**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, often called the vaccine efficacy, and the fraction vaccinated, often called the vaccine coverage.

Over time, the direct effects of some vaccines wane and render the recipient once again susceptible to the disease. Likewise, waning of indirect, or “herd”, 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 protection 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. Finally, the degree of mobility into and out of a community is recognized as an important factor for targeting vaccination, but it remains to be seen how strongly, and in what direction, population mobility should be considered.

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]. When a sufficient proportion of a population is immunized, the effective reproductive number can be reduced below one, a threshold commonly defined as herd immunity.

In this paper, we estimate the time-varying profile of oral cholera vaccine efficacy and use mathematical models to study the implications of vaccine waning and human mobility on herd protection over time. We apply our model to three case-study settings of Dhaka, Calcutta, and Juba. Finally, we provide a tool that can help guide decisions regarding the expected duration of herd immunity.

**RESULTS**

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Following the method Durham et al [1998], we estimate the time-varying vaccine efficacy using data from a set of published clinical trials, cohorts, and case-control studies [Table TBD]. We find that the whole-cell (WC) and B subunit killed whole-cell (BS-WC) vaccines provide some degree of protective efficacy for TBD and TBD years, respectively.

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Under the simplest conditions of no births, deaths, or migration, mass vaccination can provide some herd protection as long as direct vaccine efficacy remains, which we estimate to be 3.7 years for the WC vaccine and 4.2 years for the BS-WC vaccine (Figure AA, dashed grey lines). The inclusion of migration can substantially decrease these durations. In a high-migration setting with an average duration of residence of 2 years, the duration of any herd protection decreases below three years for each (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. 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). Our primary metric of DHI is defined as the number of days following a vaccination campaign with an effective reproductive number (R­e) below one. 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 a stochastic world is possible below the threshold and is not guaranteed above the threshold [Fox 1971]. For instance, if we assume a Poisson distribution of secondary cases and define an outbreak as at least ten transmission events following the introduction of a single infectious individual, the probability of an outbreak is 24.6% when the reproductive number equals one (Figure BB, horizontal grey line) and 79.7% when the reproductive number is 2 [Becker 2015]. 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. 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 to maintain herd immunity out-perform both recurring mass vaccination and strictly routine vaccination strategies. The intuition behind this complementary strategy is that recurring mass campaigns can have diminishing returns for vaccines pushing the Re further and further below the threshold, but routine vaccination alone requires a long period of time to achieve herd immunity, during 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). 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.

CASE STUDIES

**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.

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 importance of mobility 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 level 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.

**METHODS**

We developed a SEIR-type compartmental model with individuals fully susceptible to cholera (S), exposed but not yet infectious (E), infectious (I), recovered and immune (R), and vaccinated (V) (Figure CC). Key parameters for each transition are shown in Table TBD. We focus our attention on a single population being targeted for with mass vaccination.

To extend this model to account for the observation that cholera vaccine direct effects do not tend to wane exponentially, we separate the V compartment into *n* monthly stages, thereby creating an Erlang-distribution for the duration of time in any V compartment [Lloyd 2001, Krylova 2013]. The mean time residing in each of the V­n­ compartments is therefore 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] and 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. The shape of the fitted VE(t) curves can be inferred from the grey long-dashed lines in Figure AA.

We assume individuals within the population are well-mixed. Individuals emigrate from the population at a rate that is equal for all compartments. The total system size is held constant by offsetting this emigration with an equal rate of immigration that is entirely into the S compartment, thereby assuming that neighboring areas are not vaccinated. If immunity levels (via vaccination or naturally acquired infection) are nonzero in neighboring locations, migrants from those locations could instead extend herd immunity in the population of interest. The rates of migration in our model range from an average residence time of 2 years in a high-migration setting (similar to the 58% loss to follow up over two years during a recent trial in Dhaka [Qadri 2015 Lancet]) to 20 years in a low-migration setting (similar to the 9% loss to follow up over two years in a trial in Calcutta [Sur 2011 PLOSNTD]).

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].

We define the duration of herd immunity as the number of days 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*,

where is the total population size at time *t*.

We can use Re(t) 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 overdispersed distributions and different outbreak thresholds) [Becker 2015].

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.

**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, BS-WC, and a hypothetical vaccine with VE=1 increases more quickly in the presence of high migration rates of 1/2 per year (solid lines) as compared to low migration rates of 1/20 per year (dotted lines) or no migration (dashed lines). High birth rates of 1/40 per year (black lines) are similar to no demographic births/deaths due to the relative rapidity of the other competing rates. For each vaccine, VE(t) can be inferred from the grey long-dashed lines, since all changes in susceptibility are therefore due to vaccine waning.

**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, BS-WC, and a hypothetical vaccine with VE=1. Settings with basic reproductive numbers of 1 (blue), 1.5 (green), and 2 (red) have increasingly high asymptotes 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 (dotted lines).

**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%.

**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

**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. In this example, the R0 is constant over time at 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.