Four year effectiveness and safety of human-bovine reassortant rotavirus vaccine (RotaTeq®) in Finland

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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

RotaTeq® in Finland

Real life effectiveness (vs. non-vaccination)
Impact (vs. prevaccination years)
- direct impact in vaccinated children
- indirect impact in non-vaccinated persons

Immunological pressure (lack of)
Vaccine-derived double reassortants (vdG1P[8])
Vaccine virus shedding and prolonged infection
Intussusception (very rare)
Prospective follow-up in Finland in 2009–2013
Hospital admission in 4 RV seasons
2 hospital districts (North and South)

Study EIA+ PCR+ AGE cases by month of symptom onset, overall (N=143) and by study site, children <16 yrs, Finland 2009-2013
Real life effectiveness of RotaTeq® in Finland

Cases

<table>
<thead>
<tr>
<th></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><strong>95.8 (81.8–99.0)</strong></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At least one dose</td>
<td><strong>93.9 (78.6–98.3)</strong></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Impact of RV universal vaccination programme with exclusively RotaTeq vaccine in Finland (2 hospital districts)

* Prevaccination years 2001–2006 (5 seasons)

* Transition period 2006–2009 (3 seasons), (Rotarix and RotaTeq available, coverage up to 35%)

* Post NIP period 2009–2013 (4 seasons) vs. prevaccination period

Endpoints
- hospitalization with RV EIA+ gastroenteritis
- hospitalization for all cause gastroenteritis
Impact of RV universal vaccination programme with RotaTeq

Hospitalization for RVGE <2 years of age

<table>
<thead>
<tr>
<th></th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oulu (North)</td>
<td>80.4 (72.1–86.2)</td>
</tr>
<tr>
<td>Tampere (South)</td>
<td>97.0 (92.6–98.0)</td>
</tr>
<tr>
<td>Both</td>
<td>88.3 (83.8–91.5)</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>Location</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>
Indirect effect of RV vaccination

Hospitalization for RVGE in children aged 4–15 years in 2001–13 (2 hospital districts, North and South)

No reduction in RVGE hospitalizations in children too old to be vaccinated in NIP
RV G-types in Tampere after RV vaccination programme with RotaTeq®

- Canine G3
- G12
- G3+G9
- G1+G4
- G1+G3
- G9
- G4
- G3
- G2
- G1

RV G-types in breakthrough cases in vaccinated children

Do G-types still matter?
No G1 in breakthrough cases

Wild-type RV G1 - VP7 antigens

• A 20-year study period, including 10 study seasons
  • 4 from pre-vaccination period 1992-1994 2002-2004
  • 2 from the interim period 2006-2008
  • 4 from post-vaccination years 2009-2013

RESULTS of VP7:
• Sublineages G1-I and G1-II were found in each time period
• No vaccine induced selective pressure on VP7 antigenic region of G1 genotype
Immunological pressure on wild type RVG1 - VP8* antigens

RESULTS of VP8* antigen:

• Two lineages were not present at the same time

• Periodical shifting between two intragenotypic lineages P[8]-I and P[8]-III

• No strains representing P[8]-II sublineage (same as RotaTeq®) were detected

• After use of Rotarix™ in Finland in 2006-2008, a shift in sublineages was seen from P[8]-I (where Rotarix™ aligns) into P[8]-III
Vaccine-derived human-bovine double reassortant vdG1P[8]

- A new reassortant between two original vaccine viruses G1P[5] and G6P[8]
- Both outer capsid proteins originated from human rotaviruses G1 and P[8]
- Stability verified in cell culture
- Associated with gastroenteritis, but not always

Vaccine-derived human-bovine double reassortant vdG1P[8]

- 5 cases in Tampere University Hospital in post-vaccine years 2009-2013 among RVGE requiring hospitalization
- 4 recently vaccinated children
  - Admitted to the hospital for AGE symptoms
  - Had received 1st or 2nd dose of vaccine <7d before onset of symptoms
  - 3 were immunocompetent and 1 immunocompromised
  - Only 1 had another GE pathogen detected concomitantly → vdG1P[8] likely cause of symptoms
- 1 unvaccinated child
  - Immunocompetent 7-year-old girl
  - Source of the vaccine originated virus unclear
  - No other GE pathogens detected

RotaTeq® prolonged shedding

A survey in children hospitalized for RTI in 2009–2011 after the start of RV vaccine in NIP

182 children <2 years ever vaccinated
30 detected with RotaTeq derived virus by RT-PCR

14 after 1st dose
10 after 2nd dose
6 after 3rd dose

Long-time shedders after 3rd dose on days 9, 22, 39, 52, 53, 84

The time of origin of shedding not known

Hypothesis: The 1st dose may select long time shedders, who may continue to have a prolonged intestinal infection up to 6 months
RotaTeq® derived vaccine strain viruses in children hospitalized for RTI

<table>
<thead>
<tr>
<th>Genotype</th>
<th>1st dose (N=14)</th>
<th>2nd dose (N=10)</th>
<th>3rd dose (N=6)</th>
<th>Total (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1P[8]</td>
<td>57 (8)</td>
<td>20 (2)</td>
<td>17 (1)</td>
<td>37 (11)</td>
</tr>
<tr>
<td>G1P[5]</td>
<td>7 (1)</td>
<td>20 (2)</td>
<td>17 (1)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>G1+P[5]+P[8]</td>
<td>7 (1)</td>
<td>0</td>
<td>0</td>
<td>3 (1)</td>
</tr>
<tr>
<td>G1+ wild-type P[8]</td>
<td>0</td>
<td>10 (1)</td>
<td>0</td>
<td>3 (1)</td>
</tr>
<tr>
<td>G6P[8]</td>
<td>7 (1)</td>
<td>0</td>
<td>17 (1)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>G1 alone*</td>
<td>21 (3)</td>
<td>50 (5)</td>
<td>50 (3)</td>
<td>37 (11)</td>
</tr>
</tbody>
</table>

* VP4 RT-PCR negative

G1 in some combination found in 93%
vdG1P[8] found in 37%

Finland 2009–2013
IS after RotaTeq® vaccination

1 case of intussusception causally related to RV vaccination 7 days after dose 1 per 300 000 vaccinated infants

Note: 1st dose of RotaTeq® vaccine given at 6–8 weeks of age
Conclusions I

• Finland has the highest real life effectiveness of RotaTeq® vaccine reported from anywhere
  - optimal schedule 2, 3, 5 months
  - low maternal antibody levels allow high uptake

• Finland has the highest impact (on RV hospitalization) of rotavirus vaccination reported anywhere
  - high coverage of vaccination (>95%)

• 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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Conclusions II

RotaTeq® vaccination associated issues

• No measurable antigenic pressure on wild-type RVs (G1)

• vdG1P[8] double reassortants cause diarrhea which will make a sizeable proportion of RV gastroenteritis after wild-type RVGE has been largely eliminated

• Prolonged intestinal infection by G1 reassortant derivatives may be a bigger issue than held previously

• IS can be largely controlled by administration of the 1st dose at 60 days of age
Final conclusion

The benefit/risk ratio of universal immunization programme with RotaTeq® vaccine in Finland is strongly positive

but

The full story of RotaTeq® vaccination is not yet delineated and surveillance needs to be continued
Thank you!
Back-up slide
Summary of immune responses for RV5

1. Successfully completed 3-dose schedule results in strong overall immune response (RV IgA against VP6) and subsequent high level protection against severe RVGE associated with multiple G-types of RV

2. Four G-reassortants in vaccine allow repeated uptake of vaccine after 2nd and 3rd dose