Effectiveness and impact of monovalent rotavirus vaccine against hospitalisation for acute rotavirus diarrhoea in South African children: a case control study

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**Background**

- Population ~53 million; 1 084 397 births in 2013.
- Diarrhoea was a leading cause of death (18%) in South African children < 5 years of age in 2009. \(^1\)
- ~25% rotavirus detection among children hospitalised for diarrhoea in South Africa.
- Estimated to cause 17 644 to 25 630 hospitalisations. \(^2\)
- Vaccine efficacy against severe rotavirus-diarrhoea:
  - 77% (95% CI: 56%–88%) during the first year of life. \(^3\)
  - 59% (95% CI: 1%–83%) over two consecutive rotavirus seasons. \(^4\)

Background

- First African country to introduce rotavirus vaccine into national immunisation programme, beginning August 2009.
- Rotarix recommended at 6 and 14 weeks of age.
- Children receive OPV concurrent with HRV at the 6-week immunisation visit.
- The estimated national HIV prevalence in 2011 was 30% among pregnant women aged 15–49 years.
- The national HIV prevalence estimate among children < 5 years was 4.1% in 2009, decreasing to 3.5% by 2013.
- The rollout of ART in the public sector started in 2004.
Aim and methods

• We conducted a case-control study to estimate the effectiveness of the monovalent oral live-attenuated human rotavirus vaccine against hospitalisation for rotavirus gastroenteritis in children under two years of age in South Africa.

• April 2010 to October 2012 (for this analysis).

• Existing rotavirus surveillance programme, with addition of two sites.
Participants

- Children hospitalised overnight with physician-diagnosed acute diarrhoea.
- Age-eligible to have received at least one dose of HRV (i.e. born after 14 June 2009).
- Assessed for eligibility, invited to participate and consent obtained.
- Stool specimen collected within 48 hours of admission.
- Testing was done using enzyme immunoassay (ProSpecT ELISA, Oxoid, UK).
- Rotavirus-positive samples genotyped using standardized methods.
Methods

• **Cases**: hospitalised for acute diarrhoea (≤7 days duration at admission, ≥3 loose stools in a 24-hour period) with stool sample positive for rotavirus (EIA).

• **Controls**:
  • Hospitalised for acute diarrhoea with stool sample negative for rotavirus (EIA).
  • Respiratory controls (selected sites).

• Demographic indicators, clinical history: parent interview.

• Vaccination status (exposure): Road-to-Health card.

• Medical record review.

• HIV infection status.
Methods

• Primary analysis: adjusted VE (aVE) of two HRV doses compared to no vaccination against hospitalisation for acute rotavirus-diarrhoea in children 18 weeks–23 months of age using rotavirus-negative controls.

• Secondary analyses: limited to children from three hospitals where respiratory controls were enrolled.

• Stratified analyses: age (18 weeks–11 months and 12–23 months), HIV-exposure status in HIV-uninfected children.

• Exclusions: no stool sample, no vaccination history available.

• A dose was counted if administered ≥14 days before hospitalisation.

• Unconditional logistic regression models: estimate adjusted odds ratio (aOR) with associated 95% confidence intervals.

• aVE: \((1 - \text{aOR}) \times 100\%\).
Enrolled n= 2381

Fulfilling case definition
n=2295

Diarrhoea >7 days duration at admission or <3 stools in a 24-hour period n=86

No stool available/insufficient sample n=196

Rotavirus-positive cases
n=577

Rotavirus-negative controls
n=1522

No vaccination history available
n=37

Previously a case/control n=3
No vaccination history available n=85

Rotavirus positive cases
n=540

Rotavirus negative controls
n=1434
Age at vaccination

Number vaccinated

Age in weeks

First HRV dose
Second HRV dose
Results

• Compared with rotavirus negative controls, cases were:
  • Younger
  • Socioeconomic factors such as type of housing, access to electricity, toilet type and water source, as well as maternal education were similar

• Compared with respiratory controls, cases were:
  • Similar in age
  • Less access to electricity, a flush toilet and brick housing
Results

• Hospital, birth month, birth year, month by year of birth (interaction term), hospitalisation quarter, hospitalisation year, quarter by year of hospitalisation (interaction term) were included in the models a priori.

• Inclusion of gender, race, history of breastfeeding, maternal education, daycare attendance, birth weight, and variables of household characteristics did not alter the adjusted odds ratio by >5% and were, therefore, not included in the final models.
## Vaccination status and aVE estimates

<table>
<thead>
<tr>
<th>Number of HRV doses&lt;sup&gt;b&lt;/sup&gt;</th>
<th>All hospitals</th>
<th>Rotavirus-negative controls (n=1434)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%) of rotavirus-positive cases (n=540)</td>
<td>No (%)</td>
</tr>
<tr>
<td>0 (Reference)</td>
<td>136 (25)</td>
<td>244 (17)</td>
</tr>
<tr>
<td>1</td>
<td>126 (23)</td>
<td>334 (23)</td>
</tr>
<tr>
<td>2</td>
<td>278 (52)</td>
<td>856 (60)</td>
</tr>
</tbody>
</table>
**aVE estimates by age group**

<table>
<thead>
<tr>
<th>Number of HRV doses</th>
<th>All hospitals</th>
<th>Rotavirus-negative controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%) of rotavirus-positive cases</td>
<td>No (%)</td>
</tr>
<tr>
<td><strong>18 weeks to 11 months</strong></td>
<td>n=389</td>
<td>n=947</td>
</tr>
<tr>
<td>0 (Reference)</td>
<td>90 (23)</td>
<td>149 (16)</td>
</tr>
<tr>
<td>1</td>
<td>92 (24)</td>
<td>231 (24)</td>
</tr>
<tr>
<td>2</td>
<td>207 (53)</td>
<td>567 (60)</td>
</tr>
<tr>
<td><strong>12 to 23 months</strong></td>
<td>n=151</td>
<td>n=487</td>
</tr>
<tr>
<td>0 (Reference)</td>
<td>46 (30)</td>
<td>95 (20)</td>
</tr>
<tr>
<td>1</td>
<td>34 (23)</td>
<td>103 (21)</td>
</tr>
<tr>
<td>2</td>
<td>71 (47)</td>
<td>289 (59)</td>
</tr>
</tbody>
</table>
Results

• HIV-infected cases; n=45.
• Not powered to assess effectiveness in HIV-infected children.
• HIV-exposure status was available for 98% of HIV-uninfected children.
• 31% were HEU and 69% were HUU.
# aVE estimates by HIV-exposure status

<table>
<thead>
<tr>
<th></th>
<th>All hospitals</th>
<th>Rotavirus-negative controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%) of rotavirus-positive cases</td>
<td>No (%)</td>
</tr>
<tr>
<td><strong>Number of HRV doses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total HIV- uninfected</td>
<td>n=454</td>
<td>n=1174</td>
</tr>
<tr>
<td>0 (Reference)</td>
<td>110 (24)</td>
<td>191 (16)</td>
</tr>
<tr>
<td>1</td>
<td>106 (23)</td>
<td>265 (23)</td>
</tr>
<tr>
<td>2</td>
<td>238 (52)</td>
<td>718 (61)</td>
</tr>
<tr>
<td>HIV-exposed-uninfected (HEU)</td>
<td>n=131</td>
<td>n=396</td>
</tr>
<tr>
<td>0 (Reference)</td>
<td>30 (23)</td>
<td>50 (13)</td>
</tr>
<tr>
<td>1</td>
<td>26 (20)</td>
<td>90 (23)</td>
</tr>
<tr>
<td>2</td>
<td>75 (57)</td>
<td>256 (65)</td>
</tr>
<tr>
<td>HIV-unexposed-uninfected (HUU)</td>
<td>n=320</td>
<td>n=741</td>
</tr>
<tr>
<td>0 (Reference)</td>
<td>79 (25)</td>
<td>132 (18)</td>
</tr>
<tr>
<td>1</td>
<td>79 (25)</td>
<td>166 (22)</td>
</tr>
<tr>
<td>2</td>
<td>162 (51)</td>
<td>443 (60)</td>
</tr>
</tbody>
</table>
## Vaccination status and aVE estimates

<table>
<thead>
<tr>
<th>Number of HRV doses(^b)</th>
<th>Subset of hospitals(^a)</th>
<th>Rotavirus-negative controls (n=1024)</th>
<th>Respiratory controls (n=1069)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No (%)</td>
<td>No (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>aVE(^c) % (95% CI)</td>
<td>aVE(^c) % (95% CI)</td>
</tr>
<tr>
<td>0 (Reference)</td>
<td>94 (25)</td>
<td>181 (18)</td>
<td>140 (13)</td>
</tr>
<tr>
<td>1</td>
<td>87 (24)</td>
<td>238 (23)</td>
<td>232 (22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35 (4–56)</td>
<td>54 (31–69)</td>
</tr>
<tr>
<td>2</td>
<td>189 (51)</td>
<td>605 (59)</td>
<td>697 (65)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>52 (29–67)</td>
<td>63 (45–75)</td>
</tr>
</tbody>
</table>
Rotavirus strains

- The predominant rotavirus strains (n=538) over the study period:

- **G12P[8]**: 43%
- **G2P[4]**: 14%
- **G1P[8]**: 12%
- **G9P[8]**: 8%
- **G8P[4]**: 7%
- **G2P[6]**: 5%
- **Other**: 11%
- **12%**: 14%
Rotavirus strains

- aVE for two doses of HRV against G12P[8] was 71% (95% CI: 55%–82%).
- Against any homotypic/partially heterotypic strains (G protein and/or P protein were of the same type as the vaccine strain): 62% (95% CI: 45%–74%, cases: n=369).
- Against any fully heterotypic strains (both G and P proteins were different from those of the vaccine strain): 52% (95% CI: 20%–72%, cases: n=155)
Time series analysis - Soweto

- Chris Hani Baragwanath Academic Hospital.
Trends - Children under 5 years

Monthly count of diarrhoeal hospitalisations among children under 5 years, Soweto, South Africa, 2006-2013

Rotavirus vaccine introduction Aug 2009

Age group
- Under 1 year
- 1 Year
- 2-4 Years

Admission month and year

Monthly count of diarrhoeal hospitalisations among children under 5 years, Soweto, South Africa, 2006-2013

HIV-infected (assuming same prevalence in untested)

Admission month and year

Rotavirus vaccine introduction Aug 2009

Age group
- Under 1 year
- 1 Year
- 2-4 Years

Under 1 year
1 Year
2-4 Years
Trends – HIV-uninfected children <5 years

Monthly count of diarrhoeal hospitalisations among children under 5 years, Soweto, South Africa, 2006-2013

HIV-uninfected (assuming unknown are HIV-uninfected)

Rotavirus vaccine introduction Aug 2009

Age group
- Blue: Under 1 year
- Green: 1 Year
- Orange: 2-4 Years

Admission month and year

Under 1 year
1 Year
2-4 Years
Discussion

- Two doses of HRV provided protection against hospitalisation for acute rotavirus-diarrhoea of ~60% among children < 2 years using rotavirus negative controls, with similar effectiveness observed using respiratory controls in a subset of hospitals.
- Vaccine effectiveness appeared to be sustained through the second year of life.
- Similar protection among HIV-exposed and HIV-unexposed HIV-uninfected children.
- Protection against homotypic/partially heterotypic strains as well as fully heterotypic strains, but were not powered to assess strain-specific protection, except for G12P[8], or the durability of this protection into the second year of life.
- Time series analysis – deceased hospitalisations especially in < 1 year.
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