Impact of Switch to IPV on Rotavirus Vaccine Performance

Umesh D. Parashar
Lead, Viral Gastroenteritis Epidemiology Team
CDC, Atlanta GA
Efficacy of oral rotavirus vaccines is lower in resource-limited areas

Figure 1. Pooled estimates of efficacy against severe rotavirus disease by income settings for first and second generation rotavirus vaccines. These estimates are the pooled estimates and 95% confidence limits are generated from studies outlined in Tables 2 and 3 (refer to Methods).

Multiple factors affect rotavirus vaccine efficacy in resource-limited areas

- Poor response to oral rotavirus vaccine
- Transplacental and breast milk rotavirus antibodies
- Gastrointestinal pathogens
- Intestinal microbiota
- Nutrition
- Environmental enteropathy
- Interference of OPV co-administration
The Polio Eradication & Endgame Strategic Plan
2013-2018

Introduce
• at least one dose of IPV
• into routine immunization

Switch
• tOPV to bOPV

Withdraw
• of bOPV & routine OPV use

Before end 2015

2016

2019-2020

Ongoing STRENGTHENING of routine immunization services
1. Does co-administration of rotavirus vaccine affect the performance of oral polio vaccine?
<table>
<thead>
<tr>
<th>Antibody</th>
<th>Timing</th>
<th>Sero-protection rate % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-poliovirus type 1</td>
<td>RIX4414 + OPV</td>
<td>86.4 (76;94)</td>
</tr>
<tr>
<td></td>
<td>Placebo + OPV</td>
<td>90.1 (81;96)</td>
</tr>
<tr>
<td>Anti-poliovirus type 2</td>
<td>RIX4414 + OPV</td>
<td>98.5 (92;100)</td>
</tr>
<tr>
<td></td>
<td>Placebo + OPV</td>
<td>97.1 (90;100)</td>
</tr>
<tr>
<td>Anti-poliovirus type 3</td>
<td>RIX4414 + OPV</td>
<td>69.6 (57;80)</td>
</tr>
<tr>
<td></td>
<td>Placebo + OPV</td>
<td>68.1 (56;79)</td>
</tr>
</tbody>
</table>

### Seroresponse to polio vaccine with and without pentavalent rotavirus vaccine co-administration, Latin America

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Timing</th>
<th>Sero-protection rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-poliovirus type 1</td>
<td>RotaTeq + OPV</td>
<td>98.9 %</td>
</tr>
<tr>
<td></td>
<td>Placebo + OPV</td>
<td>99.4%</td>
</tr>
<tr>
<td>Anti-poliovirus type 2</td>
<td>RotaTeq + OPV</td>
<td>99.7%</td>
</tr>
<tr>
<td></td>
<td>Placebo + OPV</td>
<td>99.7%</td>
</tr>
<tr>
<td>Anti-poliovirus type 3</td>
<td>RotaTeq + OPV</td>
<td>98.3%</td>
</tr>
<tr>
<td></td>
<td>Placebo + OPV</td>
<td>98.4%</td>
</tr>
</tbody>
</table>

Ciarlet et al. PIDJ 2008; 27: 874-80
1. Does co-administration of rotavirus vaccine affect the performance of oral polio vaccine?

No!
2. Does co-administration of trivalent oral polio vaccine (tOPV) affect performance of rotavirus vaccine?
Seroconversion rates to RIX 4414 with tOPV or IPV in South African Infants

Sero-conversion rates per groups

- HRV$^{5.2}\text{ffu} + \text{tOPV}$
- HRV$^{5.2}\text{ffu} + \text{IPV}$

Steele et al, poster, ICP Cancun, 2004; Steele et al, Vaccine, 2008
Interference of tOPV on serum IgA antibody response to RIX 4414 in Bangladesh

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>N</th>
<th>n</th>
<th>Seroconversion rate % (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIX4414 + tOPV</td>
<td>69</td>
<td>39</td>
<td>57 (44; 68)</td>
<td>0.113</td>
</tr>
<tr>
<td>RIX4414</td>
<td>66</td>
<td>44</td>
<td>67 (54; 78)</td>
<td></td>
</tr>
</tbody>
</table>

Sero-conversion rate, cut-off ≤ 20U/ml

Serum neutralizing antibodies to RotaTeq with concomitant or staggered tOPV use in Latin America

Ciarlet et al. PIDJ 2008; 27: 874-80
2. Does co-administration of trivalent oral polio vaccine (tOPV) affect performance of rotavirus vaccine?

Yes!
3. Does interference with rotavirus vaccine performance also occur with co-administration of bOPV and mOPV?
• Type 2 component of tOPV replicates most efficiently

• Removal of type 2 might reduce interference on rotavirus vaccine?
RCT* of different OPV formulations in healthy infants in Bangladesh from May – December 2012

Note: Infants in Matlab received RV1; infants in Mirpur did not.

Source: Clinical Trial #NCT01633216
Post-hoc analysis

Infants in Matlab (N=528)

- **RV1+mOPV1** (n=208)
  - Excluded* from final analysis (n=59)
  - Included in final analysis (n=149)
    - Concomitant admin (n=70)
    - Staggered admin (n=79)

- **RV1+bOPV** (n=209)
  - Excluded from final analysis (n=59)
  - Included in final analysis (n=154)
    - Concomitant admin (n=72)
    - Staggered admin (n=82)

- **RV1+tOPV** (n=111)
  - Excluded from final analysis (n=5)
  - Included in final analysis (n=109)
    - Concomitant admin (n=32)
    - Staggered admin (n=74)

Exclusion criteria:
- Unknown RV1 admin
- Missing serological data
- 2nd RV dose <3 weeks to final blood collection

Emperador D et al. CID 2016;62:150-6
Groups were similar at baseline

<table>
<thead>
<tr>
<th>Characteristics (Baseline)</th>
<th>RV1+mOPV1 n=149</th>
<th>RV1+bOPV n=154</th>
<th>RV1+tOPV n=106</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male (%)</td>
<td>70 (47%)</td>
<td>84 (54%)</td>
<td>61 (58%)</td>
</tr>
<tr>
<td>Age (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>45.9 (2.5)</td>
<td>45.6 (2.4)</td>
<td>45.3 (2.5)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>46.0 (42-50)</td>
<td>45.6 (42-50)</td>
<td>45.0 (42-50)</td>
</tr>
<tr>
<td>Mother’s education &lt;5 years (%)</td>
<td>66 (44%)</td>
<td>77 (50%)</td>
<td>45 (43%)</td>
</tr>
<tr>
<td>Malnutrition (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stunting, anytime</td>
<td>15 (10%)</td>
<td>21 (14%)</td>
<td>18 (17%)</td>
</tr>
<tr>
<td>Wasting, anytime</td>
<td>60 (40%)</td>
<td>62 (40%)</td>
<td>37 (35%)</td>
</tr>
<tr>
<td>Full breastfeeding (%)</td>
<td>149 (100%)</td>
<td>154 (100%)</td>
<td>105 (99%)</td>
</tr>
<tr>
<td>Rotavirus IgA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Seropositive (IgA &gt;40) at baseline (95% CI)</td>
<td>32% (24-39)</td>
<td>30% (23-37)</td>
<td>35% (26-44)</td>
</tr>
<tr>
<td>IgA (GMT) at baseline (95% CI)</td>
<td>13 (9-17)</td>
<td>10 (8-14)</td>
<td>14 (10-19)</td>
</tr>
</tbody>
</table>
No difference in RV1 immunogenicity by OPV type

**RV-IgA seroconversion**

<table>
<thead>
<tr>
<th>RV1+mOPV1</th>
<th>RV1+bOPV</th>
<th>RV1+tOPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>% seroconversion (&gt;4-fold rise)</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

**RV-IgA geometric mean titer**

<table>
<thead>
<tr>
<th>RV1+mOPV1</th>
<th>RV1+bOPV</th>
<th>RV1+tOPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric mean titer (GMT)</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

[Graphs showing seroconversion and geometric mean titer for RV1+mOPV1, RV1+bOPV, and RV1+tOPV]
Lower RV1 immunogenicity when OPV given concomitantly...

**RV IgA seroconversion**

- Concomitant: ~45%
- Staggered: ~80%

\[ p = 0.001 \] *

**RV IgA geometric mean titer**

- Concomitant: ~50
- Staggered: ~150

\[ p = 0.001 \] **

*Chi-square test. **Non-parametric Wilcoxon test.

Emperador D et al. CID 2016;62:150-6
... regardless of OPV formulation.

RV-IgA seroconversion

% seroconversion

RV1+mOPV1  RV1+bOPV  RV1+tOPV

p=0.035*  p=0.035*

p=0.035*

RV-IgA geometric mean titer

Geometric mean titer (GMT)

RV1+mOPV1  RV1+bOPV  RV1+tOPV

p=0.037**  p=0.010**

*Chi-square test. **Non-parametric Wilcoxon test.

Emperador D et al. CID 2016;62:150-6
Serum IgA antibody response among infants given RV1 with bOPV versus IPV in Chile

<table>
<thead>
<tr>
<th></th>
<th>bOPV</th>
<th>IPV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seroconversion</td>
<td>50%</td>
<td>65%</td>
<td>0.004</td>
</tr>
<tr>
<td>Log IgA Titer</td>
<td>1.8</td>
<td>2.1</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Ramani et al. PIDJ e-pub ahead of print
3. Does interference with rotavirus vaccine performance also occur with co-administration of bOPV and mOPV?

Yes!
4. What is the impact of OPV interference on rotavirus vaccine efficacy?

- Trial of RV1 co-administered with OPV in Latin America
- Efficacy similar to high efficacy of 85% demonstrated in the Latin American study without OPV co-administration

Tregnaghi, M. et al. PIDJ 2011;30:e103-8
Summary

• Co-administered rotavirus vaccines do not interfere with the immune response of polio vaccines

• Co-administered oral polio vaccines interferes with the immune response to rotavirus vaccine

• Interference appears to be similar with all formulations of OPV (tOPV, bOPV, and mOPV)

• Switch to IPV will likely be beneficial for performance of rotavirus vaccines