Correlates of efficacy for human rotavirus vaccines

Value of anti-rotavirus immunoglobulin A antibody concentrations

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Rotavirus burden of disease

- Rotavirus (RV) is the most common cause of severe gastroenteritis (GE) in children worldwide\(^1\)

- In children <5 years, RVGE is responsible for:
  - 453,000 deaths (2008 estimate)\(^2\)
  - >25 million outpatient visits per year (1986–2000 estimate)\(^3\)
  - >2 million hospitalisations per year (1986–2000 estimate)\(^3\)

- WHO Strategic Advisory Group of Experts (SAGE) recommended the inclusion of RV vaccination in all national immunisation programmes to reduce the burden of disease\(^4\)

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Correlates of protection (COP)

- Immune response to RV infection results in production of immunoglobulin M (IgM), and later IgA and IgG antibodies
- Secretory anti-RV IgA antibodies produced in the small intestine (site of infection) thought to be important for long-term protection\(^1,2\)
  - Cell-mediated, RV-specific immune responses may also play a role\(^2\)
- Total serum anti-RV IgA is considered the best currently available marker of protection against RV\(^1\)
- Demonstration of RV vaccine efficacy (VE) requires large clinical trials and extensive follow-up
  - Could immunological responses be considered as a correlate of efficacy in RIX4414 efficacy studies?

Rotarix™

- RIX4414, oral, live-attenuated human RV (HRV) vaccine (G1P[8] strain)
- Currently licensed in ≥120 countries (Latin America, North America, Asia, Middle-East, Africa, EU)
- Worldwide Phase III studies have demonstrated sustained protection from 1 year to 3 years (in Europe, Latin America, Asia and Africa) against:¹⁻⁶
  - RVGE
  - severe RVGE (SRVGE)
  - RVGE due to vaccine and non-vaccine serotypes

COP study: analysis of immunological COP

- Aim: to assess serum anti-RV IgA as a relative marker for VE of HRV against RVGE

- Two models used to evaluate correlates of efficacy using RIX4414 study data
  - Rota-037 (large, Phase III, RIX4414 efficacy study in Malawi and South Africa):
    - Logistic regression analysis
    - To assess relationship between protection against RV and post-vaccination anti-RV IgA antibody
    - Individual subject data level
  - Meta-analysis (8 RIX4414 efficacy studies in Europe, Asia and South America):
    - Linear regression analysis
    - To predict RV VE from anti-RV IgA seropositivity rate
    - Study population level
Overview of analysis studies (1)

- Time: reported before 1 December 2011
- Design: randomised, double-blind, placebo-controlled, Phase II or III
- Study comparison: incidence of RVGE for placebo vs 2 doses of HRV, except Rota-037 that included a 3-dose group
- Time between doses: 1–2 months
- Age at first vaccination: 6–14 weeks
- Follow-up: up to 24 months post vaccination (median duration: 0.62–1.7 years)
- Severity of RVGE was assessed according to the 20-point Vesikari scale
- Measurement of serum anti-RV IgA concentration:
  - 1–2 months after completion of HRV vaccine regimen
  - IgA seropositivity assay cut-off: 20 U/mL
## Overview of analysis studies (2)

<table>
<thead>
<tr>
<th>Rota study no. / Phase</th>
<th>Country</th>
<th>Group</th>
<th>Total cohort (N)</th>
<th>Efficacy ATP cohort (N)</th>
<th>Immuno ATP cohort (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>004/II&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Finland</td>
<td>HRV placebo</td>
<td>270</td>
<td>245</td>
<td>209</td>
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<td></td>
<td></td>
<td></td>
<td>135</td>
<td>123</td>
<td>112</td>
</tr>
<tr>
<td>006/II&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Brazil, Mexico, Venezuela</td>
<td>HRV placebo</td>
<td>1618</td>
<td>1392</td>
<td>1153</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>537</td>
<td>454</td>
<td>373</td>
</tr>
<tr>
<td>023/III&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>Argentina, Brazil, Chile, Colombia, Dominican Republic, Honduras, Mexico, Nicaragua, Panama, Peru, Venezuela</td>
<td>HRV placebo</td>
<td>10,159</td>
<td>9009</td>
<td>393</td>
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<td></td>
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<td></td>
<td>10,010</td>
<td>8858</td>
<td>341</td>
</tr>
<tr>
<td>024/III&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Brazil, Panama, Colombia, Argentina</td>
<td>HRV placebo</td>
<td>4376</td>
<td>4211</td>
<td>736</td>
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<td></td>
<td></td>
<td></td>
<td>2192</td>
<td>2099</td>
<td>361</td>
</tr>
<tr>
<td>028/029/030/III&lt;sup&gt;6,7&lt;/sup&gt;</td>
<td>Singapore (028), Hong Kong (029), Taiwan (030)</td>
<td>HRV placebo</td>
<td>5359</td>
<td>5263</td>
<td>115</td>
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<tr>
<td></td>
<td></td>
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<td>5349</td>
<td>5256</td>
<td>124</td>
</tr>
<tr>
<td>036/III&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Czech Republic, Finland, France, Germany, Italy, Spain</td>
<td>HRV placebo</td>
<td>2646</td>
<td>2572</td>
<td>794</td>
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<tr>
<td></td>
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<td></td>
<td>1348</td>
<td>1302</td>
<td>422</td>
</tr>
<tr>
<td>037/III&lt;sup&gt;9*&lt;/sup&gt;</td>
<td>South Africa, Malawi</td>
<td>HRV placebo</td>
<td>3298</td>
<td>2974</td>
<td>2077</td>
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<td></td>
<td></td>
<td></td>
<td>1641</td>
<td>1443</td>
<td>1125</td>
</tr>
<tr>
<td>056/III&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Japan</td>
<td>HRV placebo</td>
<td>508</td>
<td>498</td>
<td>34</td>
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<td></td>
<td>257</td>
<td>250</td>
<td>20</td>
</tr>
</tbody>
</table>

*3 HRV doses (2 HRV doses for all other studies); Rota-007 excluded due to insufficient RV cases to assess VE; ATP, according-to-protocol.

Evaluation of correlate of protection

Based on the logistic regression analysis of Rota-037
Rota-037: study design

- To assess the efficacy, safety and immunogenicity of 2 or 3 doses of RIX4414 given concomitantly with routine Expanded Program of Immunization (EPI) vaccinations in healthy infants
- N=3166 infants in South Africa, N=1773 infants in Malawi

Randomisation (1:1:1)

Group HRV 3-dose; N=1651
Group HRV 2-dose; N=1647
Group Placebo; N=1641

Primary vaccination visits

<table>
<thead>
<tr>
<th>Visit 1, Day 0</th>
<th>Visit 2, Month 1 Dose 2</th>
<th>Visit 3, Month 2 Dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 5–10 weeks Dose 1 Blood sample from a subset of 570 subjects for IgA testing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Follow-up visit

| Visit 4, Month 3 Blood sample from all subjects for IgA testing | Visit 5, Month 4 only in subjects with initial HIV test at Visit 4 | Visit 6, one year of age End of the first efficacy period Study conclusion | Visit 7 End of the second efficacy period Study conclusion |
Rota-037 analysis of immunological correlate of efficacy: methodology (2)

- Logistic model to estimate the probability of disease occurrence (p):
  - \( \text{Logit}(p) = \alpha + \beta \times \log_{10}(\text{concentration}/20) + \gamma \times (\text{indicator on concentration } < 20 \text{ U/mL}) \)
  - Assumed RVGE occurrence was a binary variable with parameter \( p \)
Rota-037 analysis of immunological correlate of efficacy: methodology (1)

Number of subjects with any RVGE/severe RVGE by RV IgA antibody concentration class:

<table>
<thead>
<tr>
<th>RVGE type</th>
<th>Concentration class</th>
<th>HRV group n/N (%)</th>
<th>Placebo group n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any RVGE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;20</td>
<td>83/1025 (8.10)</td>
<td>127/1026 (12.38)*</td>
</tr>
<tr>
<td></td>
<td>20–50</td>
<td>12/319 (3.76)</td>
<td>6/52 (11.54)**</td>
</tr>
<tr>
<td></td>
<td>50–100</td>
<td>13/319 (4.08)</td>
<td>2/48 (4.17)</td>
</tr>
<tr>
<td></td>
<td>100–250</td>
<td>14/345 (4.06)</td>
<td>1/59 (1.69)</td>
</tr>
<tr>
<td></td>
<td>250–500</td>
<td>11/255 (4.31)</td>
<td>2/49 (4.08)</td>
</tr>
<tr>
<td></td>
<td>500–1000</td>
<td>7/231 (3.03)</td>
<td>1/31 (3.23)</td>
</tr>
<tr>
<td></td>
<td>≥1000</td>
<td>4/276 (1.45)</td>
<td>2/65 (3.08)</td>
</tr>
<tr>
<td>Severe RVGE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;20</td>
<td>29/1025 (2.83)</td>
<td>47/1026 (4.58)*</td>
</tr>
<tr>
<td></td>
<td>20–50</td>
<td>5/319 (1.57)</td>
<td>4/52 (7.69)**</td>
</tr>
<tr>
<td></td>
<td>50–100</td>
<td>7/319 (2.19)</td>
<td>0/48 (0.00)</td>
</tr>
<tr>
<td></td>
<td>100–250</td>
<td>5/345 (1.45)</td>
<td>1/59 (1.69)</td>
</tr>
<tr>
<td></td>
<td>250–500</td>
<td>2/255 (0.78)</td>
<td>1/49 (2.04)</td>
</tr>
<tr>
<td></td>
<td>500–1000</td>
<td>2/231 (0.87)</td>
<td>1/31 (3.23)</td>
</tr>
<tr>
<td></td>
<td>≥1000</td>
<td>1/276 (0.36)</td>
<td>1/65 (1.54)</td>
</tr>
</tbody>
</table>

N, total number of subjects in the specified class of concentration values; n, number of subjects with at least one event in the specified class of concentration values; %=(n/N)x100; *exploratory 2-sided Fisher exact p-value <0.005; **exploratory 2-sided Fisher exact p-value <0.05
Rota-037 COP analysis: correlate of efficacy for RVGE (HRV and placebo)

- Anti-RV IgA seropositivity in vaccinated subjects associated with a lower percentage of subjects with any RVGE or SRVGE (2-sided p value <0.005)
- IgA titre >20 U/mL correlated with protection against RVGE events
- Increased titre value in seropositive subjects does not substantially increase the level of protection (2-sided p value =0.024)
Evaluation of correlate of protection

Based on the linear regression analysis of 8 RIX4414 efficacy studies
COP analysis: data included in the analysis

- Studies Rota-004, -006, -023, -024, -028 to -030, -036, -037 and -056
  - N=45,949 in total (both HRV and placebo groups)
- 1-year efficacy and combined 2-year efficacy data for protection against any RVGE due to wild-type RV strain
  - Only studies collecting any RVGE were considered
  - Rota-024, Rota-023, Rota-028/029/030 were therefore excluded
- 1-year efficacy and combined 2-year efficacy data for protection against SRVGE due to wild-type RV strain
  - All studies were considered
  - Rota-024 was not considered for the combined 2-year analysis as it had only 1-year efficacy follow-up
### Overview of analysis studies

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<td>245/123</td>
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<td>HRV placebo</td>
<td>1618/537</td>
<td>1392/454</td>
<td>1153/373</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HRV placebo</td>
<td>10,159/10,010</td>
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**Individual modelling not possible due to very small number of subjects with both a RVGE case and immuno data**
COP analysis: methodology based on aggregated data

- If seropositivity correlates with VE, one expects that the VE inferred from immunogenicity (VEI) as follows:

\[ \text{VEI} = 1 - \left( \frac{\text{SNV}}{\text{SNU}} \right) \]

  - SNU = proportion of seronegative subjects in unvaccinated population (estimated from placebo group)
  - SNV = proportion of seronegative subjects in the vaccinated population (estimated from the HRV group)

  ...would correlate with clinical VE

- This was validated using a regression between log(1-VE) and log(1-VEI) across the Rotarix™ efficacy studies

- Slope and intercept of the regression were estimated with 95% confidence interval (CI) using imputation technique
COP analysis: scatter plot of real any RVGE data (RR for efficacy and immunogenicity)

- Estimated regression line is above the VE=VEI line therefore VEI is an over-estimate of true VE
- Estimate of slope excludes ‘0’
- Indicates a relationship between immunological response and VE

### Any RV GE - 1 year

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean estimate</th>
<th>Percentiles from 1000 imputations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2.5&lt;sup&gt;th&lt;/sup&gt;</td>
</tr>
<tr>
<td>Any RVGE by wild-type RV strains – 1-year efficacy follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.129</td>
<td>-0.846</td>
</tr>
<tr>
<td>Slope</td>
<td>0.858</td>
<td>0.323</td>
</tr>
<tr>
<td>Any RVGE by wild-type RV strains – combined 2-year efficacy follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.121</td>
<td>-0.563</td>
</tr>
<tr>
<td>Slope</td>
<td>0.850</td>
<td>0.395</td>
</tr>
</tbody>
</table>

### Any RV GE - 2 years

**Relative risk (RR)**

- 95% CI
- Regression line
- VE=VEI

100%-VEI

(VEI=vaccine efficacy predicted from seropositivity)
COP analysis: scatter plot of real SRVGE data (RR for efficacy and immunogenicity)

Severe RV GE - 1 year

- Estimated regression line is below the VE=VEI line therefore VEI is an under-estimate of true VE
- Estimate of slope excludes ‘0’
- Indicates a relationship between immunological response and VE

Severe RV GE - 2 years

Parameter | Mean estimate | Percentiles from 1000 imputations
|----------------|----------------|
|               | 2.5<sup>th</sup> | 50<sup>th</sup> | 97.5<sup>th</sup>

SRVGE by wild-type RV strains – 1-year efficacy follow-up
- Intercept: -0.453, -1.252, -0.447, 0.327
- Slope: 1.142, 0.582, 1.131, 1.732

SRVGE by wild-type RV strains – combined 2-year efficacy follow-up
- Intercept: -0.336, -1.414, -0.364, 0.924
- Slope: 1.040, 0.375, 0.998, 1.931

100%-VEI
(VEI=vaccine efficacy predicted from seropositivity)
Conclusions

- Statistical analyses were performed that provided insight into anti-RV IgA antibody titre as a correlate of efficacy
  - Logistic regression analysis based on Rota-037 efficacy data
  - Linear regression analysis based on efficacy and immunogenicity data from specified RIX4414 efficacy studies

- Both analyses support that anti-RV antibody seropositivity can serve as a relative correlate of efficacy against any RVGE and SRVGE in vaccinated children
  - Cut-off anti-RV IgA antibody titre is ≥20 U/mL

- Further studies are needed to support the use of anti-RV IgA antibody titre as a correlate of efficacy