



# Effective Allocation of Reactive Cholera Vaccines: A One or Two Dose Campaign?

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Effective Allocation of Reactive Cholera Vaccines:  
A One or Two Dose Campaign?

A thesis presented

by

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to

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## Abstract

Every year for the past five years, over 100,000 cases of cholera have been reported to the World Health Organization (WHO). Though cholera is by no means a new disease, its containment in low-income countries has proved impossible with traditional measures such as WASH interventions. To supplement these far-reaching interventions, the WHO has proposed and begun to amass a reactive vaccine stockpile. As outbreaks are reported, the WHO intends to evaluate them and determine if a reactive vaccination supplement is appropriate. Understanding how to optimally allocate reactive vaccines is essential to the WHO's evaluation of a country's need for vaccines. The primary focus of this paper is to determine which conditions are appropriate for one or two dose reactive vaccination campaigns over a variety of parameter values. Though a range of parameter values are examined, the results indicate that the incremental benefit of the second dose is relatively small.

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## Introduction

In 1969, cholera was designated as one of three diseases whose outbreaks required notification to the World Health Organization (WHO). Over 45 years later, these outbreaks continue to occur and still require notification to the WHO.<sup>1</sup> The severity and large geographic range of these epidemics is such that more than 100,000 cases have been reported every year for the past 5 years.<sup>2-6</sup> 2011 saw a number of extreme epidemics, resulting in nearly 600,000 reported cases, up from approximately 100,000 cases in 2004.<sup>4</sup> These cases and the large number of deaths associated with them are preventable.

In high-income countries, conventional water, sanitation and hygiene (WASH) interventions have proven effective in controlling epidemics.<sup>2,6</sup> However, these interventions are mostly long-term investments and require significant resources and administrative capabilities to implement. Simply, WASH interventions are often too slow to react to the fast-paced cholera epidemics that occur in Sierra Leone, Bangladesh, and similar low-income countries.<sup>7</sup> In order to supplement WASH interventions, oral rehydration therapy (ORT) is used. ORT is effective in reducing case fatality, but does little to limit transmission of the cholera vibrios.<sup>8</sup>

It is evident that both WASH and ORT contribute to the reduction of cholera's global burden, but they are not sufficient to completely control outbreaks of the disease. Cholera's short serial interval, the time between onset of symptoms in one case and onset of symptoms in someone that case infects, is indicative of the disease's rapid spreading potential. Additionally, as it is a waterborne disease, it has enormous potential for super spreading events (where a primary case can cause a disproportionately large number of secondary cases). In order to supplement current epidemic control measures, the WHO recently recommended the use of oral

cholera vaccines (OCV)<sup>9,10</sup>. OCVs would be particularly useful when WASH interventions are ineffective, such as populations for whom clean water is inaccessible (that are difficult to reach with clean water) or those that have extensive latrine and sewage problems. OCVs can be deployed relatively quickly and thus are considered for reactive epidemic control. As the WHO currently has a fixed amount of OCVs, the question becomes: how do we effectively allocate the OCVs to help reduce the epidemic burden?

## **Significance**

Though the WHO has begun creation of an OCV stockpile to combat cholera, two main factors have kept that stockpile small. First, the WHO wants to test whether or not an OCV stockpile is effective before they fully commit to the project, so they are only willing to support a relatively small stockpile at this time. Second and more limiting, the global production capacity for OCVs is quite low compared to that of other vaccines. Unless production capacity is drastically increased, demand for OCVs will continually exceed the supply of vaccines. To that end, one of the current supporters of the stockpile, the Global Alliance for Vaccines and Immunizations (GAVI), is considering significantly increasing its monetary contribution in order to augment the size of the stockpile. GAVI's new funding round will occur within three years and they must determine how much, if at all, they would like to scale up this intervention. Their decision will largely be based on the effectiveness of the current OCV stockpile and on models of the stockpile's potential.

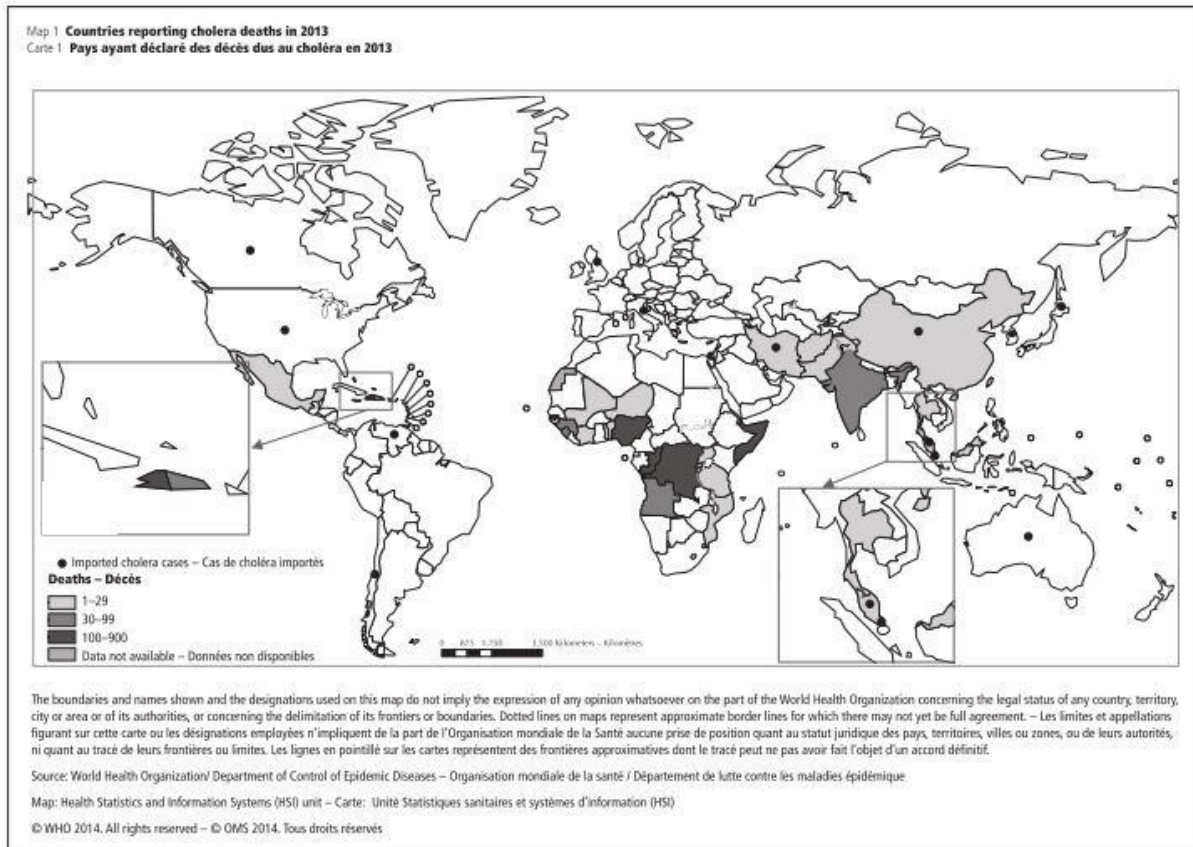
OCVs have been used both reactively and from stockpiles before, but never have they been deployed reactively from the current stockpile. However, the WHO does have a number of other stockpiles for reactive use that have been effective, including one stockpile of meningococcal vaccines. Established in 1997, the stockpile averages nine million doses a year

and is used for both emergency response and disease prevention.<sup>11</sup> When the WHO receives a request for meningococcal vaccine, it is assessed by the International Coordinating Group (ICG) which consists of partners in UNICEF, Médecins Sans Frontières, the International Federation of the Red Cross, and other WHO counterparts. A response is sent to the country within forty-eight hours and, if positive, vaccines arrive in the country within seven days. Protocol for the deployment of OCVs will be similar, though the stockpile is much smaller. A set of threshold values determining the conditions for a positive OCV response have been discussed, but have not yet been established in a rigorous manner. These quantitative decision thresholds will ensure that the timeline for vaccine deployment is quick and also allow for evaluation of the stockpile and future decision models. In this paper, we begin to explore the parameter space appropriate for a positive dose response in the hope that it will be useful to both the WHO and GAVI to inform their new and potentially growing OCV stockpile.

## **Background Information**

In 2013, 47 countries reported a total of 129,064 cases cholera to the WHO. Included in those cases were 2012 deaths, resulting in an average case fatality rate of 1.63%.<sup>10</sup> Though only 129,064 cases were reported, the global cholera burden is actually estimated to be about 2.8 million cases annually, with 1.4 billion people at risk of contracting cholera.<sup>1</sup> Disproportionately, cholera affects residents of Southeast Asia and sub-Saharan Africa, where socioeconomic status is low and sanitation is poor.





**Figure 1.** Distribution of countries reporting cholera cases to the WHO in 2008. Figure from WHO 2009 Weekly epidemiological report.<sup>6</sup>

Cholera is characterized by the onset of “rice-water” diarrhea, a very watery diarrhea that may be accompanied by vomiting or abdominal discomfort.<sup>12–14</sup> Symptoms present very rapidly after exposure, usually between 12 hours and 5 days, making cholera notorious as the pathogen with fastest onset to death.<sup>15</sup> As patients lose water through secretion at an alarming rate, dehydration is often the eventual cause of death. Dehydration may lead to a severe salt imbalance within the body, which in turn can cause convulsions and cardiac arrest, eventually resulting in the patient’s death. However, with immediate ORT, the vast majority of these deaths are preventable. Proper use of ORT in isolation can reduce the mortality of the disease below 1%. However, only with the addition of OCVs to the current WASH interventions can the global prevalence of the disease diminish.

## **Biology and Transmission**

Cholera is caused by infection with the Gram-negative bacterium *Vibrio cholerae* of the O1 or O139 serotype<sup>16</sup>. *V. cholerae* is typically found in coastal water and estuaries, usually in the presence of salt<sup>12,13</sup>. Though vibrios exist primarily in the water reservoir, they can be transmitted by water, food, or by person to person contact. In regions where latrines do not meet hygienic standards or where open defecation occurs, vibrios can be transferred from a person's feces to his or her hands. From there, the vibrios are poised to spread to other people. Once ingested, toxins released by the vibrios cause the trademark, clear watery diarrhea of cholera and are then in turn excreted from their new host. The cycle repeats if sanitation conditions are unchanged. The transfer of vibrios, while more accurately described as from feces to human and subsequently to other humans, can be represented simply as person to person transmission. Multiple different modeling approaches using humans and water as reservoirs have been undertaken, but though the models have varying amounts of complexity, the results using water or humans as a reservoir are largely similar<sup>17</sup>.

Modeling using water as the primary reservoir is difficult for a variety of reasons. First, it is difficult to determine the amount of vibrios in the entire water reservoir at a specific time. There are so many water sources and the vibrio content in each of them changes rapidly. Second, as not all water remains stagnant, flow must be accounted for within calculations. This brings the additional variables of seasonality and rainfall into the model, complicating the model further. Finally, even tracing human contact with water presents a great challenge. It is much more difficult than regular contact tracing, where infected people are asked whom they had contact with in a relatively short time period. For those reasons, this model uses human to human

transmission exclusively. The results obtained are comparable to those using a water reservoir and much less variability is introduced into the model by minimizing the number of parameters.

## **Vaccination**

The first cholera vaccines were developed in the late 1800s, soon after the discovery of *V. cholerae*. Original vaccines were composed of killed whole cells and were delivered by injection. These parenteral vaccines were used for about 80 years, but eventually recommended against when a study showed that the appropriately non-reactogenic vaccines did not confer significant protection<sup>18,19</sup>. While studies of the effectiveness of whole cell cholera vaccines were being undertaken, it was discovered that mucosal immunity in populations with endemic cholera might be the key to developing a better, safer vaccine. This was indeed the case, and Holmgren found that the most effective vaccine was one that orally introduced vaccine antigens.<sup>18-21</sup>

Currently, there are three licensed oral cholera vaccines (OCVs): mORCVAX, Dukoral, and Shanchol. Both Dukoral and Shanchol have been pre-qualified by the WHO for use by the United Nations, while mORCVAX has not been pre-qualified because it does not meet several production and standardization regulations.<sup>22</sup> Of the pre-qualified OCVs, Shanchol has been chosen by the WHO to be stockpiled for two primary reasons: price and lack of a buffer. In 2014, Shanchol cost \$1.85 per dose, while Dukoral cost between \$3.64 and \$6.00 per dose. Even at its lowest price, Dukoral is still approximately twice as expensive as Shanchol. Additionally, Dukoral requires a buffer in order to function.<sup>22,23</sup> Without the buffer, the acid in the stomach renders the vaccine ineffective. The necessary buffer is large in volume, adding to Dukoral's administrative burden and increasing the WHO's conviction that Shanchol is the superior choice for the OCV stockpile. The WHO hopes to establish a Shanchol stockpile of 2 million doses per year and has already made significant progress towards accomplishing its goal.<sup>24</sup>

## **Methods**

### **Determining Factors to Consider**

A number of factors must be considered to parameterize human-to-human cholera transmission. Geographic location, infectiousness of an infected person, the duration of infection, and vaccination status are all among potential variables. For this model, parameters were chosen based on availability and reliability of information regarding the parameter.

### **Populations**

There are multiple ways to consider populations. For the original framework, one well-mixed, homogeneous population is considered. As the model is based loosely on Sierra Leone, a country with well-defined chiefdom borders and which recently had a large cholera epidemic, population size is chosen to reflect that choice. Therefore, a population size of 25,000, the approximate median chiefdom population size, is used as the default. Populations are initially modeled as separate entities, with no immigration or emigration between populations.

One population is used because the WHO will evaluate the necessity of deployment of vaccines on a population by population basis. That is, if the WHO is considering two chiefdoms in Sierra Leone that have a certain number of reported cholera cases, they will decide whether to deploy vaccines to neither population, one population, or both populations. At this time, for logistical and ethical reasons, a population either receives the pre-determined amount of doses, or it doesn't. There is no partial allocation. Logistically, if aid is being given to a region, it is easiest to target the entire population and incentivize maximal attendance at one vaccination site. Targeting of specific groups requires additional effort and does not produce comparable results. Ethically, if the intent is to vaccinate the entire population, there is no need to choose which

people “deserve” the vaccine more than others. Full vaccination campaigns thereby remove said ethical concerns. Currently, there is no research to suggest that certain subsets of people are predisposed to gain enhanced protection from the vaccine, so we assume that everyone is equal and distribute without bias.

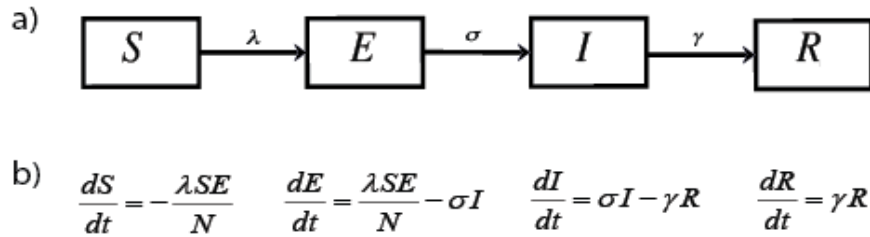
### **Stochastic vs. Deterministic**

When deciding how to model a cholera epidemic, there are two main choices: stochastic and deterministic. A stochastic model is one that uses probability to predict the outcome. Multiple trials are run in order to determine the average outcome. In contrast, a deterministic model is one in which the output is completely determined by the parameters. Probability is not accounted for. Only one trial needs to be run as the outcome is always the same. After running both deterministic and batches of stochastic models, the results from each were largely similar. Because of the programming efficiency of deterministic models, we chose to execute the majority of our model in a deterministic manner.

### **Model**

Susceptible, Infectious, and Recovered (SIR) models are a type of differential equation model commonly used to model infectious diseases.<sup>25</sup> In these models, every person in a population can be placed into one of three groups: Susceptible, Infectious, or Recovered. A person is Susceptible if he is not infected with the disease nor has he been exposed to it, Infectious if he has contracted the disease and can infect others, and Recovered if he at one point contracted the disease but is no longer infected, nor can he be infected again. For cholera, another group, Exposed, must be added because a person can be exposed to the vibrios but not yet be able to infect others. Though the exposure time for cholera is notoriously short, as we are

concerned with temporal dynamics, we include it in this model. This makes the model an SEIR model, as it will be referred to for the duration of the paper.

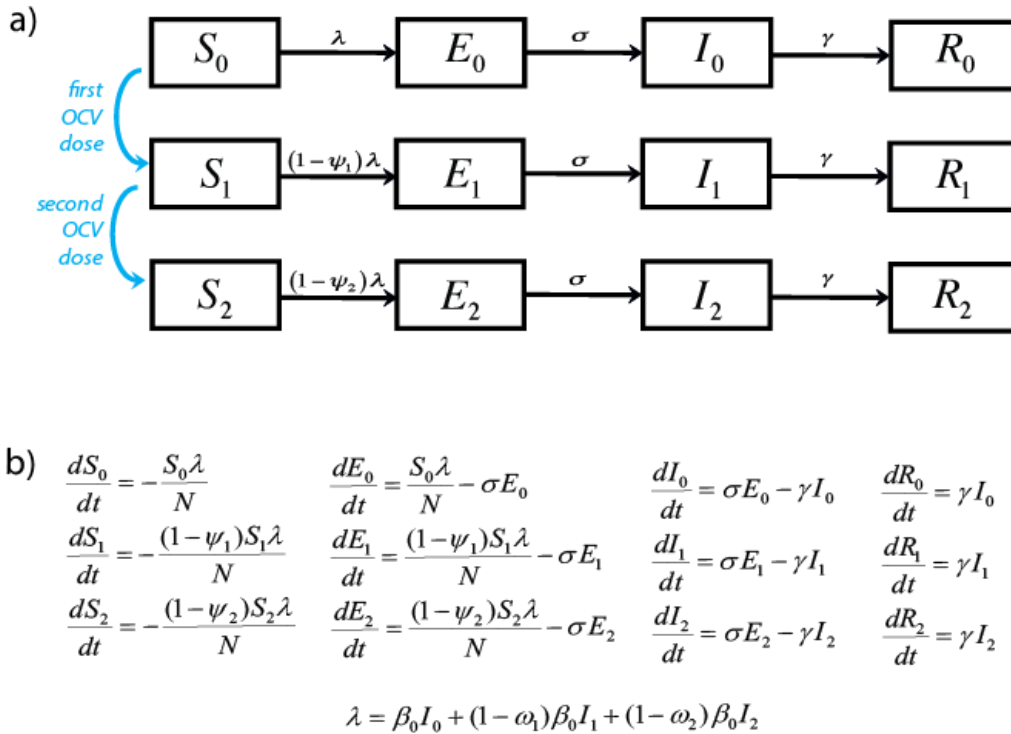


**Figure 2.** Basic SEIR Model. a) Movement between populations. b) Differential equations corresponding to sub-population change

### Accounting for Leaky Vaccines

A normal SEIR model functions linearly as in Figure 2 above, where people can only move directly from one category to another. When vaccines that are 100% effective are added to the model, people can move directly from the Susceptible category to the Recovered category. However, most vaccines are not 100% effective. Instead, they are “leaky”, meaning that they only protect against the disease with a certain probability.<sup>26</sup> In this model, we assume leaky vaccines in order to demonstrate the effects of vaccines with different leakiness on susceptible populations. Practically, this means that people that have been vaccinated are still susceptible to a large enough exposure dose and cannot be moved directly to the recovered category, where we assume complete protection for at least the duration of this epidemic. In the case of cholera, both the first and second doses are leaky, though the second dose is less leaky than the first. Additionally, both vaccines may alter the infectiousness of the person who has been vaccinated. In order to account for the vaccines and the changes they cause, the SEIR model can be expanded to have twelve categories, with each type of vaccination (none, one dose, or two doses) having its own Susceptible, Exposed, Infectious, and Recovered groups. In this new SEIR model,

we assume that all people begin in the  $S_0$  group, where they are Susceptible and unvaccinated. When a person is vaccinated he moves from the  $S_0$  group to the  $S_1$  group and when he is vaccinated a second time, from the  $S_1$  to the  $S_2$  group. From there, each susceptible population functions independently, with people moving between Susceptible, Exposed, Infected, and Recovered populations in the same linear fashion as in the most basic SEIR model. A visual representation of the movement between populations can be seen below in Figure 3, as can the differential equations that govern the movement.



**Figure 3.** Complete SEIR model. a) Visual representation of movement between populations. b) Differential equations governing movement between populations

The sum of the differential equations that comprise the model is zero because we assume that there are no births and deaths. With proper ORT, the case fatality rate of cholera is below one percent, so this assumption is reasonable. Thus the total number of people is the same both at the beginning and the end of the epidemic. We measure the effect of the epidemic by examining the recovered population, which indicates the number of people who were ever infected. In a real population, the size of the epidemic would need to be approximated by the number of people who recover in addition to those who died from the disease.

## **Parameters**

Because Shanchol trials are still ongoing, sensitivity analysis will be a key portion of this model. Parameters like vaccine efficacy and time until vaccine deployment have not been significantly determined yet. As such, it is to the WHO's and GAVI's benefit to have a model that details a variety of possible parameter values.

Vaccine efficacy,  $\psi_1$  or  $\psi_2$  from the equations above, is perhaps the most sensitive parameter considered in this model, as it is related to number of doses given and varies with different OCVs. For this model, it was assumed that the vaccine could be administered in one or two doses. A dose is considered effective if it prevents contraction of the disease when vibrios are ingested. The effectiveness of a dose is the sum total of the effects of the given dose and any previous doses. In the case of Shanchol and Dukoral the second dose may have a higher efficacy than the first dose, though the first dose does appear to have its own efficacy.<sup>14,27</sup>

Current testing in Bangladesh of vaccine efficacy suggests that the first dose of Shanchol is 50% effective and the second dose is 85% effective.<sup>28</sup> However, there is a great deal of uncertainty surrounding the estimated first dose efficacy as these data was drawn from an



ongoing study. The first dose efficacy used here is the current best estimate, but more data is needed for precise estimation as well as the longevity of the vaccine's effectiveness.<sup>29</sup> Sensitivity analysis of the first dose's efficacy will be a crucial component of our model. The efficacy of the first dose is expected to have large implications on the choice between one and two dose campaigns.

The basic reproductive number, or the number of subsequent primary infections caused by one infection in a fully susceptible population, is another parameter which warrants a sensitivity analysis. When the basic reproductive number is high, the epidemic spreads more quickly and broadly because each person is expected to infect a larger number of people on average. Published estimates of cholera's reproductive number range from 1.5 to 8.7, so this model will consider the same range of reproductive numbers in its sensitivity analysis.<sup>30-32</sup>

The next parameter considered is the transmission coefficient ( $B_0$ ). Here, transmission is defined as transfer of sufficient vibrios from one person to another to induce infection. The transmission coefficient is the product of the contact rate and the average probability of transmission given contact. This parameter applies specifically to interactions between non-vaccinated infectious and non-vaccinated susceptible persons. Basic reproductive number is determined in part by the transmission coefficient, so sensitivity analysis of the basic reproductive number will correspond with that of the transmission coefficient.

Once vaccinated, the probability of onwards transmission may change. The current hypothesis is that if a person has been vaccinated and still becomes infected, the infection is not as severe.<sup>30,33</sup> It follows that an infected person who was vaccinated would not be as infectious, so a parameter for relative infectiousness ( $B_0$  modified by  $\omega_1$  and  $\omega_2$ ) needs to be introduced.

More simply, when a vaccinated person is infected, he or she does not shed as many vibrios and therefore infects fewer people. Because a non-vaccinated, infected person ( $I_0$ ) will be the most infectious, he or she is set to have infectiousness equal to 1. All other vaccinated, infected persons ( $I_1, I_2$ ) have infectiousness below 1, as they only infect a fraction of the people infected by a non-vaccinated infected person. In our model, we assume that both  $\omega_1$  and  $\omega_2$  are set to zero because there is no current evidence strong enough to support the hypothesis that they are non-zero. Thus  $I_0, I_1,$  and  $I_2$  all have the same infectiousness. However, if strong evidence of non-zero values of  $\omega_1$  and  $\omega_2$  is produced, our model is flexible enough to accommodate such results.

After contact with and transfer of the vibrios, an infected person has a window of time in which he or she is not yet infectious. The time during which he or she remains in this window is referred to as the incubation rate ( $\sigma$ ). During this time, the *V. cholerae* are multiplying but symptoms are not present. The length of the incubation period is important in determining the timeline of disease spread. Additionally, we assume the person is unable to infect others, meaning that he or she must be treated separately from the general infected population. As *V. cholerae* are able to multiply faster in some people than in others, the parameter used as an estimate of the time spent in the exposed but not yet infectious category.

The recovery rate ( $\gamma$ ) is similar to the incubation rate. Essentially, it is the length of time after which an infectious person sheds fewer vibrios than the critical infectious dose. Note, this is movement from the infectious population to the recovered population only. It does not include the amount of time it takes for someone to pass away.

In general, we seek to understand the epidemic dynamics for one population in order to evaluate whether or not that population needs to be given vaccines. Here, we are examining reactive vaccination, not preventative vaccination. We do this for two primary reasons. First, there are not enough vaccines available to vaccinate everyone living in at-risk regions and current predictive measures are not accurate enough to predict the location or timing of an epidemic. Second, vaccines only provide immunogenic protection for up to 5 years, meaning that childhood vaccination, which is an appropriate strategy for many diseases, does not work for cholera. Combined, these two reasons have made reactive vaccination a more appealing choice than preventative vaccination for use of the OCV stockpile.

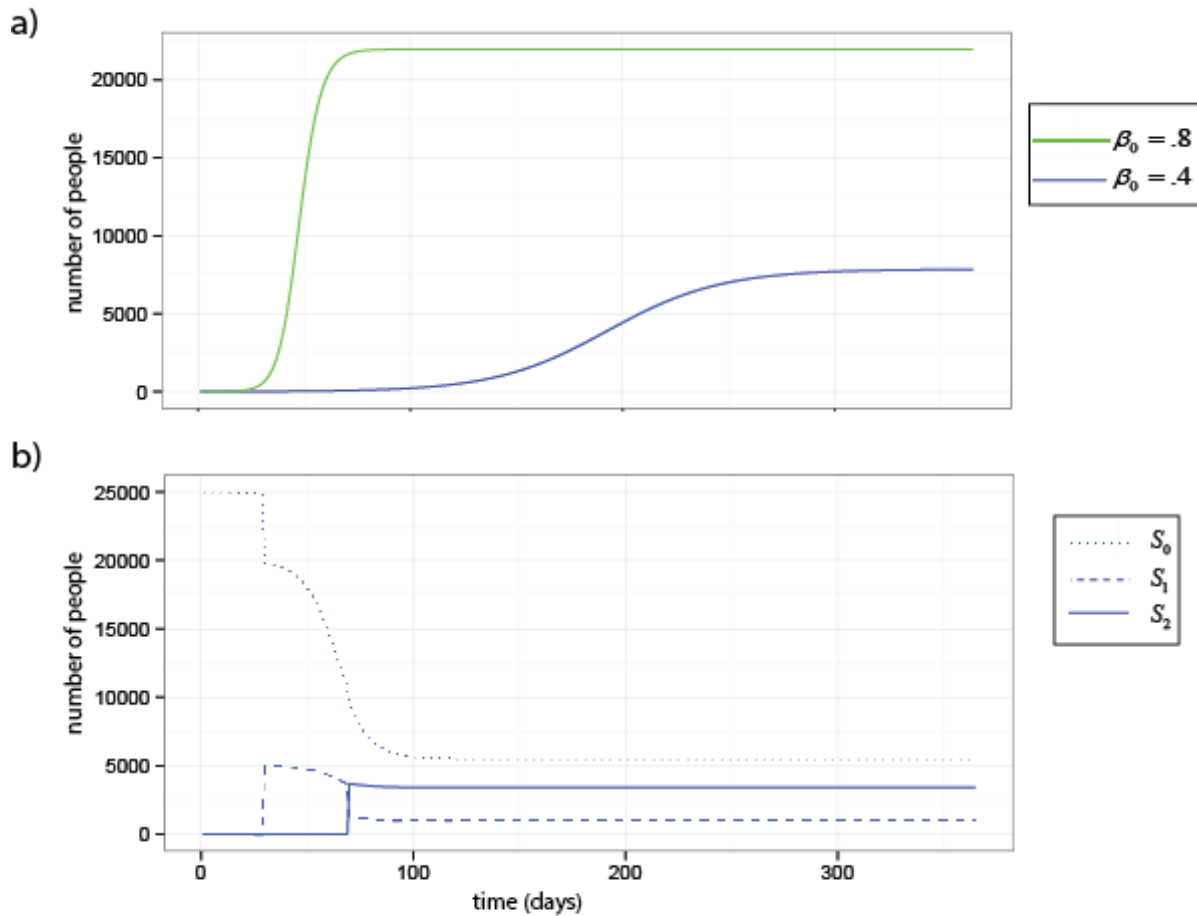
Currently, as the vaccine stockpile is in early stages, the WHO has a limited number of vaccines. Global production capacity is the primary limitation on the number of vaccines, though GAVI is attempting to increase this capacity. In the meantime, because there are only so many vaccines, the dose allocation between populations has practical importance. In the results section, we detail the effects of parameter modifications on one population. We do so in order to provide evidence for the conclusions drawn regarding dose allocation in the discussion section that immediately follows. As Shanchol trials are ongoing in Bangladesh, it will be useful to have a model that details the optimal vaccination strategy for a range of 1<sup>st</sup> and 2<sup>nd</sup> dose vaccine efficacies.

# Results

## Model Performance

As this project was primarily a theoretical one intended to explore generalizable cholera epidemic principles, the model is not based on a significant past outbreak. That is, the parameters of the model do not reflect a single past epidemic because the results produced would be too specific to that region. The WHO is interested in a broadly applicable strategy for OCVs, so the model created must reflect that. An additional reason for choosing not to base this model on past epidemics is that fitting models to messy data is often unproductive and inaccurate because outbreaks vary greatly and are largely affected by the economic and health conditions of the area in which they occur. Thus, when testing the model for performance only general trends were examined.

The three main criteria for analyzing model performance are as follows. First, that when no birth, death, or immigration occurs within the population, the sum of the susceptible, exposed, infected and recovered sub-populations is always equal to the total population. Second, when parameters such as infectiousness are set to high values, the number of recovered people, and thus people who were ever infected, is higher. This difference is also evident in the timeline. When infectiousness is higher, infections occur more quickly and thus the number of recovered people increases more quickly. Third and finally, when vaccines are introduced, the change in the  $S_0$  and  $S_1$  or  $S_1$  and  $S_2$  populations is equal and opposite. The first criteria can be confirmed analytically, while the final two can be seen graphically, as below.



**Figure 4.** Testing the functionality of the model. a) Number of people who have been infected for different values of infectiousness. When infectiousness ( $\beta_0$ ) is large, the epidemic spreads more rapidly. b) Demonstration of a two dose vaccination. The first dose occurs at 30 days and the second occurs at 70 days.

## Epidemic Size and Duration

Epidemic size is highly affected by modification of parameters such as vaccine efficacy, ( $\psi_1$  or  $\psi_2$ ), population size (N), and delay time before vaccination. Assuming the parameters in Table 1 and enough vaccines to vaccinate each member of the population once with 90% coverage and a second time with 80% coverage,<sup>34-36</sup> we examine the change in epidemic size upon changing initial vaccination day. We observe that cumulative epidemic size varies greatly with initial vaccination date. If the first dose is administered within two weeks of discovering the first case, the total number of infections is approximately .001% of the total number of

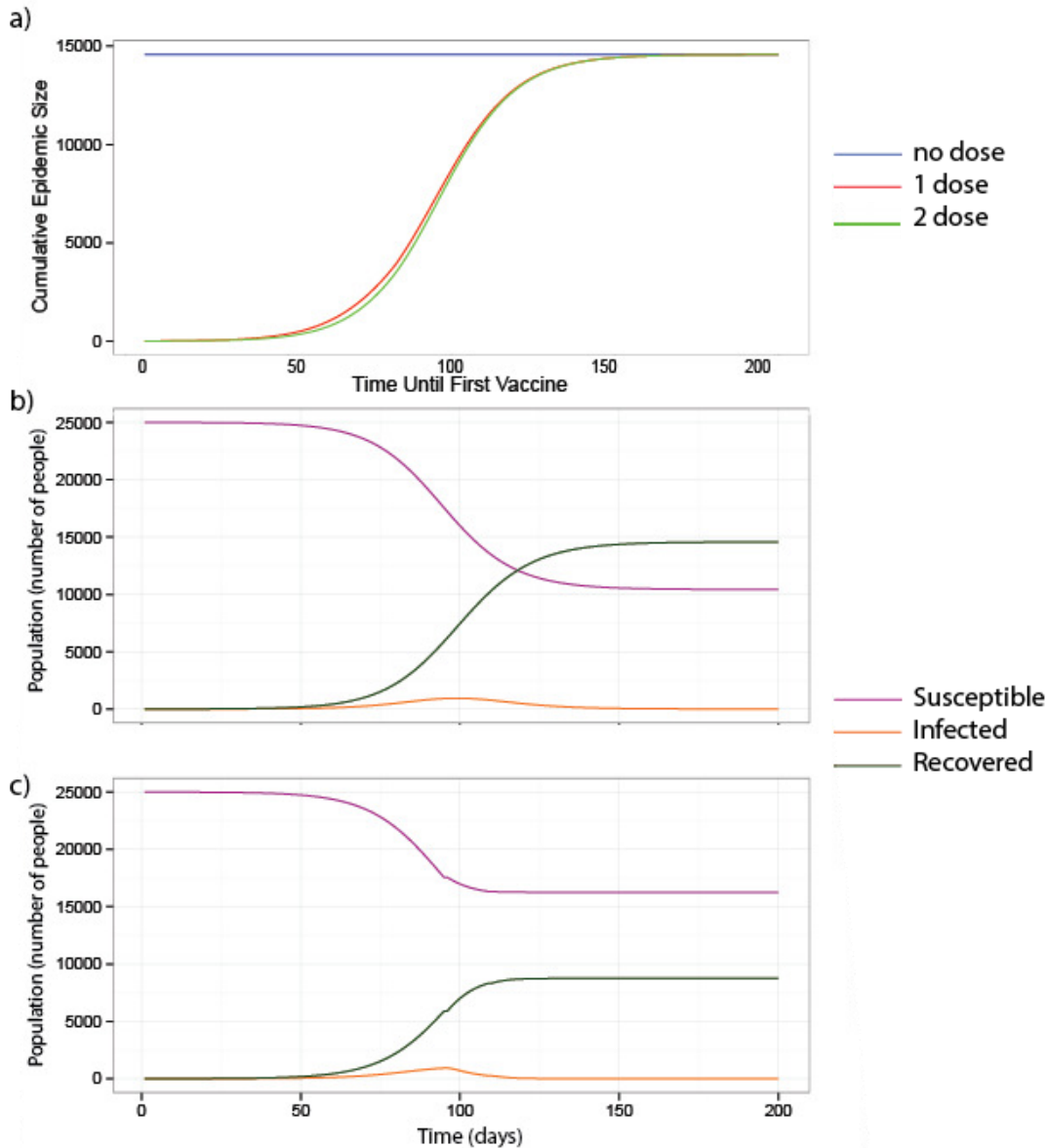
infections that would occur if no vaccines were administered. This would be an extremely fast reactive campaign and is highly unlikely, if not impossible. Nevertheless, it demonstrates how effective the vaccines can actually be if used quickly.

**Table 1.** Parameters used in the model. Values are used throughout the paper unless otherwise specified.

Parameter	Variable	Value	Sensitivity	Reference
Infectiousness of a completely susceptible person	$\beta_0$	.50	[.33, .99]	Chao 2011 PNAS <sup>30</sup>
Protective efficacy of first dose	$\psi_1$	.50	[0, .85]	Luquero 2014 NEJM <sup>37</sup>
Protective efficacy of second dose	$\psi_2$	.85	[.75, .95]	Luquero 2014 NEJM <sup>37</sup>
Incubation rate	$\square$	.50	N/A	Azman 2013 JID <sup>38</sup>
Recovery rate	$\square$	.33	N/A	Weil 2009 CID <sup>39</sup>
Time first dose is administered (days)	N/A	50	[6, 200]	WHO 2006 <sup>40</sup>
Delay between doses (days)	N/A	14	[2, 24]	Reyburn 2011 PLoS <sup>41</sup>

Under default settings for the model, the cumulative epidemic size following one and two dose campaigns appears similar, while the no dose campaign is simply a horizontal line (this is because epidemic size without vaccination is not dependent on vaccination day) (Figure 5a). Intuitively, when the first dose is administered very early on (before 50 days, or at 25% of the epidemic's duration), we expect the one and two dose curves to be roughly the same because the first dose is sufficient to quench the epidemic. The second dose has very little additional effect, so the curves from both campaigns are almost the same. At 49 days, the difference between the one and two dose campaigns' cumulative epidemic size is 152 cases, or just over 1% of the total potential cumulative epidemic size. Between 49 and 104 days, the difference in the two campaigns is always greater than 1% of the total potential cumulative epidemic size, which we

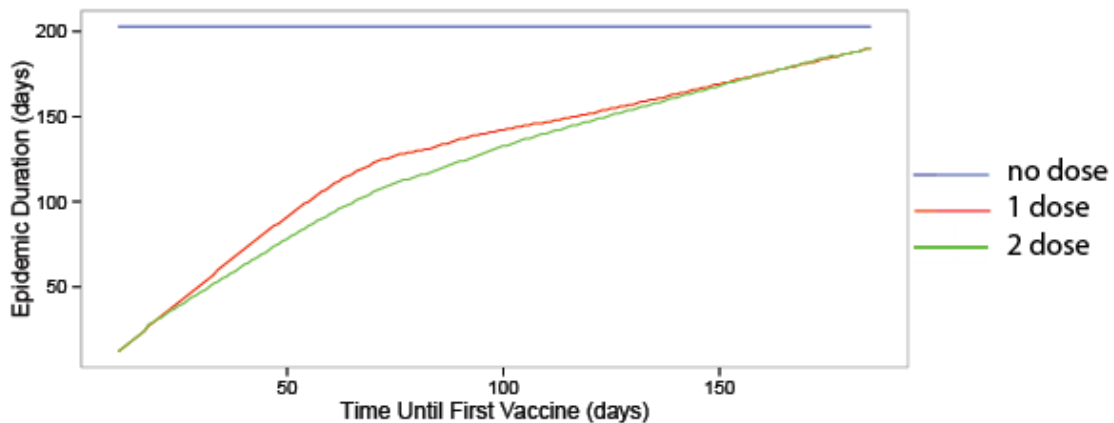
consider to be a significant difference. This is the time where the first dose is administered late enough that it cannot curtail the epidemic and where the second dose is beneficial in reducing cumulative epidemic size. After 104 days, the two curves are once again separated by fewer than 147 cases, partly because the number of cases remaining in the epidemic is so few that vaccination makes little impact.



**Figure 5.** Epidemic size a) Epidemic size across campaign with variable time until first vaccine. Parameters used are those in Table 1 and also include a two week delay between vaccines (where applicable). b) SEIR curve with no vaccination (Exposure curve not shown). c) SEIR curve where vaccination occurs at week 14 (day 96).

In an unvaccinated epidemic lasting 28 weeks and with 14571 infections, about 50% of the infections (7128 infections) occur before the 14<sup>th</sup> week. If the first dose of a 2 dose vaccine campaign is administered just before the beginning of week 14, only an additional 1909 cases occur after vaccination in comparison to the 7443 infections that arise when vaccination does not occur. This can be seen in Figure 5b) and 5c), where the population curves are identical until day 96 (roughly 14 weeks) and then diverge sharply, with Figure 5b) (the unvaccinated epidemic) showing a total recovered population of 14571 persons and Figure 5c) (the 2 dose campaign) showing a total recovered population of 9037 persons.

In addition to epidemic size, it is important to consider epidemic duration when deciding how to allocate vaccines due to the social and economic disruptive nature of epidemics. Epidemic duration dictates the amount of time available for resources to be deployed to the site of outbreak and thus greatly affects the financial burden of the epidemic. Figure 6 shows the epidemic duration increases as the time until vaccination increases.



**Figure 6.** Epidemic duration across campaign with variable time until first vaccine. Vaccine efficacy of dose 1 is set to .65, but otherwise parameters used are those in Table 1 (including a two week delay between vaccines where applicable). Epidemic duration is defined as the time where the total number of infected and exposed persons is less than 1.



The duration of epidemics when no vaccines are deployed is also always longer than the epidemic duration when one or two vaccine doses are deployed. As long as the first dose is allocated before the end of the epidemic, vaccine campaigns shorten the epidemic duration. Epidemics with campaigns using a single dose are at most 17 days (or 17%) longer in duration than epidemics with two-dose campaigns. We find that the difference in epidemic duration when using two dose campaigns compared to one dose campaigns is maximized when the response lag is approximately 30% of the unvaccinated epidemic's duration. This difference becomes less substantial for both shorter and longer response lags. The second dose has the largest reduction in epidemic size compared to that of the first dose when it is applied roughly at the peak of the epidemic (around 75 days in Figure 6). Additionally, we find that the observed difference between one and two dose campaigns is decreased when the delay time between doses is increased and when the protective efficacy of the first dose is increased, though the time at which the maximum difference is observed is qualitatively preserved.

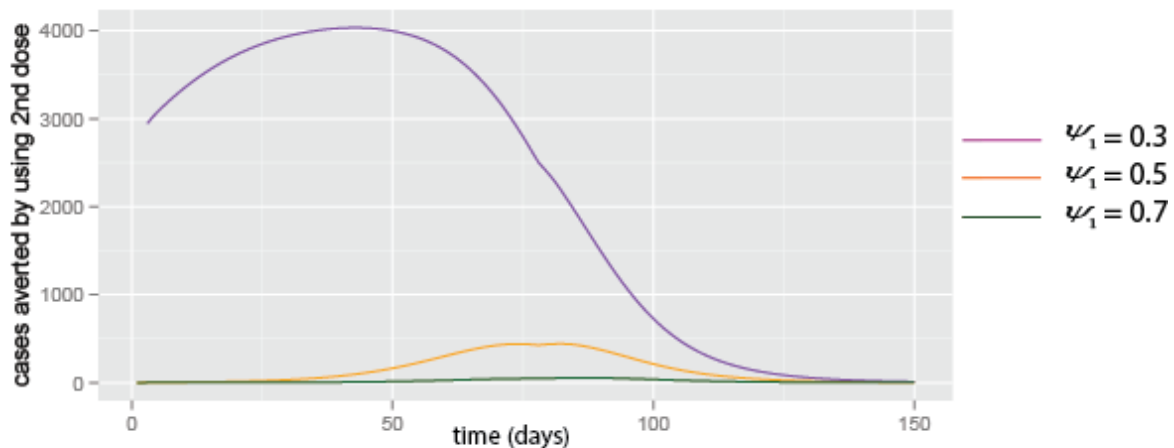
### **Incremental Benefit of a Second Dose**

The WHO is currently faced with the decision of how to allocate their vaccines. If a population is selected to receive aid, then the question becomes: one or two vaccines? In approaching this problem, it is worthwhile to note the incremental benefit of the second dose. That is, how many additional cases are averted when the second dose is applied? The incremental benefit of the second dose is affected by the timing of the first and second doses and the expected efficacy of the first dose.

### **Timing of 1<sup>st</sup> Dose**

As previously discussed, the timing of the first dose heavily influences the cumulative epidemic size and epidemic duration. However, initiation date of the vaccination campaign also

changes the incremental benefit of the second dose is. For example, if the first dose is applied before 30 days and at 90% coverage, the second dose has little incremental value because the first dose may be sufficient to drive the  $R_0$  below 1 and suppress epidemic growth. Conversely, if the vaccine campaign is initiated very late in the epidemic, neither vaccine dose makes very much of an impact on the waning epidemic. In both cases the second dose may not provide sufficient incremental benefits and would be better saved for different population. However, there is a range of deployment times in which the second dose's marginal benefit is large. Depending on the WHO's criteria for deciding when a population is at significant risk of an epidemic, it would be possible to determine how incrementally effective a second dose would be.



**Figure 7.** Cases averted by adding a second dose to the campaign strategy over a variety of first dose vaccine efficacies ( $\psi_1$ ). First dose vaccine efficacies examined are .30, .50, and .70, while second dose vaccine efficacy ( $\psi_2$ ) remains fixed at .85. All other parameters are the same as in Table 1.

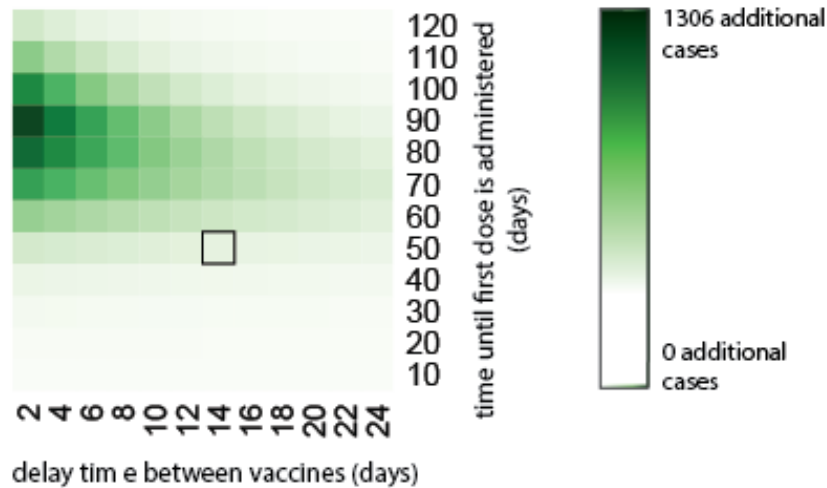
Figure 7 shows the incremental benefit of the second dose with a sensitivity analysis of the vaccine efficacy of the first dose. When the vaccine efficacy is varied, there relative effectiveness of the second dose changes drastically. At the lower first dose vaccine efficacy shown (30%), the maximum incremental benefit of the second dose is nearly 10 times greater than the default 50% protective efficacy of the single dose. When first dose vaccine efficacy is

set to 70%, the maximum number of cases averted by using the second dose is 55 cases, approximately one order of magnitude smaller than the default single dose efficacy of 50%.

Using the default protective efficacy (50%), at least 30% of the potential 440 cases averted are actually averted when the first dose is deployed between 48 and 105 days. To avoid at least 30% of the potential 55 cases when using a protective efficacy of 70%, the first vaccine must be administered between 54 and 110 days, a very similar range. In contrast, to achieve the same 30% avoidance using the low vaccine efficacy (30%), the first dose must be administered before 94 days.

### **Timing of 2<sup>nd</sup> Dose**

The time lag between doses also affects the incremental benefit of the second dose. Due to biological and administrative constraints the second dose is typically administered at least 14 days after the first dose.<sup>23,41</sup> Administrative barriers in certain areas could cause the delay period to be even longer than 14 days, though longer delays have recently been found to generate similar immune responses.<sup>42</sup> To account for these potential changes, we model the effects of second dose's timing on the incremental benefit of the second dose.



**Figure 8.** Incremental benefit of the second dose for various first dose application days and delays between first and second dose. The boxed outcome is that which occurs when parameters in Table 1 are used.

The incremental benefit of the second dose is maximized when the first dose is administered within roughly 90 days of the first case and when the second dose is administered as soon as logistically and biologically feasible (Figure 8). As the delay between doses increases, the incremental benefit of the second dose monotonically decreases. When the first dose is administered 90 days after the first case and the second dose is administered two days later, 1306 cases can be averted by adding a second dose. However, when the delay time is 14 days, 163 cases are averted and when the delay time is 24 days, only 108 cases can be averted. A delay time of 14 days is a reduction in potential cases averted of 50% compared to 24 days. If the delay period between vaccines could be reduced to 10 days instead of the current 14, 193 cases can be averted, an 18% reduction in cases compared to the 14 day delay. As seen in Figure 7, the incremental benefit of the second dose is maximized when vaccination begins near the epidemic peak. Using the default parameters, if the first vaccine is deployed before 50 days, the incremental benefit of the second dose is almost non-existent. This is shown by the very pale

squares at the bottom of the heatmap. Between 50 and 120 days, the incremental benefit of the second dose increases until it peaks around 90 days, then decreases until 120 days, where it again becomes insignificant.

## Discussion

As we begin to discuss our results, it is important to keep in mind the driving question behind our research: in what parameter spaces are one or two dose campaigns effective? OCV campaigns are currently being proposed as supplemental only, but reactive vaccination can still reduce cholera's morbidity in outbreak areas.

Both epidemic duration and epidemic size are highly dependent on the deployment day of the first vaccine. As expected, the sooner the vaccines are deployed, the shorter and smaller the epidemic will be. Effective in-country diagnosis of cholera cases as well as quick responses by the WHO and its affiliates to deploy vaccines also will help reduce this time. However, though early response time is always best, not all reported cases eventually lead to epidemics, meaning that a critical case threshold could be an indication of a population that is prone to an outbreak. Our findings indicate that, assuming the parameters in Table 1 as well as 90% coverage with the first dose and 80% coverage with the second dose, if vaccines reach the outbreak area at latest 50 days after the initial case, 95% of cases can be averted. In the simulated epidemic conditions, this 50 day mark corresponds with approximately one-fourth of the epidemic duration when no vaccines are used. Assuming 10 days between a request for aid from the WHO and actual vaccine arrival, this means that requests for help would need to be sent 40 days after the initial case is observed.

While earlier deployment times in general lead to a greater reduction in the number of cholera cases, the incremental benefit of the second dose does not always increase with earlier deployment time. For the parameters in Table 1 as well as a protective first dose efficacy of 70%, we found the incremental benefit of the second dose is greater than 30% when vaccination

campaigns begin roughly between 50 and 100 days after the first case is observed. Part of this effect is due to the fact that as the time until initial deployment is delayed, more cases occur. Thus the second dose has more cases to avert. However, once deployment time is so late that the epidemic has already taken off (this occurs when deployment is after 100 days), the second dose does little to minimize the impact of the epidemic, simply because there are not enough people that will be aided by the additional protection of the vaccine.

While holding the second doses protective efficacy constant at 85%, we examined the incremental benefit of the second dose at three protective first dose efficacies (30%, 50%, and 70%). Respectively, we observed a maximum of 55, 440, and 4033 cases averted for the three protective first dose efficacies. Though these maxima occur at different days, they are each roughly an order of magnitude apart. Thus we conclude that a reduction in first dose vaccine efficacy of 20% results in a gain in cases averted by second dose on approximately one order of magnitude. More plainly, the weaker the first dose is, the greater the benefit of the second dose. Though the incremental benefit of the second dose varies with the administration of the first dose, at default settings, the maximum number of cases averted is 440 cases. This is a mere 3% of the unvaccinated epidemic size of 14571 cases. While those 440 lives are absolutely worth saving, it is important to consider whether averting 3% of cases merits the introduction of a second dose.

Finally, delay time until first vaccine deployment is critical and changeable, but delay time for the second vaccine is also important. While not currently alterable, shorter delay times can greatly reduce the cumulative epidemic size. Assuming that the first dose administration is at 90 days, creation of OCVs that are capable of being administered a second time 10 days after the first dose will lead to a 44% increase in cases averted over the current delay time of 14 days.

## **Conclusion**

In this paper, the parameter space for deployment of one or two dose reactive OCV campaigns was examined. As the parameter space spans a very large range of values, it is impossible to make a bold declaration stating that one dose campaigns are more effective than two dose campaigns. Instead, we identify here qualitative relationships that are preserved in a range of plausible parameters. We find the incremental benefit of the second dose is limited when vaccination is performed very early, very late, and as the delay between vaccine doses increases. Depending on the cost of vaccines and the value placed on reducing the number of cholera infections, there are situations in which a second dose of OCV would be worthwhile. As outbreaks are reported to the WHO, the results in this paper will help inform officials which campaign strategy – one or two dose – is most effective.



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