Incorporating geographic context into intervention evaluation: cholera and malaria vaccine trials

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and a whole bunch of other people listed on last slide

Bangladesh cholera hospital  Malawi malaria trial site
Motivation

- Ecological vaccine trials
  - Spatial factors may contribute to non-uniform distribution of disease/infection risk across a target population (Ali et al., 2005 Lancet; Emch et al., 2007 H&P)
  - Environmental factors (built, social, biophysical) can contribute to heterogeneity of infection risk (Emch et al., 2009 SSM; Root et al., 2011 PLoS One)

- Integration of spatial factors and environmental characteristics can be used to determine how vaccine efficacy is modified by geographic context
Malaria Vaccine Trial (GSK RTS,S)
# Efficacy of RTS,S in phase II trials: Efficacy and Transmission Vary by Trial Site

<table>
<thead>
<tr>
<th>Study site</th>
<th>Age group</th>
<th>Efficacy</th>
<th>Follow-up</th>
<th>Adjuvant</th>
<th>Transmission intensity †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya</td>
<td>5-17 mos</td>
<td>45.8%</td>
<td>15 mos</td>
<td>AS01E</td>
<td>22-53 EIR</td>
</tr>
<tr>
<td>Tanzania</td>
<td>5-17 mos</td>
<td>39.0%</td>
<td>12 mos</td>
<td>AS01E</td>
<td>30-100 EIR</td>
</tr>
<tr>
<td>Mozambique</td>
<td>1-4 yrs</td>
<td>35.3%</td>
<td>21 mos</td>
<td>AS02A</td>
<td>38 EIR</td>
</tr>
<tr>
<td>The Gambia</td>
<td>18-45 yrs</td>
<td>35.0%</td>
<td>9 wks*</td>
<td>AS02</td>
<td>1-50 EIR</td>
</tr>
</tbody>
</table>
Does the RTS,S vaccine work?
Phase III trial results

• In kids vaccinated at 5-17 months of age it reduces malaria by 46% and in babies vaccinated at 6-12 weeks of age it reduced malaria by 27%.

• However, this is for 11 sites in 7 countries in Africa and it might work better in some places than others which is what we are studying now in Malawi.

• It is not effective enough by itself so other interventions especially bed nets will need to be used in conjunction with the vaccine.
Conceptual framework of effect modifiers on malaria vaccine efficacy
Contracting malaria

- Mosquitos bite at dusk and night
- Most houses in Africa don’t keep mosquitoes out
- People often fetch water at dusk
- Anopheles habitat: wet, muddy areas
- Reservoir: many people living in area with malaria
Ecological variables

- Age
- Sex
- ITN use by each family member
- Malaria in household member
- Household insecticide spraying
- Travel destination malaria prevalence for household members
- Proximity of stagnant water from house
- Vegetation and type near house
- Household wall materials
- Window presence and materials
- Roof materials
- Holes in house
- Malaria transmission intensity
- Population density near house
Household and Neighborhood Ecology
Human Interaction with Anopheles mosquito habitat
ITNs are Main Intervention
Household distribution by study arm overlaid on satellite image

**Treatment**
- RTS,S vaccine
- RTS,S vaccine and booster
- Placebo
Malaria prevalence, bed net use, and wealth by year

<table>
<thead>
<tr>
<th>Malaria prevalence by age group, $n$ (%)</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 years</td>
<td>46 (12.5)</td>
<td>25 (6.3)</td>
<td>14 (3.5)</td>
</tr>
<tr>
<td>5-19 years</td>
<td>38 (19.0)</td>
<td>30 (15.0)</td>
<td>16 (8.0)</td>
</tr>
<tr>
<td>&gt;20 years</td>
<td>19 (9.5)</td>
<td>9 (4.5)</td>
<td>15 (7.5)</td>
</tr>
<tr>
<td>All age groups</td>
<td>103 (12.9)</td>
<td>64 (8.0)</td>
<td>45 (5.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individual bed net use by age group, $n$ (%)</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 years</td>
<td>232 (58.0)</td>
<td>254 (63.5)</td>
<td>330 (82.5)</td>
</tr>
<tr>
<td>5 to 19 years</td>
<td>86 (43.0)</td>
<td>90 (45.0)</td>
<td>140 (70.0)</td>
</tr>
<tr>
<td>&gt;20 years</td>
<td>112 (56.0)</td>
<td>129 (64.5)</td>
<td>159 (79.5)</td>
</tr>
<tr>
<td>All age groups</td>
<td>430 (53.8)</td>
<td>473 (59.1)</td>
<td>629 (78.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Household wealth index, $n$ (%)</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>335 (41.9)</td>
<td>346 (43.3)</td>
<td>296 (37.0)</td>
</tr>
<tr>
<td>Medium</td>
<td>368 (46.0)</td>
<td>346 (43.3)</td>
<td>360 (45.0)</td>
</tr>
<tr>
<td>High</td>
<td>97 (12.1)</td>
<td>108 (13.5)</td>
<td>144 (18.0)</td>
</tr>
</tbody>
</table>
Within-site variation of bed net use and malaria prevalence

Bed Net Use

2011: 53.8%
2012: 59.1%
2013: 78.6%

Malaria Prevalence

2011: 12.9%
2012: 8.0%
2013: 5.6%
The figure suggests that *csp* strains in Lilongwe are clustered in several major groups.
### Distribution of HLA Class II alleles in Malawian women

<table>
<thead>
<tr>
<th>Supertype</th>
<th>Frequency Allele 1</th>
<th>%</th>
<th>Frequency Allele 2</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR1</td>
<td>13</td>
<td>11.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DR3</td>
<td>24</td>
<td>20.5</td>
<td>8</td>
<td>7.7</td>
</tr>
<tr>
<td>DR4</td>
<td>3</td>
<td>2.6</td>
<td>3</td>
<td>2.9</td>
</tr>
<tr>
<td>DR7</td>
<td>5</td>
<td>4.4</td>
<td>15</td>
<td>14.4</td>
</tr>
<tr>
<td>DR8</td>
<td></td>
<td></td>
<td>10</td>
<td>9.6</td>
</tr>
<tr>
<td>DR9</td>
<td></td>
<td></td>
<td>8</td>
<td>7.7</td>
</tr>
<tr>
<td>DR10</td>
<td></td>
<td></td>
<td>12</td>
<td>11.5</td>
</tr>
<tr>
<td>DR11</td>
<td>27</td>
<td>23.1</td>
<td>15</td>
<td>14.4</td>
</tr>
<tr>
<td>DR12</td>
<td>5</td>
<td>4.3</td>
<td>6</td>
<td>5.8</td>
</tr>
<tr>
<td>DR13</td>
<td>5</td>
<td>4.3</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>DR15</td>
<td>35</td>
<td>29.9</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>117</strong></td>
<td><strong>100</strong></td>
<td><strong>104</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>
Cholera Background

*Vibrio cholerae*: curved gram-negative rods with a polar flagellum

Cholera toxin

Watery diarrhea

Dehydration

If untreated ~50% case fatality rate, if treated ~1%
Cholera Vaccine Trial

- Vaccine trial conducted through the International Centre for Diarrhoel Disease Research, Bangladesh (ICDDR,B) starting in 1985

- All children (2-15 yrs old) and women (> 15 yrs old) randomly assigned to one of three treatment assignments: 2 different vaccine treatments (B subunit-killed whole-cell and killed whole-cell-only oral cholera vaccines) and 1 placebo group.

- Two vaccine doses were given to 50,499 people and two placebo doses were given to 25,252 in the target group in six-week intervals.

- ~50% efficacy
Bangladesh Study Area

ICDDR,B

142 villages

Longitudinal DSS since 1966

CHWs conduct health surveillance

Diarrhea hospital & laboratory

Best cholera time series in the world

Bangladesh (Top) and the study area superimposed on a satellite image (bottom)
Research Questions

Does the oral cholera vaccine provide an indirect effect (i.e., is there herd protection)? Does neighborhood vaccination proportion affect disease incidence?

Is the answer different when defining neighborhoods by Euclidean distance, environmental connectivity, and social connectivity?
Oral cholera vaccine coverage
Protective efficacy is the proportionate reduction of the incidence of the target infection by vaccination.

\[ \alpha_i = (1 - \frac{\vartheta_i}{\lambda_i}) \times 100 \]

\( \alpha_i \) = protective efficacy in neighborhood \( i \)

\( \vartheta_i \) = vaccinee incidence rate in neighborhood \( i \)

\( \lambda_i \) = nonvaccinee incidence rate in neighborhood \( i \)

<table>
<thead>
<tr>
<th>Identification Number</th>
<th>Vaccinee Population</th>
<th>Placebo Population</th>
<th>Vaccinee Disease Cases</th>
<th>Placebo Disease Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>7</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>22</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>32</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>25</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>45</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>23</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>34</td>
<td>25</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>204</td>
<td>230</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

Vaccinee Incidence: 0.0098
Placebo Incidence: 0.022
Efficacy: 0.55
Herd Protection

- Herd protection is protection of an individual from a disease because others are immune to the disease.

- This is called herd protection because non-immunized people in the population are protected since most people in the population, i.e., the herd, are protected.
Cholera incidence rate and protective efficacy (PE) among ≥2 dose recipients by the level of cholera vaccine coverage

<table>
<thead>
<tr>
<th>Level of vaccine coverage#</th>
<th>All recipients of ≥2 doses</th>
<th>Vaccinees</th>
<th>Placebo recipients</th>
<th>PE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% of total</td>
<td>N</td>
<td>Cases</td>
</tr>
<tr>
<td>&lt;28%</td>
<td>8,479</td>
<td>11.5</td>
<td>5,627</td>
<td>15</td>
</tr>
<tr>
<td>28-35%</td>
<td>13,312</td>
<td>18.0</td>
<td>8,883</td>
<td>22</td>
</tr>
<tr>
<td>36-40%</td>
<td>16,275</td>
<td>22.0</td>
<td>10,772</td>
<td>17</td>
</tr>
<tr>
<td>41-50%</td>
<td>17,314</td>
<td>23.4</td>
<td>11,513</td>
<td>26</td>
</tr>
<tr>
<td>51%+</td>
<td>18,623</td>
<td>25.1</td>
<td>12,541</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>74,003</td>
<td>100</td>
<td>49,336</td>
<td>96</td>
</tr>
</tbody>
</table>

‡Spearman’s rank P=0.02  § Spearman’s rank P=0.08 * P<.01 † P<.001

Note 1: A multivariate model (generalized estimating equations with logit link function) controlled for the potential confounding variables (age, gender, river distance, treatment center distance, dysentery).

Note 2: There was not an inverse relationship between dysentery incidence and coverage (Spearman’s rank -.3-, p=0.62).

Are young children who can’t be vaccinated also protected?

- Killed oral cholera vaccines are not licensed for infants and young children.

- Cholera is known to be an important problem in these younger age groups.

- We investigated whether older children and adults can confer herd protection to children too young to be vaccinated by determining whether the incidence was lower with higher coverage during the first year of surveillance.

Incidence of cholera among children too young to be vaccinated* by level of vaccine coverage

<table>
<thead>
<tr>
<th>Level of vaccine coverage†</th>
<th>Total no. of children&lt;24 mos</th>
<th>Cases</th>
<th>Risk/1,000‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28%</td>
<td>2,378</td>
<td>45</td>
<td>18.92</td>
</tr>
<tr>
<td>28-35%</td>
<td>2,371</td>
<td>27</td>
<td>11.38</td>
</tr>
<tr>
<td>36-40%</td>
<td>2,297</td>
<td>36</td>
<td>15.67</td>
</tr>
<tr>
<td>41-50%</td>
<td>2,207</td>
<td>29</td>
<td>13.14</td>
</tr>
<tr>
<td>51%+</td>
<td>2,205</td>
<td>19</td>
<td>8.61</td>
</tr>
<tr>
<td>Total</td>
<td>11,458</td>
<td>156</td>
<td>13.61</td>
</tr>
</tbody>
</table>

•Defined as children <24 months of age at the time of dosing in the trial
† Within 500 meters of bari
‡ P= .004 for trend.
### Predictors of the risk of cholera among children too young to be vaccinated* during one year of follow-up in the Bangladesh cholera vaccine trial

<table>
<thead>
<tr>
<th>Factors</th>
<th>Model 1 †</th>
<th>Model 2 §</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95%CI</td>
</tr>
<tr>
<td>Age (in years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.46</td>
<td>1.10-1.92</td>
</tr>
<tr>
<td>Male</td>
<td>1.11</td>
<td>0.81-1.53</td>
</tr>
<tr>
<td>Muslim</td>
<td>1.10</td>
<td>0.67-1.82</td>
</tr>
<tr>
<td>Distance of the child’s residence to nearest river (km)</td>
<td>1.06</td>
<td>0.89-1.26</td>
</tr>
<tr>
<td>Distance of the child’s residence to nearest treatment center (km)</td>
<td>1.02</td>
<td>0.93-1.13</td>
</tr>
<tr>
<td>Experienced dysentery during follow-up</td>
<td>4.19</td>
<td>2.00-8.74</td>
</tr>
<tr>
<td>Overall vaccine coverage of the child’s bari</td>
<td>0.98*</td>
<td>0.96-0.99</td>
</tr>
<tr>
<td>Vaccine coverage of women &gt;15yrs in the child’s bari</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vaccine coverage of children aged 2-15 yrs in the child’s bari</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Defined as children <24 months of age at the time of dosing in the trial
† Multivariate odds ratio for the cited variable, adjusted for all other variables in the table, in a model using Generalized Estimating Equations (GEE) with the logit link function.
‡ In Model 1, the level of coverage is based on all persons eligible for vaccination
§ In Model 2, the level of coverage is expressed separately for adult women (>15y) and for children (2-15y)
Spatial and Environmental Risk Factors

  - Addressed how environmental networks could influence risk of cholera infection among placebo recipients.
  - Digitized ponds using Quickbird satellite imagery to define pond networks.
  - Defined vaccine coverage at the *bari*-level as proportion of vaccinated individuals that were connected by shared ponds.
  - Found that the risk of cholera among placebo recipients declined as vaccine coverage within pond networks increased.
Social Network analysis in oral cholera vaccine evaluation

  - Addressed how vaccine coverage within *bari*-level and household-level kinship networks were associated with cholera incidence among placebo recipients
  - Risk of cholera inversely related to level of vaccine coverage in *bari*-level social networks
After running a Bayesian variable selection procedure on main effects and interaction terms and vaccine coverage were found to be important to predicting cholera incidence.

Areas with higher levels of vaccine coverage had lower levels of average predicted incidence.

Areas with lower levels of vaccine coverage had higher levels of average predicted incidence.

Implications for policy

- The oral cholera vaccine confers indirect herd protection.
- It works better than we thought.
- We wouldn’t know this if we hadn’t incorporated space into the study.
- WHO stockpiling oral cholera vaccine; PAHO developed post-epidemic Haiti vaccination program considering herd protection.
Contributors (abridged version)

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PATH
The Spatial Health Research Group at the University of North Carolina at Chapel Hill is led by Dr. Michael Emch. Research activities focus on exploring spatio-temporal patterns of disease, primarily infectious diseases of the developing world. Disease patterns are studied using a holistic approach by investigating the role of social, natural, and built environments in disease occurrence in different places and populations. Diverse statistical and spatial analytical methods are informed by theory from the fields of medical geography, epidemiology, ecology, and others. These theories and methods are used to examine topics such as how social connectivity contributes to disease incidence, the role of population–environment drivers in viral evolution, and using environmental indicators to predict disease outbreaks.