the WC vaccine is more commonly used, especially through the World Health Organization Oral Cholera Vaccine Stockpile, we focus our main results on the WC vaccine and present results for the BS-WC vaccine in the supplement.

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). Key parameters for each transition are shown in Table TBD.

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 assume that immigration is entirely into the S compartment (see the supplement for alternative assumptions regarding immune migrants).

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 1/20 years from the observation that only 9% of the population in Calcutta had changed in the two years following vaccination in 2006 [Sur 2011 PLOSNTD]. Secondly, to represent a highly mobile population, we estimate a migration rate of 1/2 years from the observation that 58% of the target population in Dhaka had relocated over two years [Quadri 2015 Lancet]. Thirdly, we observe that after rapid growth beginning in May 2014, the population of the Bentiu PoC camp in South Sudan remained stable near 104,000 between February and October 2016. During this time, IOM reports that approximately 2,000 individuals entered and exited the Camp each month, which equates to a migration rate of approximately 1/4.3 years [cite].

The system of ordinary differential equations generated by the model were solved using the *deSolve* package [Soetaert 2010 JSS] 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>.

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) [Becker 2015]. The closed-form solution for the probability of an outbreak of size () initiated by a single infectious case is defined by the Borell-Tanner distribution [Becker 2015, Mott 1963]:

We consider vaccination strategies that allocate vaccines on a routine basis; strategies that implement periodic mass vaccination campaigns; and also combinations thereof. Routine vaccination can be performed daily for a particular fraction of immigrants, births, and other individuals who happen to be susceptible at the time. Because the timeliness of interest are in years, not days, we assume mass vaccination campaigns elapse over a single day.

**RESULTS**

Under the simplest conditions of 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). 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 substantially alter the waning of herd protection – even pessimistic estimates of a life expectancy of 40 years only results in an approximately 2% decrease in the duration of herd protection as compared to rates of birth and death set 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.

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 [Fox 1971]. 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. For each simulation, the DHI can be observed by the time when the horizontal grey line is crossed. See Supplemental Information for dependence on other factors such as vaccine coverage, seasonality, and birth/death rates.

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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 can have diminishing returns for vaccines which push the Re further and further below the threshold, but routine vaccination alone requires a long period of time to achieve herd immunity, until which the population is still vulnerable to outbreaks. We found that in a population of size N with R0=1.5 and moderate population turnover (mean residence time = 10 years and mean life expectancy = 70 years), herd immunity can be sustained through a “Mass then Maintain” strategy for X years, as compared to Y and Z years using recurring mass vaccination or routine vaccination, respectively (Figure TBD). We find that the difference between the strategies increases with R0(Supplemental Information). 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). 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.

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In addition to its strong influence on the duration of herd immunity, we may also suspect that communities with higher migration rates are also more likely to have cholera imported. A natural extension of this model can be used to explore priority setting for remote versus highly mobile communities. 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 this particular example where R0=1.5 and the probability an incoming migrant is infectious is 1/N, we find that the migration rate observed in Bentiu in mid-2016 is near the optimal condition for maximizing the impact of a single mass vaccination campaign. Intuitively, 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.

**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 guide decision-makers on 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.

Current guidelines for the optimal use of the OCV stockpile recommends 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 1/20 and 1/5 years. 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.

Our results depend on several simplifying assumptions...

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.

**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 1/20 per year (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 1/2 per year (solid lines) demonstrate substantially faster growth in the probability of an outbreak than settings with low migration rates of 1/20 per year (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.** The 5-year probability of an outbreak of at least 10 cases in the absence (red line) and the presence of mass vaccination (blue line) is most different (grey bars) in settings with intermediate rates of migration. Vertical grey lines denote the estimated migration rates for Calcutta [cite], Bentiu [cite], and Dhaka [cite] 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.

**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 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.