Rotavirus and norovirus vaccines: potential for herd protection?

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Tampere, Finland

Academic Expertise in Vaccine Research
Live oral rotavirus vaccine

Two vaccines licensed in 2006

Worldwide introduction

Real-life effectiveness and impact data available

• vaccine effectiveness
• vaccine impact in target population
• Indirect effect on unvaccinated (older children and adults)
Norovirus vaccine

Live vaccine not possible
- human NoV does not grow in cell culture

Virus-like particle (VLP) and P-particle vaccines are being developed
- administration intramuscularly or intranasally
- limited protection data available from challenge studies

Herd protection, if any, is pure speculation
Mechanisms of indirect protection by RV vaccine

1. Shedding of live RV vaccine virus and transmission to susceptible contacts (like OPV)
   - rare event for RV vaccines

2. Break of transmission chain by immune (immunized) subjects
   - real phenomenon in a RV vaccinated community
Rotarix™ shedding

G1P[8] human rotavirus vaccine multiplies effectively in the intestines

• At least 60% of immunized infants shed virus after 1st dose at a titer that is detectable by EIA (Vesikari T, et al. Vaccine 2004;22:2836–46.)

• Transmission up to 18%, in twins (Rivera L, et al. Vaccine 2011;29:9508–13.)

• Real life significance of transmission is small
RotaTeq® shedding

More common than initially reported (by cell culture)

• About 50% of immunized infants shed vaccine virus by RT-PCR, in most of the cases G1 (Markkula J, et al. PIDJ 2015;34;296–298.)

Transmission has been documented in immunocompromised subjects and healthy children (Boom et al, JID 2012;206:1275, Payne et al, Pediatrics 2010;125:e438, Hemming and Vesikari, PIDJ 2012;31:992–4)

• Transmitted vdG1P[8] may cause diarrhea, but rarely (Hemming and Vesikari, PIDJ 2014;33:655–6.)
RV vaccine-induced immunity prevents disease better than infection.

RRV-TV
Seroconversion rates for serum neutralizing antibodies after 3 doses


Strong overall response (IgA against VP6), but weak G-type specific neutralizing antibody responses
Does not support “serotype hypothesis”
RV5 seroconversion rates
(at least a threefold rise from baseline to ~42 days after dose 3) for serum neutralizing antibodies against serotypes G1 through G4, P[8], and serum antirotavirus IgA

Strong overall response of RV IgA against VP6
"Rotarix"
Seroconversion rates after 2 doses of 89-12 G1P[8] prototype vaccine

Bernstein et al, Vaccine 1998;16:381
Summary and conclusion

All live oral RV vaccines induce strong overall immune response, but only incomplete serotype-specific immune response

→ Protection against intestinal infection will be incomplete

→ Break of RV transmission and effect on herd protection will be incomplete
Rotavirus – does it affect adults and will infant vaccination protect adults?

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RV infection transmitted from children to adults

About one third of adults caring for children with RV gastroenteritis will become infected with RV

→ usually mild symptoms

→ possibility of further transmission
ESCMID, Barcelona, 21 April 2008
Historical slide

Epidemic rotavirus gastroenteritis in adults

Geriatric hospital
Izraeli Kibbutz
Finnish military
College students in the US

RV gastroenteritis - adult travellers

Visitors to Mexico
Role of RV 15 to 40 % of all travellers’ diarrhea
Rotavirus gastroenteritis in adults

Endemic gastroenteritis

- UK: 4%
- Switzerland: 3%
- Sweden: 3%
- Netherlands: 2–4%
- Michigan US: 4%
- Thailand: 5%

Endemic RV diarrhea in adults in Japan
Lack of winter seasonality

Impact RV vaccination in adults

- Less exposure with families, contact cases in parents and medical personal will be reduced
- Adult RV disease may be a separate entity
- RV disease in high risk groups: origin of RV not known
- RV outbreaks in special populations: origin of RV not known

→ vaccination of children may not have impact
Independent US Hospital-based Studies Reported
84-95% Reduction in Rotavirus Cases
2008 vs Previous Years

Missouri 4
88% reduction
Hospitalization

Louisiana 7
88% reduction
Hospitalization

Texas 3
91% reduction
Hospitalization or Emergency Department Visit

Florida 8
91% reduction
Hospitalization

Wisconsin 9
84% reduction
Hospitalization

Massachusetts 5
95% decline
Hospitalization, Emergency Department, Outpatient

New York 6
85% reduction
Hospitalizations

Pennsylvania
87% reduction 1
Rotavirus positive stool samples at Children's Hospital of Philadelphia
94% decrease 2
Rotavirus hospitalizations - St Christopher's Hospital for Children

Figure 4. Observed New Vaccine Surveillance Network (NVSN) hospitalization rates, compared with those hospitalization rates that would be expected on the basis of NVSN vaccine effectiveness and NVSN vaccine coverage, 2006–2009.
Infant Rotavirus Vaccination May Provide Indirect Protection to Older Children and Adults in the United States

Ben A. Lopman, Aaron T.CURIS, Catherine Yen, and Umesh D. Parashar
Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Unexpected Benefits of Rotavirus Vaccination in the United States

Roger I. Glass
Fogarty International Center, National Institutes of Health, Bethesda, Maryland
Figure 2. Monthly rotavirus hospitalizations in the prevaccine era (2000–2006), are shown in panels A to E with the monthly mean in black line and the range in shaded area. The age-specific monthly rate ratios of cause-unspecified hospitalizations in 2008 compared with the prevaccine era are shown in panels F to J (relative rate in red points; black bars represent the 95% confidence interval).
Interpretation of Lopman et al.

- RV disease in epidemic season was reduced in adults
- RV disease outside the season was not reduced

Question remaining

- Follow-up time since introduction of RV vaccination was short
  → longer follow-up needed

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>2000-2006 Unweighted Annual Meana</th>
<th>2008 Unweighted No.</th>
<th>2008 Weighted RR (95% CI)b</th>
<th>2009 Unweighted No.</th>
<th>2009 Weighted RR (95% CI)b</th>
<th>2010 Unweighted No.</th>
<th>2010 Weighted RR (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus-coded gastroenteritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>6651</td>
<td>2058</td>
<td>0.22 (0.14-0.33)</td>
<td>2562</td>
<td>0.29 (0.19-0.42)</td>
<td>663</td>
<td>0.07 (0.03-0.13)</td>
</tr>
<tr>
<td>5-14</td>
<td>372</td>
<td>155</td>
<td>0.29 (0.18-0.45)</td>
<td>227</td>
<td>0.43 (0.29-0.65)</td>
<td>114</td>
<td>0.16 (0.09-0.29)</td>
</tr>
<tr>
<td>15-24</td>
<td>26</td>
<td>14</td>
<td>0.35 (0.14-0.85)</td>
<td>25</td>
<td>0.73 (0.34-1.60)</td>
<td>10</td>
<td>0.32 (0.12-0.87)</td>
</tr>
<tr>
<td>25-44</td>
<td>24</td>
<td>22</td>
<td>0.68 (0.35-1.30)</td>
<td>17</td>
<td>0.57 (0.27-1.20)</td>
<td>10</td>
<td>0.33 (0.13-0.82)</td>
</tr>
<tr>
<td>45-64</td>
<td>35</td>
<td>35</td>
<td>0.77 (0.45-1.30)</td>
<td>56</td>
<td>1.24 (0.72-2.10)</td>
<td>23</td>
<td>0.43 (0.21-0.89)</td>
</tr>
<tr>
<td>≥65</td>
<td>54</td>
<td>78</td>
<td>0.79 (0.51-1.20)</td>
<td>114</td>
<td>1.08 (0.68-1.70)</td>
<td>34</td>
<td>0.25 (0.13-0.47)</td>
</tr>
</tbody>
</table>
Indirect protection of older children after introduction of RV UMV

Belgium 20–64% reduction in RV 1–2 years after UMV, children >24 months (Raes et al PIDJ 2011;30:E120)

Austria 38% decrease in RV hospitalizations 1–2 years after UMV, age group 5–15 years (Paulke-Korinek et al, Vaccine 201;28:2791)
Finland

Pop. 5.5 million
Birth cohort 60,000

• Universal rotavirus vaccination programme introduced in September 2009
• RotaTeq® vaccine exclusively
• Schedule 2, 3 and 5 months
• 300,000 infants vaccinated as of today
• A unique situation to study effects of RotaTeq® vaccination as a whole
Rotavirus AGE cases in Tampere, Finland in 2006-2014

RV infections of all AGE cases
- 2006-2008: 52%
- 2009-2011: 26%
- 2012-2014: 13%

Age distribution of RVGE in Tampere University Hospital

Real life effectiveness of RotaTeq® in Finland

<table>
<thead>
<tr>
<th>Cases</th>
<th>RVGE</th>
<th>EIA+</th>
<th>RT-PCR+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>GE</td>
<td>EIA-</td>
<td>RT-PCR-</td>
</tr>
</tbody>
</table>

Children eligible for vaccination

<table>
<thead>
<tr>
<th></th>
<th>Adjusted VE (95% C.I.)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully vaccinated</td>
<td>95.8 (81.8–99.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At least one dose</td>
<td>93.9 (78.6–98.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Impact of RV universal vaccination programme with RotaTeq

Hospitalization for all-cause AGE <2 years of age

<table>
<thead>
<tr>
<th>Area</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oulu (North)</td>
<td>73.9 (69.6–77.4)</td>
</tr>
<tr>
<td>Tampere (South)</td>
<td>69.5 (58.6–69.5)</td>
</tr>
<tr>
<td>Both</td>
<td>70.2 (66.9–73.1)</td>
</tr>
</tbody>
</table>
Conclusions

• Finland has the highest real life effectiveness of RotaTeq® vaccine reported from anywhere
  - optimal schedule 2, 3, 5 months
  - high coverage of vaccination (>95%)

• Finland has the highest impact (on RV hospitalization) of rotavirus vaccination reported anywhere

Still, indirect protection of unvaccinated children is not seen in long-term follow-up (early observation of indirect protection may be “honeymoon effect”)

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RVGE in 4–15 year-old children

<table>
<thead>
<tr>
<th></th>
<th>Incidence/1000 children</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001–2006 (before vaccinations)</td>
<td>0.0712</td>
</tr>
<tr>
<td>2009 – 2013 (after vaccinations)</td>
<td>0.0685</td>
</tr>
</tbody>
</table>

4% decrease, not significant
Incidence of RVGE and all AGE cases per 1000 children in children aged 4-15 years.
Conclusion on RV vaccine-induced herd protection

• RV will continue to circulate even at high level of vaccine coverage

• RV will "pick-up" unvaccinated older children and adolescents sooner or later

• For adults, RVGE resulting from exposure within families will be reduced

but

• “true” adult RV disease may continue to live its own life and form a RV reservoir
Norovirus gastroenteritis

1. Endemic ("sporadic") NoVGE in children
2. Outbreak related NoVGE in all age groups
   - military
   - cruise ships
   - should etc.
   - the elderly in nursing homes

The same are potential targets of NoV vaccination
Norovirus gastroenteritis in Tampere University Hospital

2006–2008: 24% (28%/47%)
2009–2011: 34% (29%/62%)
2012–2014: 27% (19%/67%)

RV vaccine in NIP
The frequency of NoV infections and the levels of NoV specific IgG in different children age groups

Nurmininen et al. 2011
Development of NoV immunity

Natural immunity is serotype-specific and lasts for a maximum of 2 years.

Repeated exposures to different NoVs build up immunity against disease but not infection.

Every 2 years approximately a new variant of GII.4 NoV emerges (“escape from herd immunity”) causing GE in children and adults.

Current candidate VLP vaccines may protect against disease but not infection.
The seroprevalence of NoV antibodies in Finnish children

Nurminen et al. 2011
Norovirus Vaccine Against Experimental Human GII.4 Virus Illness: A Challenge Study in Healthy Adults


1Cincinnati Children’s Hospital Medical Center, University of Cincinnati College of Medicine, Ohio; 2Baylor College of Medicine and Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; 3Emory University School of Medicine, Atlanta, Georgia; 4University of Rochester Medical Center, New York; 5University of Maryland School of Medicine, Baltimore; 6Centers for Disease Control and Prevention, 7Emory University Rollins School of Public Health, Atlanta, Georgia; 8Shin Nippon Biomedical Laboratories, Baltimore, 9The EMMES Corp, Rockville, Maryland; 10Takeda Vaccines Inc, Deerfield, Illinois; and 11Takeda Pharmaceuticals International, Zurich, Switzerland

Journal of Infectious Diseases Advance Access published October 6, 2014

EDITORIAL COMMENTARY

Norovirus Vaccine: One Step Closer

Timo Vesikari and Vesna Blazevic

Vaccine Research Center, University of Tampere, Finland
Ligocyte/Takeda
Candidate norovirus vaccine

• Bivalent G1 / GII combination, 50µg each
• Produced in baculovirus/SF9 cell system
  – GI Original Norwalk virus sequence GI-1
  – GII “Consensus” sequence of three GII-4 viruses
• MPL+aluminum adjuvant
• administered intramuscularly
Norovirus GI/GII vaccine (Takeda) Challenge study in healthy volunteers

Vaccine given intramuscularly in 2 doses
Challenge on Day 42 with GII-4 Farmington NoV
50 vaccinees and 48 control

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Protection</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe vomiting/diarrhea</td>
<td>100 %</td>
<td>0.054</td>
</tr>
<tr>
<td>Moderate to severe vomiting/diarrhea</td>
<td>68 %</td>
<td>0.068</td>
</tr>
<tr>
<td>Any vomiting/diarrhea</td>
<td>47 %</td>
<td>0.074</td>
</tr>
<tr>
<td>Infection</td>
<td>14 %</td>
<td>0.420</td>
</tr>
</tbody>
</table>

Norovirus GI-1/GII-4 vaccine (Takeda) Challenge study in healthy volunteers

2 doses of vaccine i.m.
Challenge on Day 42 with GII-4 Farmington NoV

Reduction of disease severity measured by modified Vesikari scale

<table>
<thead>
<tr>
<th>Vaccinees (N=50)</th>
<th>Controls (N=48)</th>
<th>p=0.002</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.3</td>
<td>7.3</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: NoV by a heterovariant GII.4 vaccination reduces the severity of NoV infection, but does not prevent infection

Analogy with RV vaccine induced protection against severe RVGE

Intranasally administered norovirus vaccine (LigoCyte)

100 µg Norwalk virus GI.1 VLP
+ Monophosphoryl lipid A (GSK)
  Chitosan (Archimedes)

Healthy volunteers aged 18 to 50 years
Two intranasal doses 3 weeks apart
Challenge with the homologous Norwalk virus

Intranasally administered norovirus vaccine (LigoCyte)

Proof-of-principle of VLP-vaccine-induced protection

Protection against experimental challenge with GI.1 Norwalk virus (10 x infectious dose)

<table>
<thead>
<tr>
<th></th>
<th>Vaccine (N=45)</th>
<th>Placebo (N=41)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norwalk virus gastroenteritis</td>
<td>37 %</td>
<td>69 %</td>
<td>0.006</td>
</tr>
<tr>
<td>Median duration of illness (h)</td>
<td>44</td>
<td>37</td>
<td>N.S.</td>
</tr>
<tr>
<td>Severity score when ill</td>
<td>6.4</td>
<td>6.7</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Intranasally administrered NoV GI.1 challenge VLP vaccine protected (moderately well) against homologous GI.1. challenge NoV infection but did not reduce disease severity

Conclusions from NoV VLP challenge studies

1. Intramuscularly administered NoV VLP vaccine reduced severity of gastroenteritis induced by heterovariant NoV

2. Intransansally administered NoV VLP vaccine protected against homologous NoV infection (but not at a high level)
Alternative NoV vaccine

- P-particle (or VLP) with variable part of P-domain changed for every emerging variant
- "Flu-like" vaccine to be given every 2 years?
- Might induce better homologous protection of short duration
- Impractical concept
Our NoV vaccine design concept

• A NoV VLP vaccine should contain representatives of the two major genogroups, GI and GII, because vaccine-induced immunity is genogroup restricted

• Within genogroups the NoV vaccine should, and can, induce broadly protective immunity against NoVGE

• Such a vaccine will not induce much protection against NoV infection

→ effect on herd protection is likely to be small
NoV GII-4 VLPs + GI-3 VLPs + RV VP6
vaccine design

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Sample year</th>
</tr>
</thead>
<tbody>
<tr>
<td>NoV GII-4 VP1</td>
<td>1999</td>
</tr>
<tr>
<td>NoV GI-3 VP1</td>
<td>2002</td>
</tr>
<tr>
<td>RV VP6</td>
<td>2007</td>
</tr>
</tbody>
</table>

Actual sequences from named patients in Finland, and intellectual property of University of Tampere
Proposed uses of trivalent RV rVP6 + NoV GII-4 + NoV GI-3 combination vaccine

1. Infant vaccine
   - Primary vaccination ages 2-6 months
     - Booster vaccination at 12 months

2. Toddler vaccine
   - (Primary vaccination with live oral RV vaccine)
   - RV-NoV combo vaccine 2 doses at age 12-15 months

These vaccinations (RV VP6 + NoV VLP) will not have much effect on herd protection.
Thank you!