The costs and effectiveness of large pre-licensure phase III clinical trials: time for a new paradigm?

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Disclosures

- I am a consultant for GSK Vaccines, Protein Sciences, Takeda and WHO.
- As a clinical trialist, I performed or participated in many of the trials I am going to discuss.
Overview

• The goal of phase three studies
• An historical perspective on the size of phase three clinical trials for vaccine licensure
• Large phase III safety trials – How well have we done?
• Large phase III efficacy trials - How well have we done?
• What are the financial and opportunity costs of mandating large phase III trials before licensure
• The alternatives:
  – The evolution of post-licensure safety surveillance
  – Epidemiologic disease surveillance infrastructure
  – The potential for further mutual regulatory reciprocity
  – What might a new paradigm look like?
Goals of Large Phase III trials for vaccines

• Efficacy: Obtain a precise estimate of vaccine efficacy in a target population
  – To allow licensure
  – To inform public health decisions
  – To evaluate cost effectiveness
  – To prioritize introductions

• To assure the safety of the vaccine in the target population
## Historical Trends in Phase III Trial Size

<table>
<thead>
<tr>
<th>Year</th>
<th>Vaccine</th>
<th>Clinical Trial Size Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>Hepatitis B inactivated</td>
<td>1,083&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>1985</td>
<td>Hepatitis B recombinant</td>
<td>2,200&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>1990</td>
<td>Hib (HbOC)</td>
<td>61,080</td>
</tr>
<tr>
<td>1993</td>
<td>DTaP</td>
<td>17,995&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>2000</td>
<td>PCV7</td>
<td>37,868</td>
</tr>
<tr>
<td>2006</td>
<td>Rotarix</td>
<td>63,225</td>
</tr>
<tr>
<td>2006</td>
<td>Rotateq</td>
<td>34,035</td>
</tr>
<tr>
<td>2007</td>
<td>HPV (Gardasil)</td>
<td>17,662</td>
</tr>
<tr>
<td>2008</td>
<td>HPV (Cervarix)</td>
<td>16,162</td>
</tr>
</tbody>
</table>

How is trial size determined?

• Initially sample sizes for large trials were based upon efficacy considerations and safety evaluation was a secondary concern
  – Hib efficacy trials – > 60,000 vaccinated children
  – Pneumococcal conjugate efficacy trials- PCV 7: > 37,000 children

• This changed following identification of the risk of intussusception for Rotashield rotavirus vaccine post licensure
  – Safety trials for GSK and Merck rotavirus vaccines were sized based upon the outcome of intussusception. > 35,000 vaccinees
**Evaluation of New Vaccines: How Much Safety Data?**

**Considerations of Statistical Power**

**Total Study Population Size Required to Detect a Selected Increased Levels of Risk**

<table>
<thead>
<tr>
<th>Control Incidence (person-yrs)</th>
<th>Study Population to Detect 2 Fold Increased Relative Risk</th>
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<td>4,710,650</td>
<td>1,570,208</td>
<td>588,822</td>
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Assuming the test and control group have a 1:1 ratio, that the background incidence in treated = incidence in controls, two tailed alpha=0.05, 80% power.

Strom, B.L., *Pharmacoepidemiology, 2nd Ed.*, John Wiley and Sons, 1994
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Phase Three Safety and Efficacy Trials

SO HOW HAVE WE DONE?
Phase III **Safety** Trials

How well have we done?

**Rotateq and Rotarix as examples**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Clinical Trial Result for Intussusception Risk</th>
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<tr>
<td>Rotateq</td>
<td>Clinical Trial 34,035 infants&lt;br&gt;R&lt;br&gt;R= 1.6&lt;br&gt;(95% CI= 0.4-6.4)&lt;br&gt;“Met trial safety criteria”&lt;br&gt;“No evidence of increased risk”¹</td>
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<td>Rotarix</td>
<td>Clinical Trial in 63,225 infants&lt;br&gt;6 cases in vaccinees, 7 in placebo&lt;br&gt;R&lt;br&gt;R= 0.86&lt;br&gt;(P= ns)&lt;br&gt;“No evidence of an increased risk”²</td>
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## Phase III Safety Trials

How well have we done?

**Rotateq and Rotarix as examples**

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<tr>
<th>Vaccine</th>
<th>Clinical Trial Result for Intussusception Risk</th>
<th>Intussusception Risk Post Licensure &lt; 7 days of Dose One Total Birth Cohort ~ 1 million</th>
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<td>Rotateq</td>
<td>Clinical Trial 34,035 infants <strong>RR= 1.6</strong> (95% CI= 0.4-6.4) “Met trial safety criteria” “No evidence of increased risk”¹</td>
<td><strong>RR= 9.9</strong> 95% CI= 3.7–26.4³</td>
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<td>Clinical Trial in 63,225 infants 6 cases in vaccinees, 7 in placebo <strong>RR= 0.86</strong> (P= ns) “No evidence of an increased risk”²</td>
<td><strong>RR= 6.8</strong> 95% CI = 2.4–19.0;³</td>
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### Evaluation of New Vaccines: How Much Safety Data?

#### Considerations of Statistical Power

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**Phase III Efficacy Trials**

How well have we done?

**PCV7 as an example**

<table>
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<th>Outcome</th>
<th>Clinical Trial Result</th>
</tr>
</thead>
</table>
| Invasive Disease                      | 93.9 %\(^1\)  
(95% CI=79.6-98.5)                      |
| Otitis Media                          | 7.0 %\(^1\)  
(95% CI =4.1-9.7)                        |
| All Cause Pneumonia                   | 6 %\(^2\)  
(95% CI= -1.5 to 11%)                    |
| Cost Effectiveness                    | US$ 80,000/ QALY\(^3\)                     |
| Of Childhood Vaccination              |                                            |

# Phase III Efficacy Trials

How well have we done?

**PCV7 as an example**

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<tr>
<th>Outcome</th>
<th>Clinical Trial Result</th>
<th>Post Introduction Result</th>
</tr>
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<td><strong>Invasive Disease</strong></td>
<td>93.9 %(^1)*</td>
<td>&gt; 99 %(^4)</td>
</tr>
<tr>
<td></td>
<td>(95% CI=79.6-98.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Otitis Media</strong></td>
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<td>20%(^5)*</td>
</tr>
<tr>
<td></td>
<td>(95% CI =4.1-9.7)</td>
<td>(95% CI= 4-34%)</td>
</tr>
<tr>
<td><strong>All Cause Pneumonia</strong> &lt; 5 yo</td>
<td>6 %(^2)</td>
<td>39%(^6)</td>
</tr>
<tr>
<td></td>
<td>(95% CI= -1.5 to 11%)</td>
<td>(95% CI 22–52)</td>
</tr>
<tr>
<td><strong>Cost Effectiveness</strong> Of Childhood Vaccination</td>
<td>US$ 80,000/ QALY(^3)</td>
<td>US$7500/ QALY(^7)</td>
</tr>
</tbody>
</table>

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Other Examples

• Rotavirus effectiveness

• Acellular Pertussis Effectiveness
## Rotavirus Vaccine Effectiveness

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Primary Efficacy Trial Severe Disease</th>
<th>Other Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentavalent Rotavirus (Merck)</td>
<td>98% (88.3-100%)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Asia: 48.3% (22.3-66.1%)&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Pertussis Vaccine Effectiveness

• Acellular pertussis vaccines were evaluated in numerous large phase three trials in Europe leading to licensure of several vaccines based upon short term efficacy

• Post licensure follow up has revealed
  • A lack of duration of protection
  • Lack of ability to prevent transmission
What are the financial and opportunity costs of the current system?

<table>
<thead>
<tr>
<th>Time and financial cost</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Current cost for large phase III trials is estimated to be up to 150 million Euros.</td>
<td><strong>Opportunity Cost:</strong> Manufacturers will only consider bringing a very few potential candidates into clinical development</td>
</tr>
<tr>
<td>• Time from inception to completion is 4-5 years.</td>
<td>– This increases risk of vaccine development for each manufacturer and likely increases cost for successful vaccines</td>
</tr>
<tr>
<td></td>
<td>– Risk limits manufacturer interest and investment</td>
</tr>
<tr>
<td></td>
<td>– Limiting development decreases the number of vaccines available to prevent disease</td>
</tr>
<tr>
<td></td>
<td>• <strong>Time lost:</strong> There is a delay in the time until a beneficial vaccine becomes available.</td>
</tr>
<tr>
<td></td>
<td>• <strong>Risk of a false assessment</strong> – rejecting a useful vaccine</td>
</tr>
</tbody>
</table>
Summary so far

• In the last three decades, the size of phase III trials has increased dramatically
  – This has caused
    • An increase in the time to market and the cost of pre-licensure evaluation
    • A reduction and slowing in the vaccine development pipeline
  – This has not resulted in a concomitant
    • Increase in the predictive value of pre-licensure evaluations of efficacy or cost-effectiveness
    • A dramatic increase in our ability to assess safety
What resources might an alternative approach employ?

- **Efficacy**: Extensive disease surveillance networks exist in the US, UK, several countries in Europe, Asia, and Latin America.
  - **Example**: the approach used by the UK for Men C

- **Safety**
  - More rapid and comprehensive techniques
    - VSD routine, rapid cycle, outcome scanning
    - ADVANCE in Europe
    - Beginning network within PAHO
Skipping Phase III: Men C Epidemiology in the UK post introduction Men C conjugate

![Graph showing meningococcal disease rates over time](http://cvi.asm.org/content/17/5/840/F1.large.jpg)
VSD Rapid Cycle Analysis (RCA)

• Sequential monitoring of adverse events following immunization
  – Automated weekly updates of files

• Basic technique
  – For each vaccine, choose specific outcomes to monitor
  – Each week, evaluate the number of events in vaccinated persons
  – Compare it to the expected number of events based on a comparison group
  – Adjust for multiple comparisons
Rapid Cycle Analysis Example: Rotavirus vaccine and intussusception (historical analysis)

Vaccine licensed Aug 98

Log likelihood ratio

Critical value = 3.3

MaxSPRT analysis would have signaled in May 1999

Thanks to Roger Baxter & Tracy Lieu for slide
Outcome Based Surveillance (OBS)
A Technique for Surveillance on a Large Number of Outcomes

• RCA requires that you pre-specify outcomes of interest
• OBS makes it possible to do surveillance on large numbers of outcomes
• Can use all ICD9/ICD10 codes alone or in groupings

Thanks to Roger Baxter for slide
Hepatitis A vaccine: ED Visits
Elevated Odds Ratios, $p < 0.01$

<table>
<thead>
<tr>
<th>Risk Interval</th>
<th>Diagnosis</th>
<th>Risk Interval Cases</th>
<th>Rest of 9 months Cases</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Days</td>
<td>Syncope</td>
<td>37</td>
<td>1417</td>
<td>2.29</td>
<td>(1.63,3.15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Skin infections</td>
<td>48</td>
<td>1825</td>
<td>2.15</td>
<td>(1.59,2.84)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2 Weeks</td>
<td>Other skin disorders</td>
<td>111</td>
<td>1347</td>
<td>1.34</td>
<td>(1.10,1.62)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Allergic reactions</td>
<td>249</td>
<td>3093</td>
<td>1.32</td>
<td>(1.16,1.50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>739</td>
<td>9592</td>
<td>1.22</td>
<td>(1.13,1.31)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6 Weeks</td>
<td>Other skin disorders</td>
<td>299</td>
<td>1160</td>
<td>1.24</td>
<td>(1.09,1.41)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>1963</td>
<td>8370</td>
<td>1.10</td>
<td>(1.04,1.15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Respiratory infections</td>
<td>3303</td>
<td>15555</td>
<td>1.05</td>
<td>(1.02,1.10)</td>
<td>0.006</td>
</tr>
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Thanks to Roger Baxter for slide
Another issue

• Currently there is lack of mutual recognition by US regulatory authorities and the EMA.
• This can lead to duplication of large studies for US submission and delays in vaccine availability.
  – The is very inefficient especially for well characterized vaccine (increase in valency, known platform, etc.)
And yet Another issue

• Phase III trials have tended to be performed in developed country settings in Europe or the US.
• The morbidity and mortality associated with diseases such as rotavirus is in poor LMICs
• The results of RCTs are difficult to generalize
  – Difference in impact on mortality following PCV in Gambia versus US
• Vaccine introduction “vaccine probe” demonstration studies (much as was done for Men C in the UK) might be better suited to define impact in LMIC
Putting this all together: possible approaches

• “Conditional” licensure of vaccines

• Regulatory harmonization and increased mutual recognition by the EU and FDA.
One possible approach: Conditional Licensure

• “Conditional” licensure of vaccines could be considered following phase 2b studies with permanent licensure linked to results of mandated safety evaluations within a two year period.

• Manufacturers could charge for vaccine and the vaccine would be approved for use during this period.

• A conditional licensure fee could be assessed to fund the post-conditional licensure evaluations.

• The relevant regulatory agency would review data at the end of the conditional period to consider routine licensure and recommending bodies could adjust vaccine use recommendations if warranted.
Conditional Licensure Schematic

Phase One candidates

Phase 2 A
~ 500 participants per target population

Phase 2 B
Known Platform
2000 participants
Per target population

Conditional Licensure
Safety and Effectiveness Surveillance in ≥ 100,000 recipients

Phase 2 B
New technology platform

Classic Phase III Trial

Full Licensure

End of Licensure
A different path for “known” entities

• For vaccines where there is only a change in valency (PCV7 to PCV13 for example)
• For vaccines where the platform is well known—CRM or tetanus conjugates

• One could envision a much reduced pre-licensure requirement augmented by post licensure surveillance for safety and effectiveness.
Another option

Increased Reciprocity and Harmonization

• Currently, the FDA, EMA and others set trial requirements and path to licensure separately
• This can lead to different population and study requirements which can dictate that two studies be performed.
• This introduces resource and time constraints and time delays to vaccine availability.
What are the barriers?

• Inertia

• False assurance that “large” RCTs provide a “better” assessment of safety and efficacy.
  – RCTs do indeed avoid some potential biases
  – However, they are limited in scope, have limited power, are time consuming and have difficulty assessing
    • Indirect effects
    • Effects in special populations which may be excluded from phase three studies.
What is the risk of the status quo?

• Opportunity cost for vaccine development
  – Limitation of pipeline
  – Focus on “high ROI” targets by manufacturers
• False conclusions regarding potential impact from RCT
  – Inappropriate CE analysis
  – Over or underestimation of impact in target population
The challenge

I would propose that stakeholders review the track record of the past three decades, the new post licensure technologies available and the negative impact of the requirement for large phase three studies on vaccine development pipelines and timelines and consider how our current approach might be improved.

Thank you.