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Discovery of Rotavirus to a Vaccine 25 Years

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Finland
Descriptive history of rotavirus vaccines or
Have we learned anything from history?

Lessons

Ancient history 1982 – 1987
— ”Best is the enemy of good”

Renaissance history 1998 – 1999
— ”Intussusception forever”

Modern times
— ”Cherish the new vaccines”
Bovine rotavirus candidate vaccine RIT 4237

Nebraska Calf Diarrhea Virus (NCDV)
Mebus et al.

A. Delem et al

NCDV heterologous resistance to human RV in fetal calves
Wyatt et al. Science 1979; 203:548-550

RIT 4237 vaccine
1978 animal studies
G. Zissis et al.
1982 human studies
T. Vesikari et al.
RIT 4237 testing in children, Tampere

2-year-old children
Pilot group 5
Main group 15
8-12 month-old infants
Pilot group 5

Results
No diarrhea
Shedding 3/25
No increase in SGOT
Neut ab response
13/19 seronegatives
1/6 seropositives

Safe and immunogenic!

October 1982
Efficacy of a single dose of RIT 4237 vaccine in infants aged 8-11 months
January 1983 through RV season 1983
(Lancet 1984;1(8384):977-81)

<table>
<thead>
<tr>
<th>No. episodes</th>
<th>RIT 4237 (N=86)</th>
<th>Placebo (N=92)</th>
<th>Protection rate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any RV</td>
<td>9</td>
<td>18</td>
<td>50 %</td>
<td>N.S.</td>
</tr>
<tr>
<td>Severe RV</td>
<td>2</td>
<td>18</td>
<td>88 %</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- efficacious when given right before RV epidemic season at the age of greatest risk
- efficacy better for severe RV diarrhea
1983 – 1984 study, Efficacy vs. immune response
Efficacy of two doses of RIT 4237 vaccine in 6 - 12 month-old infants vaccinated before RV epidemic season  (J Pediatr. 1985 Aug;107(2):189-94)

Table III. Rotavirus-associated diarrhea in relation to vaccine and serologic response in the initially rotavirus-seronegative infants

<table>
<thead>
<tr>
<th></th>
<th>Clinically significant rotavirus diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episodes</td>
</tr>
<tr>
<td>RIT 4237 vaccine Seroconversion</td>
<td>1</td>
</tr>
<tr>
<td>(n = 77)</td>
<td></td>
</tr>
<tr>
<td>No seroconversion</td>
<td>4</td>
</tr>
<tr>
<td>(n = 69)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>No seroconversion</td>
<td>24</td>
</tr>
<tr>
<td>(n = 149)</td>
<td></td>
</tr>
</tbody>
</table>

- EIA antibody response correlates with protection, but is not a surrogate for protection
## 1983 – 1984 study

### Efficacy of RIT 4237 against serotypes of RV (Collaboration with Tom Flewett)

<table>
<thead>
<tr>
<th>RV serotype</th>
<th>No. cases with severe RV diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RIT 4237</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

**Protection across G – types of RV**

= heterologous protection
Prefeeding before RV vaccination, 1984
One dose of RIT 4237 titer $10^{8.1}$ TCID$_{50}$

<table>
<thead>
<tr>
<th>RV EIA seroconversion</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Empty stomach</td>
<td>9 / 19</td>
<td>(47%)</td>
</tr>
<tr>
<td>Milk – filled stomach</td>
<td>14 / 16</td>
<td>(88%)</td>
</tr>
</tbody>
</table>

- RV is acid labile
- buffering needed

Lancet 1984 Sep 22;2(8404):700
Prefeeding with breast or bottle milk, 1985

One dose of RIT 4237 titer $10^{8.1}$ TCID$_{50}$

6 – 12 month – old infants

<table>
<thead>
<tr>
<th></th>
<th>RV EIA seroconversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast milk</td>
<td>26 / 32 (81%)</td>
</tr>
<tr>
<td>Bottle milk</td>
<td>32 / 37 (86%)</td>
</tr>
</tbody>
</table>

- Breast milk does not suppress uptake of RV vaccine

Bishop et al, NEJM 1983;309:72-6

44 infected with RV <14 days of life
37 not infected
Follow – up 3 years

<table>
<thead>
<tr>
<th></th>
<th>Neonatal RV</th>
<th>No neonatal RV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases with RV</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Severe cases</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>
Neonatal vaccination with RIT4237 Follow-up over 2–3 RV epidemic seasons 1984–1987

<table>
<thead>
<tr>
<th>Severity</th>
<th>No. cases</th>
<th>Vaccine (N=362)</th>
<th>Placebo (N=336)</th>
<th>Vaccine efficacy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td></td>
<td>56</td>
<td>65</td>
<td>14%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Severe (score ≥ 11)</td>
<td></td>
<td>8</td>
<td>32</td>
<td>71%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Very severe (score ≥ 15)</td>
<td></td>
<td>0</td>
<td>11</td>
<td>100%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Ruuska 1991
Bovine rotavirus strain RIT4237
Summary of findings
in Finland 1982 – 1987

● efficacious against severe RV gastroenteritis
● optimal efficacy at 6 – 12 months of age, neonatal vaccination protective against severe disease
● one dose as good as 2 doses (homologous vaccine)
● heterologous protection
● no obvious side effects (IT not seen)
● buffering against stomach acidity needed
● breast – feeding did not interfere
● OPV interfered (studies in Italy and Jugoslavia)
Other studies of RIT 4237 in Native Americans, Africa, and Peru 1984 - 1985 (- 1987)

<table>
<thead>
<tr>
<th>Location</th>
<th>No. doses</th>
<th>Age</th>
<th>Any RV</th>
<th>Severe RV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whiteriver, USA</td>
<td>1</td>
<td>2–6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>The Gambia</td>
<td>1–3</td>
<td>2–6</td>
<td>33 %</td>
<td>N.D.</td>
</tr>
<tr>
<td>Lima, Peru</td>
<td>3</td>
<td>2–18</td>
<td>40 %</td>
<td>75 %</td>
</tr>
</tbody>
</table>

- Variable efficacy, either nil or less than expected
- Explanations?? Whiteriver: a long time interval (1 yr) between vaccine and challenge
Bovine rotavirus vaccine RIT4237
Situation in 1986

- Vaccine almost ready to be launched
- High efficacy in Finland
- Lower efficacy in Latin America and Africa
- In Europe, few people were aware of rotavirus, much less interested in a vaccine
- Globally, other priorities, particularly OPV
- Manufacturer (SK-RIT) gave priority to HBV
Criticism on RIT 4237, mid 1980’s (WHO SC and others)

- RV vaccine should protect against all, not only severe RV gastroenteritis
- RV vaccine should induce protective immunity by itself, not upon reinfection by natural RV
- RV vaccine must not interfere with OPV
Rhesus rotavirus vaccine (RRV)

Virus isolated from 3.5 month-old rhesus monkey
9 passages in primary monkey kidney cells
7 passages in FRhL-2 cells culture

• virus concentration $10^4 – 10^5$ per dose
• relies on virus multiplication to induce immune response
• supposedly more immunogenic than bovine RVs
• VP7 close to human G3 – advantage?
Febrile reactions after RRV and RIT4237
Head to head comparison in 5–6 month–old Finnish infants  (JID 1986;153:833)

Should RRV have been stopped at this point?
"We know it works, but do we know why it works?"

We still don’t know

Empiric data vs. theory

"Grau, teurer Freund, ist alle Theorie, and grün des Lebens goldner Baum"

JW Goethe
"G – hypothesis" 1985 approx.

G – type specific neutralizing antibodies are critical for RV–vaccine – induced protection → basis for reassortant vaccine development

Rhesus-human Reassortant Rotavirus Vaccine

- 10 genome segments from rhesus RV
- 1 genome segment from human RV
- G-types 1, 2 or 4
- RotaShield = RRV-TV = combination of RRV and G1, G2 and G4 reassortants of RRV
- more immunogenic than bovine rotavirus
- much more reactogenic than BRV
RotaShield
Seroconversion rates for serum neutralizing antibodies after 3 doses

Clinical protection against

- any RV GE 68%
- severe RV GE 91%


G – hypothesis effectively refuted!
The Rise and Fall of Rotashield

Licensed in the US  31 August 1998
Association with intussusception in July  1999

Since July 1999, safety has been
A key issue for any rotavirus vaccine
RotaShield is a standard for safety evaluation

RotaShield remains a standard for vaccine efficacy
Incidence of 1\textsuperscript{st} dose associated intussusceptions and 1\textsuperscript{st} doses received, by age, in 19 Study States during the 9-month RotaShield use period, by age US 1998–1999

<table>
<thead>
<tr>
<th>Age at 1st dose Group</th>
<th>Days</th>
<th>Intussusception</th>
<th>Nº of 1st dose</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>0</td>
<td></td>
<td>1.935</td>
<td>[0]</td>
</tr>
<tr>
<td>Young 30-59</td>
<td>0</td>
<td></td>
<td>69.123</td>
<td>0</td>
</tr>
<tr>
<td>infants 60-89</td>
<td>9</td>
<td></td>
<td>197.144</td>
<td>5</td>
</tr>
<tr>
<td>&lt; 90</td>
<td>9</td>
<td>(20 %)</td>
<td>268.202 (62 %)</td>
<td>3</td>
</tr>
<tr>
<td>90-119</td>
<td>6</td>
<td></td>
<td>35.441</td>
<td>17</td>
</tr>
<tr>
<td>120-159</td>
<td>17</td>
<td></td>
<td>77.413</td>
<td>22</td>
</tr>
<tr>
<td>160-189</td>
<td>2</td>
<td></td>
<td>15.088</td>
<td>13</td>
</tr>
<tr>
<td>Older 190-209</td>
<td>11</td>
<td></td>
<td>32.534</td>
<td>34</td>
</tr>
<tr>
<td>infants 210-239</td>
<td>0</td>
<td></td>
<td>779</td>
<td>[0]</td>
</tr>
<tr>
<td>240-269</td>
<td>0</td>
<td></td>
<td>868</td>
<td>[0]</td>
</tr>
<tr>
<td>270-299</td>
<td>0</td>
<td></td>
<td>2.896</td>
<td>[0]</td>
</tr>
<tr>
<td>300-359</td>
<td>0</td>
<td></td>
<td>0</td>
<td>[0]</td>
</tr>
<tr>
<td>&gt; 90</td>
<td>36</td>
<td>(80 %)</td>
<td>165.019 (38 %)</td>
<td>22</td>
</tr>
<tr>
<td>All</td>
<td>&lt; 365.</td>
<td>45 (100 %)</td>
<td>433.222(100 %)</td>
<td>10</td>
</tr>
</tbody>
</table>
New rotavirus vaccines

- Bovine-human reassortant (RotaTeq, Merck)
- UK-bovine reassortant
- Human RV (Rotarix, GSK)

Are these different from RotaShield with regard to (fever and) intussusception? Should we refrain from administering the vaccines to older infants?
Intussusception in REST
total: 6 Vaccine : 5 Placebo

Vesikari T et al, NEJM 2006;354:23-33
Rota 023 Results
Occurrence of Definite IS Cases\textsuperscript{1} Compared to RotaShield\textsuperscript{TM}-Associated Cases\textsuperscript{2}

\textbf{Dose 1}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{dose1_graph}
\caption{Occurrence of Definite IS Cases at Dose 1.}
\end{figure}

\textbf{Dose 2}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{dose2_graph}
\caption{Occurrence of Definite IS Cases at Dose 2.}
\end{figure}

\textsuperscript{1} Ruiz-Palacios GM et al. N Engl J Med. 2006 Jan 5;354(1):11-22

\textsuperscript{2} Murphy TV et al, N Engl J Med. 2001 Feb 22;344(8):564-72

\textbf{V = Vaccine}
\textbf{P = Placebo}
Rota – 036  Europe 2004 – 2006
IS surveillance

- 1 case of IS reported in RIX4414 group (N=2572) on Day 8 post – Dose 2 (4 months of age) in a male infant in Czech Republic

- Reposition through laparotomy performed

- Fully recovered after 7 days

- Only case of IS recorded throughout the study

Lancet 2007 Nov 24;370(9601):1757-63
Finland experience

WC-3 reassortant (RotaTeq), protocol 005
One case of intussusception occurred in 1998 in a 7.6 month-old male 8 days after receiving dose #1 of PRV vaccine

UK-bovine reassortant vaccine trial (Wyeth)
5 month-old boy, first dose of study vaccine July 14, 1999. On July 20, 1999 started vomiting and had bloody and mucoid stools and developed IT. The boy was operated. Reintussusception occurred 5 days later, followed by a second operation. Recovery was normal
Intussusception in Finnish Children, 316 cases in 1980-2000

Age Distribution (0-24 months)

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>1</td>
</tr>
<tr>
<td>2-3</td>
<td>2</td>
</tr>
<tr>
<td>4-5</td>
<td>5</td>
</tr>
<tr>
<td>6-7</td>
<td>13</td>
</tr>
<tr>
<td>8-9</td>
<td>32</td>
</tr>
<tr>
<td>10-11</td>
<td>32</td>
</tr>
<tr>
<td>12-13</td>
<td>33</td>
</tr>
<tr>
<td>14-15</td>
<td>20</td>
</tr>
<tr>
<td>16-17</td>
<td>20</td>
</tr>
<tr>
<td>18-19</td>
<td>13</td>
</tr>
<tr>
<td>20-21</td>
<td>8</td>
</tr>
<tr>
<td>22-23</td>
<td>4</td>
</tr>
<tr>
<td>24-25</td>
<td>4</td>
</tr>
<tr>
<td>26-27</td>
<td>6</td>
</tr>
<tr>
<td>28-29</td>
<td>2</td>
</tr>
<tr>
<td>30-31</td>
<td>1</td>
</tr>
<tr>
<td>32-33</td>
<td>1</td>
</tr>
<tr>
<td>34-35</td>
<td>2</td>
</tr>
<tr>
<td>36-37</td>
<td>3</td>
</tr>
</tbody>
</table>

90 days
Have we learned anything from the history of 1998 – 1999?

- All live oral rotavirus vaccines may be associated with IS
- Rotarix and RotaTeq are different from RotaShield, i.e. much less likely to cause intussusception
- Based on the RotaShield experience and natural history of IS, if Rotarix or RotaTeq were to cause IS, such cases were more likely to happen in infants receiving the 1st dose of vaccine when aged 90 days or more
Why vaccinate older infants?
(1st dose over 90 days of age)

For efficacy reasons, vaccination across a wide age range before the rotavirus epidemic season is optimal.

Parents’ requests put pressure on physicians to vaccinate a ”missed” child.

Marketing interests, greater sales at launch.

Age issue not appreciated or believed.

(ACIP 1st draft recommendation in 2005 included a catch – up programme !)
Lessons from modern times

Personal opinion
Postmarketing surveillance shows, in rare cases, temporal association of IS with 1st dose of both RotaTeq™ and Rotarix™

Response strategies
1. Zero risk assumption held until proven otherwise
2. Low but finite risk accepted
   → risk minimization by adherence to early age at 1st vaccination
Let us not throw away the baby with the bathwater, again!