Moving a New Vaccine from Bench to Bedside: Rotavirus Vaccine as a Model

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Moving a New Vaccine from Bench to Bedside

- Research – basic and clinical
- Product development
- Clinical trials
- FDA review and licensure – regulation
- Recommendations for use
  - Universal vs selective
  - Advisory committees – public and private sectors
  - Economic assessment
Vaccine Development

• Preclinical development and testing
  – Laboratory
  – Animals

• Clinical trials – FDA IND application
  – Immunogenicity
  – Efficacy
  – Safety
# Phases in Development of a Vaccine

<table>
<thead>
<tr>
<th>Phase</th>
<th>Studies</th>
<th>No. of Persons Usually Studied</th>
<th>Rate of Detectable Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Safety, immunogenicity</td>
<td>10-100</td>
<td>10-20%</td>
</tr>
<tr>
<td>2*</td>
<td>Dose, ranging, immunogenicity, safety</td>
<td>100-1000</td>
<td>1-10%</td>
</tr>
<tr>
<td>3*</td>
<td>Efficacy, safety, immunogenicity</td>
<td>500-20,000</td>
<td>0.5-5%</td>
</tr>
<tr>
<td>4</td>
<td>Postlicensure studies, postmarketing surveillance</td>
<td>10,000-100,000</td>
<td>Millions</td>
</tr>
</tbody>
</table>

*Prelicensure
Prelicensure Human Studies

- Numbers of subjects are usually limited
- Common reactions are identified
- Poorly detected reactions:
  - Rare
  - Delayed onset
  - Subpopulations
Licensing of Vaccines in the US

• Food and Drug Administration (FDA) licenses vaccines
  • FDA Advisory Committee (VRBPAC)
• Licensure based on results of clinical trials
• Vaccines are not available for use in the US until licensed
Postlicensure Surveillance

- Identify rare reactions
- Monitor increases in known reactions
- Identify risk factors for reactions
- Identify vaccine lots with increased rates of reactions
- Identify signals
Postlicensure Vaccine Safety Activities

• Phase IV Trials
  - \( \sim 10,000 \) participants
  - limited
• Large-Linked Databases
• VAERS
Vaccine Adverse Event Reporting System (VAERS)

- Jointly administered by CDC and FDA
- National reporting system
- Passive (depends on healthcare providers and others to report)
- Receives ~10,000 reports per year

- Detects
  - new or rare events
  - increases in rates of known events
  - patient risk factors
- Additional studies required to confirm VAERS signals
- Not all reports of adverse events are causally related to vaccine
Recommendations for New Vaccines

- Advisory Committee on Immunization Practices (ACIP)
- Committee on Infectious Diseases of the American Academy of Pediatrics
Advisory Committee on Immunization Practices (ACIP)

• Consists of 15 experts in fields associated with immunization
  - Non-voting liaison representatives from many organizations

• Develops written recommendations for the routine administration of vaccines to the pediatric and adult populations
  - ACIP is the only entity in the federal government which makes such recommendations
ACIP Process for Approval

- Recommendations are developed in Working Groups
  - Have a mixture of ACIP members, liaisons from AAP, AAFP, FDA, NIH, CDC and other interested parties
  - Present proposed recommendations to the full ACIP
- ACIP members comment on proposed recommendations
- Working group revises recommendations as needed based on feedback from full ACIP
- Final recommendations require approval of the full ACIP
American Academy of Pediatrics
Recommendations

• Vaccine recommendations authored by the Committee on Infectious Diseases
  - Appointed committee of experts with 13 members
  - Nonvoting liaisons from CDC, FDA, NIH, CPS, AAFP, NVPO

• AAP issues policy statements on use of vaccines
  - Reviewed by the whole Board of Directors of AAP
  - Published in Pediatrics
  - Published on the Pediatrics website (www.pediatrics.org)
Childhood Vaccine Financing in the US

Table 1. The role of programs in vaccination

<table>
<thead>
<tr>
<th>Program</th>
<th>Target Population(s)</th>
<th>Principal Benefit(s)</th>
<th>Population Covered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine for Children Program (VFC)</td>
<td>Medicaid-eligible children</td>
<td>Vaccines</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Uninsured children</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>American Indians</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alaska Natives</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Underinsured, ie, children with insurance that does not cover vaccines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Section 317</td>
<td>Low-income children not eligible for VFC</td>
<td>Vaccines and administration</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Underinsured children</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children of working poor/with insurance deductibles or other costs that parents</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cannot cover</td>
<td></td>
<td></td>
</tr>
<tr>
<td>State programs</td>
<td>Varies by state: may include all or some children, all or some vaccines, regardless</td>
<td>Vaccines and administration</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>of insurance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicaid</td>
<td>Low-income and disabled children</td>
<td>Administration</td>
<td></td>
</tr>
<tr>
<td>(criteria vary by state)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State Child Health Insurance Program</td>
<td>Low-income children up to 200% of federal poverty level (sometimes more, depending on</td>
<td>Vaccines and administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>state)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private insurance</td>
<td>Vaccines and administration; may require copays, deductibles, or other cost sharing</td>
<td></td>
<td>45%</td>
</tr>
</tbody>
</table>
Barriers to Vaccine Implementation

- Limitations in both federal and state vaccine financing: the dominant barriers
- Vaccine supply or allocation
Rotavirus Vaccine as a Model
Rotavirus Structure

- Outer layer made of VP7 and VP4 proteins
  - VP7 determines G-serotype
  - VP4 determines P-serotype

- VP7 and VP4 are important for immunity
  - Induce serotype-specific neutralizing antibodies in vivo

Figure adapted from Estes MK. *J Infect Dis.* 1996;174(Suppl 1):S37-S46.
Natural Immunity and Rotavirus Gastroenteritis

- Many children infected more than once
  - First infections more likely to result in severe gastroenteritis than subsequent infections
- Protective immunity develops after natural infection,
  - Strongest against moderate-to-severe disease
  - Serotype specific
  - Serologic correlates of immunity have not been established
- As a result field studies have been necessary to demonstrate the efficacy of rotavirus vaccines
Goals for a Rotavirus Vaccine

- To duplicate the degree of protection that follows natural infection
- To prevent moderate to severe disease but not mild disease from rotavirus
- To reduce the disease burden
- Vaccine most needed in developing countries where mortality with rotavirus is high
Vaccine -Development Approaches

• Monovalent animal rotavirus vaccines
• Multivalent human-animal reassortant vaccines
• Attenuated human strains
Multivalent Human-Animal Reassortant Vaccines

• Vaccines contain genes from an animal parent virus and VP4 and/or VP7 gene from human strain

• Simian-based vaccines
  - Rotashield®

• Bovine-based vaccines
  - RotaTeq™
Reassortant Human-Rhesus Rotavirus Vaccine (Rotashield)
Rotashield Story

- **FDA approves Rotashield**
- **August 1998**: Rotashield is universally recommended for US infants
- **October 1998**: CDC reports preliminary data from VAERS suggesting association with intussusception
- **July 1999**: CDC presents data confirming association with intussusception
- **October 1999**: Universal recommendation rescinded
  - Vaccine withdrawn from market
Rotavirus Vaccine and Intussusception - CDC Case Control Study

Murphy, et al. NEJM 20:410, 2001
Implications of Rotashield Withdrawal on Development of New Rotavirus Vaccines

• Estimated rate of intussusception with Rotashield
  – 1 case per 10,000 doses

• Studies of new vaccines need to be quite large to exclude the possibility of intussusception (>60,000 subjects)
Bovine Rotavirus Vaccine – RV5
[RotaTeq™]

- 5 human-bovine reassortants
  - G serotypes - Human G1, G2, G3, G4
  - P serotype - Human P[8]
- Phase II studies - efficacious and generally well tolerated
REST Organization and Objectives

Large-Scale Study
N=69,625

- Intussusception, Serious Adverse Events, Hospitalizations for Rotavirus Gastroenteritis
- Other Adverse Events

Detailed Safety Substudy
N=9,605

- Other Adverse Events

Efficacy Substudy
N=5,673

- Clinical Efficacy, Immunogenicity, Fecal Shedding
REST: Intussusception Cases

6 Vaccine : 5 Placebo

<table>
<thead>
<tr>
<th>Interval After Any Dose (Days)</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>35</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

# Efficacy of RV5 Against G1–G4 Rotavirus AGE


<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Vaccine</th>
<th>Placebo</th>
<th>% Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>82</td>
<td>315</td>
<td>74</td>
<td>67, 80</td>
</tr>
<tr>
<td>Severe*</td>
<td>1</td>
<td>51</td>
<td>98</td>
<td>88, 100</td>
</tr>
</tbody>
</table>

*As defined by clinical scoring system.
## Efficacy of PRV to Reduce Health Care Visits

<table>
<thead>
<tr>
<th>Type of Health Care Contact</th>
<th>Number of Cases</th>
<th>% Rate Reduction</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>6</td>
<td>144</td>
<td>96</td>
</tr>
<tr>
<td>Emerg. Dept. Visits</td>
<td>14</td>
<td>213</td>
<td>93</td>
</tr>
<tr>
<td>Non-urgent Visits</td>
<td>13</td>
<td>99</td>
<td>86</td>
</tr>
</tbody>
</table>

Live Attenuated Human Rotavirus Vaccine RV1 [Rotarix®]

- Contains one strain of human rotavirus (G1P[8])
  - Shares neutralizing epitopes with G1, G3, G4 and G9 serotypes
- Several small efficacy studies showed that RV1 was efficacious and generally well tolerated
Phase III Study of RV1 in Latin America & Finland

Primary Immunization Phase:
Analysis of Intussusception & Safety
>63,000 infants

1-Year follow-up:
Nested Analysis of Efficacy & Safety
>20,000 infants

Ruiz-Palacios et al.  NEJM 2006;354:11-22
Occurrence of IS Cases with RV1

Dose 1

Dose 2

Days after Vaccination
RV1 Vaccine Efficacy

- Phase III trials included more than 67,000 infants
- Efficacy in Latin America
  - Severe rotavirus disease - 85%
  - Rotavirus-related hospitalization - 85%
- Efficacy in Europe
  - Severe rotavirus disease - 96%
  - Rotavirus-related hospitalization - 100%
  - Medical attention for RV AGE - 92%
  - For any rotavirus disease after one dose - 87%
### Rotavirus Vaccine Licensing and Recommendations in the US

<table>
<thead>
<tr>
<th>Event</th>
<th>RV5</th>
<th>RV1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Licensed</td>
<td>2/3/06</td>
<td>4/3/08</td>
</tr>
<tr>
<td>ACIP added to recommended vaccine schedule</td>
<td>2/21/06</td>
<td>6/28/08</td>
</tr>
<tr>
<td>MMWR statement published</td>
<td>8/11/06</td>
<td>2/6/09</td>
</tr>
<tr>
<td>AAP recommendations published in Pediatrics</td>
<td>January 2007</td>
<td>April 2009</td>
</tr>
</tbody>
</table>
Rotavirus Vaccine Implementation

• Factors Associated With Adoption
  - Perception of a high burden of rotavirus disease
  - A high level of confidence in pre-licensure studies of vaccine safety

• Barriers
  - Concerns about uniform coverage of vaccine by insurers
  - Lack of adequate reimbursement
  - Concern about parental reluctance because of withdrawal of previous rotavirus vaccine
Questions