Herd Protective Effects of Vaccines

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Promising Vaccine Candidate

Phase I. Safe and Immunogenic in Healthy Adults?
- Yes
- No

Phase II. Safe and Immunogenic in the Target Population?
- Yes
- No

Phase III. Safe and Protective in the Target Population?
- Yes
- No

Introduce Into Public Health Practice

Phase IV. Suitably Safe and Protective in Practice?
- Yes
- No
Strengths of Pre-licensure Randomized Trials

- Ethical propriety
- Protection against bias
- Statistically meaningful estimates
- Clear definitions of study populations, regimens, outcomes
Common Uncertainties about Vaccine Effectiveness after Phase 3 Trials

- Acceptability to communities, providers, and policymakers?
- Ease of incorporation into public health programs?
- Affordability?
- Impact?
  - In a wide spectrum of recipients
  - Under routine conditions
  - Against all clinical outcomes of practical importance
  - Including both direct and herd vaccine effects
Herd Protective Effects of Vaccines

- Are demonstrated by a protective impact of a vaccine in a population that exceeds the impact expected on the basis of:
  1. The proportion of the population vaccinated
  2. The direct vaccine protection of vaccinees
- These are population-level effects, resulting from protection of non-vaccinees or enhanced protection of vaccinees or both
Herd Protective Effects of Vaccines

- Can result from:
  1. Transmission of a live vaccine from vaccinee to neighboring non-vaccinee
     * OPV
Herd Protective Effects of Vaccines

• Can result from:

2. Passive transfer of vaccine-induced immunity from one person to another

* Maternal immunization (tetanus toxoid, influenza vaccine, pertussis vaccine)
Herd Protective Effects of Vaccines

• Can result from:

3. Reduction of transmission of the target pathogen in a population in which a proportion become immune due to vaccination ("herd protection").

  -- Can occur with either live or inactivated vaccines

  -- Applies only to pathogens transmitted from person to person.
Average annual notification rates of hepatitis A in north Queensland before and after implementation of the vaccination program*

* The vaccination program was implemented from February 1999.
Transmissability of Pathogens from Person to Person

- The transmissability of an infectious agent can be quantified by "basic reproduction number ($R_0$)"

- Average number of transmissions expected from a single primary case introduced into a fully susceptible population

- The higher the $R_0$, the greater the intensity of transmission
Pictorial Depiction of $R_0$
$R_0$ Depends on Several Factors

* Biological properties of the infectious agent and host
* Rate and pattern of contacts
* Characteristics of the site
$R_0$ Measures Spread in a Completely Susceptible Population

- $R_0$ is an idealized concept
  - One major deviation of reality from the ideal is *population immunity*
  - If some contacts of infectious individuals are immune, the contacts may fail to lead to transmission
  - Effective reproduction number ($R_n$) is actual number of transmissions under *realistic* conditions
  - Vaccines that can generate vaccine herd protection due so by inducing population immunity and lowering $R_n$
\( R_n \) vs. \( R_0 \)

- \( R_n = R_0 \times S \) (proportion susceptible)
  - If \( S = 1/R_0 \), \( R_n = 1 \), and the incidence of the disease should be stable
  - If \( S < 1/R_0 \), \( R_n < 1 \), and the incidence of the disease should die out over time
  - \( H \) (Herd immunity threshold) = \( 1 - 1/R_0 \)
Approximate Basic Reproduction Numbers (in Developed Countries) and Implied Crude Herd Immunity Thresholds ($H$, Calculated as $1 - 1/R_0$) for Common Vaccine-Preventable Diseases

<table>
<thead>
<tr>
<th>Infection</th>
<th>Basic Reproduction Number ($R_0$)</th>
<th>Herd Immunity Threshold (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>6-7</td>
<td>85</td>
</tr>
<tr>
<td>Influenza</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Measles</td>
<td>12-18</td>
<td>55-94</td>
</tr>
<tr>
<td>Mumps</td>
<td>4-7</td>
<td>75-86</td>
</tr>
<tr>
<td>Pertussis</td>
<td>12-17</td>
<td>92-94</td>
</tr>
<tr>
<td>Polio</td>
<td>2-15</td>
<td>50-93</td>
</tr>
<tr>
<td>Rubella</td>
<td>6-7</td>
<td>83-85</td>
</tr>
<tr>
<td>Smallpox</td>
<td>5-7</td>
<td>80-85</td>
</tr>
<tr>
<td>Ebola</td>
<td>1.5-2.5</td>
<td>33-60</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Varicella</td>
<td>8-10?</td>
<td>?</td>
</tr>
</tbody>
</table>
Epidemiologic Analyses of Vaccine Herd Protection

• Typically conducted *after* licensure and deployment of a vaccine in public health practice

• Rely on analyses of yearly trend of infection in relation to yearly trend of vaccine coverage
Rate* of Vaccine-Type (VT) Invasive Pneumococcal Disease (IPD) before and after Introduction of Pneumococcal Conjugate Vaccine (PCV7), by Age Group and Year – Active Bacterial Core Surveillance, United States, 1998-2003 (CDC, 2004)

* Per 100,000 population.
† For each age group, the decrease in VT IPD rate for 2003 compared with the 1998-1999 baseline is statistically significant (p<0.05).
Assembly     Allocation     Surveillance

Figure 1 A schematic of the sequence of events in a two-group, randomized controlled trial. In this sequence, the study population is assembled from a target population and is then Randomized to constitute the experimental vaccine and comparison groups, which are then Followed longitudinally and concurrently for ascertainment of the occurrence of target infections.
Conventional Analysis of Vaccine Protection in Phase III Trials

Protective Efficacy (PE) =

\[
\frac{(\text{Incidence}_{\text{controls}} - \text{Incidence}_{\text{vaccinees}})}{\text{Incidence}_{\text{controls}}} \times 100\% 
\]
Vaccine Protective Efficacy (PE) Calculated from an Individually Randomized Trial

• PE is intended to measure the *direct* protective benefit of vaccination to an individual *in isolation from other persons in the same population*

• In other words, the individually randomized trial design aims to estimate vaccine protection *independent of vaccine herd effects*
Options for Assessing Herd Protection against Clinical Disease in Randomized Trials

- Cluster-randomized trials
Elements of Cluster-Randomized Trials

• Unit of randomization = cluster of people

• Eligible, consenting individuals within cluster receive agent (vaccine or control agent) assigned to the cluster

• Randomization of clusters is typically done before enrollment of individuals in the clusters

• Longitudinal follow-up for target outcomes
Figure 1  A schematic of the sequence of events in a two-group, randomized controlled trial. In this sequence, the study population is assembled from a target population and is then randomized to constitute the experimental vaccine and comparison groups, which are then followed longitudinally and concurrently for ascertainment of the occurrence of target infections.
Evaluation of Vaccine Protection in CRTs

- Study Vac
  - $AR_{1v}$
- Nonvac
  - $AR_{1u}$

- No Control Agent
  - $AR_{2u}$
- Control Agent
  - $AR_{2c}$

Overall

Direct

Indirect

Total
Kolkata Bustees
# Analysis of Total Protection against Typhoid Fever by Vi Polysaccharide

Vi vaccinees \((N=18,869)\)  
Hep A vaccinees \((N=18,804)\)  

<table>
<thead>
<tr>
<th></th>
<th>Vi vaccinees</th>
<th>Hep A vaccinees</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typhoid Episodes</td>
<td>34</td>
<td>96</td>
</tr>
<tr>
<td>Rate (per 1,000 person-years)</td>
<td>0.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Total Protection</td>
<td>65% (P&lt;.0001; 95% CI:42%, 79%)</td>
<td>-</td>
</tr>
</tbody>
</table>
Analysis of *Indirect Protection* against Typhoid Fever by Vi Polysaccharide

<table>
<thead>
<tr>
<th></th>
<th>Non-vaccinees Vi clusters (N=12,206)</th>
<th>Non-vaccinees Hep A clusters (N=12,877)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typhoid Episodes</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td>Rate (per 1,000 person-years)</td>
<td>0.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Indirect Protection</td>
<td>45% (P&lt;.05; 95%CI:1%,70%)</td>
<td>-</td>
</tr>
</tbody>
</table>
## Analysis of Overall Protection against Typhoid Fever by Vi Polysaccharide

<table>
<thead>
<tr>
<th></th>
<th>All residents Vi clusters (N=31,075)</th>
<th>All residents Hep A clusters (N=31,681)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typhoid Episodes</td>
<td>50</td>
<td>127</td>
</tr>
<tr>
<td>Rate (per 1,000 person-years)</td>
<td>0.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Overall Protection</td>
<td>60% (P&lt;.0001; 95%CI:39%,74%)</td>
<td></td>
</tr>
</tbody>
</table>
Options for Assessing Herd Protection in Randomized Trials

• Individually randomized trials
Use of Individually Randomized Trials to Analyze Herd Effects

• In any individually randomized trial there will be geographic differences in vaccine coverage of the target population due to chance variations in randomized assignments and to different rates of eligibility and participation.

• If suitable geographic clusters can be identified and if there is sufficient variation in vaccine coverage between these clusters, vaccine herd effects can be assessed by evaluating the correlation of disease incidence with levels of vaccine coverage in these clusters.
1985 Efficacy Trial of Orally-Administered, Killed Whole Cell-based Cholera Vaccines

- Compared agents: BS-WC vaccine; WC vaccine; *E.coli* K12 placebo
- Site: Matlab, Bangladesh (ICDDR,B)
- Eligibility: Children aged 2-15 yrs; Women older than 15
- Regimens: 3 doses, at 6-week intervals
- Allocation: Individually randomized
- Enrollment: 89,596; 62,285 received complete 3 dose regimens
1985 Field Trial of Killed Oral Cholera Vaccines: Analysis of Data for First Year of Surveillance

<table>
<thead>
<tr>
<th>Feature</th>
<th>BS-WC</th>
<th>WC</th>
<th>K12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholera Episodes</td>
<td>41</td>
<td>52</td>
<td>110</td>
</tr>
<tr>
<td>Cholera Risk (per 1,000)</td>
<td>1.9</td>
<td>2.5</td>
<td>5.2</td>
</tr>
<tr>
<td>PE</td>
<td>63%</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(P&lt;.0001; 95%CI: 46%, 74%)</td>
<td>(P&lt;.0001; 95%CI: 33%, 66%)</td>
<td></td>
</tr>
</tbody>
</table>
Research Questions

• Was the risk of cholera among non-vaccinated neighbors of vaccinees inversely related to the level of vaccine coverage? This would indicate *indirect* protection of non-vaccinees.

• Was the risk of cholera among vaccinees inversely related to the level of vaccine coverage? This would indicate *direct plus indirect* ("total") protection of vaccinees.
Strategy for Defining Geographic Units

- Geographic unit of analysis: bari, which is a patrilineally linked cluster of households (N=6,423). Most transmission of cholera thought to occur within rather than between baris.
Levels of Vaccine Coverage, Matlab, 1985
# Cholera Risk by the Level of Cholera Vaccine Coverage, Matlab, Bangladesh 1985-1986

<table>
<thead>
<tr>
<th>Level of vaccine coverage</th>
<th>Target population</th>
<th>Vaccinated group</th>
<th>Placebo group</th>
<th>Risk/1000 persons*</th>
<th>Risk/1000 persons**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>Cases</td>
<td>N</td>
</tr>
<tr>
<td>&lt;28%</td>
<td>24,954</td>
<td>20.6</td>
<td>5,627</td>
<td>15</td>
<td>2.66</td>
</tr>
<tr>
<td>28-35%</td>
<td>25,059</td>
<td>20.7</td>
<td>8,883</td>
<td>22</td>
<td>2.47</td>
</tr>
<tr>
<td>36-40%</td>
<td>24,583</td>
<td>20.3</td>
<td>10,772</td>
<td>17</td>
<td>1.57</td>
</tr>
<tr>
<td>41-50%</td>
<td>24,159</td>
<td>19.9</td>
<td>11,513</td>
<td>26</td>
<td>2.25</td>
</tr>
<tr>
<td>51%+</td>
<td>22,394</td>
<td>18.5</td>
<td>12,541</td>
<td>16</td>
<td>1.27</td>
</tr>
<tr>
<td>Total</td>
<td>121,149</td>
<td>100</td>
<td>49,336</td>
<td>96</td>
<td>1.94</td>
</tr>
</tbody>
</table>

* P=.05 for trend  
** P<.0001 for trend
Cost-Effectiveness of Killed Oral Cholera Vaccine

Cost per DALY by WHO region

- Threshold for “Very cost-effective” is the weighted avg. regional GDP per capita.
- Threshold for “Cost-effective” is 3x weighted avg. regional GDP per capita.

<table>
<thead>
<tr>
<th>Region</th>
<th>1-14</th>
<th>1+</th>
<th>With herd</th>
<th>Without herd</th>
<th>Cost/DALY, best estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR</td>
<td>148</td>
<td>285</td>
<td>317</td>
<td>559</td>
<td>350</td>
</tr>
<tr>
<td>EMR</td>
<td>350</td>
<td>782</td>
<td>760</td>
<td>1471</td>
<td>359</td>
</tr>
<tr>
<td>SEAR</td>
<td>359</td>
<td>889</td>
<td>731</td>
<td>1599</td>
<td>359</td>
</tr>
</tbody>
</table>
Summary

• Introduction of vaccines into public health practice may reveal protective effects at the population level that are not predicted by individual level protection.

• Vaccine herd protection may be crucial to the ability of a vaccine to control a disease under realistic public health conditions, and also to a vaccine’s cost-effectiveness.

• Traditionally, herd protection by vaccines has been assessed with observational studies done after a vaccine is licensed and introduced.

• More recently, the cluster-randomized, controlled clinical trial has been proposed as a design that allows evaluation of herd protection in a fashion that minimizes biases that affect observational studies.
Summary (cont.)

- Although it had traditionally been thought that individually randomized, controlled clinical trials of vaccine protection were suited only for measurement of direct vaccine protection of individual vaccinees, recent methodological advances in the analyses of these trials provide the opportunity to analyze population-level vaccine herd protection.

- The potential suitability of both cluster-randomized and individually randomized trials for measurement of herd protection offers the opportunity to assess this type of protection even before a vaccine is licensed.

- Exploiting these newer approaches may offer improved information at an earlier stage to inform decisions on vaccine introduction.