Supplemental information for:

“Using private demand studies to calculate socially-optimal vaccine subsidies in developing countries”

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1. Cholera

Cholera is a water-borne bacterial disease characterized by intense, watery diarrhea. It is easily treated by quickly re-hydrating the patient with intravenous fluids; antibiotics are generally unnecessary and ineffective (Schaecter et al. 1998; Todar 2006). Cholera can kill a patient within 24-48 hours, though in practice cases are rarely fatal as long as patients have access to IV rehydration (CFR estimates are on the order of 1% with adequate access to treatment ¹). Since Vibrio cholerae lives in estuarine waters and has hosts besides humans, it is impossible to completely eradicate cholera. Once the bacteria crosses from the aquatic environment into an index human case, it may spread rapidly only where water and sanitation conditions are poor. Large population centers near estuaries with poor sanitation often have cholera endemically, with cases occurring nearly every year and where a large fraction of the population has acquired some immunity through prior infection (examples include Kolkata (Calcutta), India; Matlab, Bangladesh; and Beira, Mozambique). “Epidemic” numbers of cases can occur where the population has no acquired immunity (i.e. refugee camps or after natural disasters) and where an index case passes into very poor water and sanitation conditions. For the purposes of this paper, we will focus on endemic cholera, where cases occur nearly every year.

One approach to controlling endemic cholera is the use of oral cholera vaccines (OCVs). These vaccines have mainly been used in trials of effectiveness and to limit the spread of large outbreaks (Clemens et al. 1986; Clemens et al. 1990; Naficy et al. 1998; Calain et al. 2004; Lucas et al. 2005, WHO 2006). Dukoral is a two-dose oral recombinant B-subunit (WC/rBS) vaccine evaluated in a series of case-control studies in Bangladesh, Peru and Mozambique. Field trials in Bangladesh and Peru indicated 85-90 percent protection for 6 months followed by declining effectiveness to about 50 percent over three

¹ According to the WHO’s monitoring of cholera cases (WHO 2006), there were 131,943 cholera cases worldwide and 2,272 deaths, for a gross worldwide case fatality rate of 1.7%. Worldwide CFR from same source is 2.3%. This average, however, reflects wide differences in access to treatment: Naficy et al (1998) use a CFR of 1% for treated cases but 30% for untreated cases. CFRs may also differ by age: Murray et al (1998) use 0.7% for children under five years old but a much lower CFR (0.14%) for children over five and adults.
years (Clemens et al. 1986; Clemens et al. 1990); in Mozambique, effectiveness over the first year was 78 percent (Lucas et al. 2005). A less-expensive variant of the vaccine (without the subunit) is now produced in Vietnam by VaBioTech and has been shown to be effective in trials in Son La, Vietnam and Kolkata, India Institute 2007. A technology-sharing agreement between VaBioTech and Shanta Biotechnic of Hyderabad, India is near completion, so that the vaccine should be available to the Indian market soon Institute 2007.

2. Estimating indirect protection effects of cholera vaccines from evidence in Matlab, Bangladesh

Placebo-control trials are the gold standard in epidemiology because they eliminate problems such as yearly variation in incidence and potential differences between those who choose to be vaccinated and those who do not. However, by ignoring herd protection effects for placebo recipients, these studies may underestimate the vaccine program’s community-level risk reduction relative to results from non-placebo controlled campaigns (Trach et al. 1997; Lucas et al. 2005; Thiem 2006). There has therefore been interest recently in re-examining evidence from placebo-control trials based on new techniques for estimating direct as well as indirect effects (Haber 1999).

One such re-examination was performed on data from a 1985 cholera vaccine trial in Matlab, Bangladesh (Clemens et al. 1986, Ali et al. 2005). The trials targeted all children between the ages of 2 and 15 as well as women older than 15 years. Vaccine coverage varied significantly within neighborhoods called baris, from 28% to over 51% of the target population (Table A1), or 15% to 37% of the overall population in the bari. This variation allowed the authors to test for herd protection effects. They found an inverse monotonic relationship between the coverage rate and the incidence rate in a bari, such that incidence among placebo recipients declined as coverage increased (leftmost column of Table A1). This inverse relationship was also observed for children less than two years of age who were not eligible for vaccination (Ali et al. 2007). Herd protection effects are especially important for children less than one year of age because the existing vaccine is not considered safe for that age group and because their cholera incidence and diarrhea mortality rates are especially high ((ICDDB) 2005). Ali et al. also found evidence of borderline significance that incidence declined among vaccinated individuals as vaccine coverage increased.

<table>
<thead>
<tr>
<th>Level of coverage(^a)</th>
<th>Vaccine recipients</th>
<th></th>
<th>Placebo recipients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Target Population</td>
<td>N</td>
<td>Cases</td>
<td>Incidence (per 1,000)</td>
</tr>
<tr>
<td>&lt;28%</td>
<td>24,954</td>
<td>5,627</td>
<td>15</td>
<td>2.67</td>
</tr>
<tr>
<td>28-35%</td>
<td>25,059</td>
<td>8,883</td>
<td>22</td>
<td>2.48</td>
</tr>
<tr>
<td>36-40%</td>
<td>24,583</td>
<td>10,772</td>
<td>17</td>
<td>1.58</td>
</tr>
<tr>
<td>41-50%</td>
<td>24,159</td>
<td>11,513</td>
<td>26</td>
<td>2.26</td>
</tr>
<tr>
<td>&gt;51%</td>
<td>22,394</td>
<td>12,541</td>
<td>16</td>
<td>1.28</td>
</tr>
<tr>
<td>Total</td>
<td>121,149</td>
<td>49,336</td>
<td>96</td>
<td>1.95</td>
</tr>
</tbody>
</table>

\(^a\) Percent coverage is defined as the fraction of the target population (women and children) who were vaccinated, not the fraction of the entire population (which would include men). The 1986 trial targeted 124,000 people from a total population of 188,000 (i.e. 66%).

We now turn to modeling the data in Table A1. Let \(u(x)\) = cholera incidence at any coverage \(x\) for unvaccinated persons, and \(v(x)\) = cholera incidence at coverage \(x\) for vaccinated persons. We define coverage here over the entire population of the study area, not only the target population (which was 66% of the whole population). For vaccinated persons, \(d[v(x)]/dx\) is the change in incidence per unit change in vaccination coverage \(x\). One approach for explaining this change is to assume that it is proportional to the incidence for vaccinated persons at coverage \(x\); i.e. when the incidence in vaccinated persons is high, the change in incidence per unit change in coverage is correspondingly high. Thus we have \(dv/\ dx \sim v\), which yields

\[
dv/\ dx = -kv \cdot v
\]

where \(kv\) = proportionality (rate) constant for vaccinated persons, with the same units as \(x\). The negative sign indicates that incidence decreases as coverage increases, which is evident from the data in Table A1.

The assumed model for unvaccinated persons is similar but with a slight difference. We assume that it is not \(u(x)\), the entire amount of cholera incidence among unvaccinated persons, that is subject to reduction due to herd immunity but only part, or \((u – v)\). This assumption simply means that the incidence among the unvaccinated can never be lower than the incidence among the vaccinated; it is limited by \(v(x)\). Hence, \(d[(u – v)]/dx\) is the change in the amount of incidence among the unvaccinated that is subject to change due to herd immunity per unit change in coverage, which is assumed to be proportional to \((u – v)\). The corresponding differential eq for unvaccinated persons is

\[
d[(u – v)]/dx = -ku \cdot (u – v)
\]
where \( ku \) = proportionality (rate) constant for unvaccinated persons. As before, the negative sign indicates that the change in incidence decreases as coverage increases.

Eqs. 1 and 2 constitute the set of differential equations that we assume represent the phenomenon of herd immunity. These equations must be solved simultaneously because \( v \), the incidence for vaccinated persons, appears in both of them. However, they can be integrated sequentially starting with Eq. 1 because it contains only \( v \) and not \( u \). The integral of Eq. 1 is

\[
v(x) = v_o \exp(-kv \cdot x)
\]

(3)

where \( v_o \), the boundary condition, is the cholera incidence in vaccinated persons when vaccination coverage is zero, e.g. when only one or a few people in the community are vaccinated. Inserting Eq. 3 for \( v \) into Eq. 2 yields the non-homogeneous differential equation in Eq. 4, which can be integrated using the integrating factor method; the result is in Eq. 5, where \( u_o = \) the incidence among unvaccinated persons and \( ku = \) the rate constant for unvaccinated persons.

\[
du/dx + ku \cdot u = v_o \cdot (ku - kv) \cdot \exp(-kv \cdot x)
\]

(4)

\[
u(x) = v_o \cdot \exp(-kv \cdot x) + (u_o - g_o) \cdot \exp(-ku \cdot x)
\]

(5)

The parameters for Eq. 3 can be estimated with a simple OLS regression of each quintile’s percent coverage of the entire population on the log of incidence rates among the vaccinated. The intercept in this regression model (\( v_o \)) is 4.5 cases per 1000 (\( p = 0.03 \)) and the rate constant (\( kv \)) is -0.029 (\( p = 0.10 \)). The \( R^2 \) for the regression is 0.65. With the estimated parameters for Eq. 3 in hand, we then estimate the parameters of Eq. 5 with a simple non-linear least squares model. The \( R^2 \) for this model is 0.97 and the intercept (\( u_o \)) is significant at the 10% level (\( p = 0.07 \)), but the rate constant (\( ku \)) has a \( p \)-value of 0.15. Rewriting Eqs. 3 and 5 with these estimated parameters gives:

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1 We take the average number of vaccinated people in each quintile by dividing the total number of vaccinees by the total number of eligible people (Table 1). We then adjust this to reflect the percent coverage for the entire population, assuming that the target population is 66% of the entire population. For example, in the first quintile in Table 4.5, 5,627 people were vaccinated from the eligible population of 24,494 (23%). This represents a total population coverage rate of 15% (23% * 0.66). We also fit a model using midpoints of the coverage quintiles but we preferred this approach because it fit the results from Longini et al (2007) better.
\[ v(x) = 4.5 \cdot \exp(-0.03 \cdot x) \]  \hspace{1cm} (6) \\
\[ u(x) = 4.5 \cdot \exp(-0.03 \cdot x) + (13.6 - 4.5) \cdot \exp(-0.047 \cdot x) \]  \hspace{1cm} (7) 

Figure A1 plots the observed Matlab data against these exponential fits. As coverage increases, the incidence for unvaccinated individuals approaches that for the vaccinated subgroup. As coverage increases from 0 to 100%, the expected annual incidence for the vaccinated subgroup decreases from 4.5 cases per 1,000 persons to near zero cases, while the expected incidence for the unvaccinated subgroup similarly declines from 13.6 cases per 1,000 persons to near zero.

**Figure A1.** Observed incidences in Matlab vs. predictions from exponential fit

Using these exponential functions of incidence as a function of coverage, we can calculate the percentage reduction in incidence for vaccine recipients compared to a baseline of zero coverage (i.e. \( u(0) = u_0 = 10 \) cases per 1,000 persons) with Eq. 8. The percentage reduction in incidence among the unvaccinated is calculated similarly, in Eq. 9.

\[ V(x) = \frac{U_0 - V(x)}{U_0} = 1 - \frac{V_0}{U_0} \exp(kv \cdot x) \]  \hspace{1cm} (8)
\[ U(x) = \frac{U_0 - U(x)}{U_0} = \left[ 1 - \frac{V_0}{U_0} \exp(kv \cdot x) \right] - \left[ 1 - \frac{V_0}{U_0} \exp(ku \cdot x) \right] \] (9)

Figure A2 plots percent reduction in incidence (i.e. the probability of protection) for both vaccinated and unvaccinated individuals in the population using Eqs 8 and 9 (see also Figure 5 in main paper). Note that when coverage is near zero, the vaccine reduces incidence by about 67% (13.6 to 4.5). Thus, the inferred vaccine protection in the absence of herd protection would be about 65%, somewhat higher than the 50% protection level originally reported for the Matlab trial (Clemens et al. 1990).

As shown in Figure A2, the marginal change in effectiveness (or probability of protection) resulting from taking the vaccine is dependent on coverage. At low coverage, there is a greater private incentive to be vaccinated because the marginal increase in protection is large. At high coverage rates, though, more of the total protection derives from the indirect effects of herd protection, and the additional protection from taking a vaccine is small. Thus, from a social perspective, the marginal benefit per vaccine distributed decreases monotonically based on our functional forms in Eqs. 1 - 9 (this is shown in Figure A2 as dashed vertical lines showing the marginal benefits of distributing more vaccines at coverage rates of 10%, 30% and 60%). Intuitively, the socially efficient outcome will equate this marginal benefit with the marginal cost of producing the vaccine, which may occur at some coverage rate between 0 and 100%.

**Figure A2.** Effective protection for vaccinated and unvaccinated individuals.
3. **Optimality conditions for social benefits**

**No indirect protection**

For the case in which there is no herd protection, without loss of generality, we rewrite \( q = NP(p) = Naexp(\beta p) \), and the optimization problem is simply:

\[
\text{Maximize } NB_{NP(p)=q} = p \cdot q - c \cdot q
\]

(10)

The first order condition (B2) which gives maximum net benefits can then be written and solved:

\[
\frac{dNB}{dp} = 0 = p^* - c \quad \Rightarrow \quad p^* = c
\]

(11)

In this case, net benefits are maximized when the price (or marginal private benefit WTP) is set equal to the marginal cost of vaccination. This is the familiar market equilibrium.

**Social Net Benefits with indirect protection**

We next add the various components of social benefits (see Eq. 5-8 in main text) for the vaccinated and the unvaccinated due to herd protection effects. As above we write \( q = NP(p) \), and redefine \( V(q/N) = V(P(p)) \):

\[
\text{Maximize } NB_q = p \cdot q + \sum_{t=1}^{Durr} \left[ \text{PubCOI} \cdot \left\{ CA_{vacc} + CA_{unvacc} \right\} \\
+ \text{PrivCOI} \cdot \left\{ CA_{vacc,herd} + CA_{unvacc} \right\} \\
+ VSL \cdot CFR \cdot \left\{ CA_{vacc,herd} + CA_{unvacc} \right\} \right] (1 + r)^{-t} - c \cdot q
\]

\[= p \cdot q + \sum_{t=1}^{Durr} \left( \text{Inc} \cdot \text{PubCOI} \cdot \left\{ V(q/N) - U(q/N) \right\} \cdot q + U(q/N) \right) (1 + r)^{-t} \]

\[+ \sum_{t=1}^{Durr} \left( \text{Inc} \cdot \text{PrivCOI} \cdot \left[ U(q/N) - U(q/N) \cdot q \right] \right) (1 + r)^{-t} \]

\[+ \sum_{t=1}^{Durr} \left( \text{Inc} \cdot VSL \cdot CFR \cdot \left[ U(q/N) - U(q/N) \cdot q \right] \right) (1 + r)^{-t} \]

\[+ \sum_{t=1}^{Durr} \left( \text{Inc} \cdot \left[ \text{PrivCOI} + VSL \cdot CFR \cdot \left[ V(q/N) - Ef \cdot q \right] \right] \right) (1 + r)^{-t} - c \cdot q. \]

(12)
The optimal solution is now:

\[
\begin{align*}
p^* = c - \sum_{t=1}^{DUR} & \left[ \frac{\left( Inc \cdot \left[ PubCOI \cdot \left( V'(q / N) + V'(q / N) \cdot (q / N) \right) \right] \right)}{(1 + r)^{t-1}} - \frac{\left( Inc \cdot \left( PrivCOI + VSL \cdot CFR \right) \cdot \left( V'(q / N) - Ef \right) + V'(q / N) \cdot (q / N) \right)}{(1 + r)^{t-1}} \\
& - \frac{\left( Inc \cdot \left( PubCOI + PrivCOI + VSL \cdot CFR \right) \cdot \left( V'(q / N) \cdot (q - q) / (N - U(q / N)) \right) \right)}{(1 + r)^{t-1}} \right] \\
= c - \sum_{t=1}^{DUR} \left( mb_{pubCOI,vacc} + mb_{privCOI,vacc,herd} + mb_{VSL,vacc,herd} \right) \left( mb_{pubCOI,unvacc} + mb_{privCOI,unvacc} + mb_{VSL,unvacc} \right) (1 + r)^{t-1}, \tag{13}\end{align*}
\]

4. Value of a statistical life calculations

Some readers may be puzzled why we use VSL estimates from two other studies in India and Bangladesh when we could theoretically calculate a VSL from our WTP estimates. For example, we found median WTP for adults in Tiljala was \(~\text{US$2.1}\) (after adjusting for time to think). If adult incidence is 0.9 cases per 1000 in Tiljala, and the case fatality rate is 1%, then an adult has a \(9 \times 10^{-6}\) chance of dying from cholera each year, or a \(2.7 \times 10^{-5}\). Dividing median WTP by this risk reduction gives a VSL of \$77,800. This estimate is in the range \($30k - $100k\) found by Maskery et al (2008) and Bhattacharya et al (2007). There are, however, problems with this calculation. First, respondents may value other elements of the risk reduction besides its effect on mortality risk (in particular, avoided private cost of illness), so that the VSL is overestimated. More importantly, respondents were never given either their baseline risk of contracting cholera or the case fatality rate. This was partly because this is very difficult, probabilistic information to convey in a setting with low levels of education, and partly because it would be ethically problematic to provide respondents with values that are in fact not known with much certainty (the disease surveillance study was still ongoing during the time of our fieldwork).

For these reasons we prefer to use the midpoint of the Bhattacharya and Maskery VSL studies.
References


