Explaining reduced rotavirus vaccine efficacy in low socio-economic settings

Ben Lopman, MSc PhD
Division of Viral Diseases
CDC
Point estimates of Rotarix* and RotaTeq† vaccine efficacy

Nelson & Glass, Lancet 2010
Objectives

• Interpret rotavirus clinical trial observations in a range of SES
• Illustrate how different factors may contribute to reduced efficacy of vaccination.
• Using a dynamic mathematical model
Why model?

• Rotavirus immunity is complex
• Mechanism of RV vaccination
  – Each dose mimics a natural infection
• The order of infection is important – but not observed
Maternally protected

S1

Susceptible
Infected
Diagram showing a network of nodes labeled M, S1, I1, S2, I2, S3, I3, S4, and I4. The arrows indicate the direction of influence or interaction between the nodes.
Model

Vaccine efficacy
Natural immunity

Model

Vaccine efficacy
## Parameters: Natural Immunity

<table>
<thead>
<tr>
<th></th>
<th>High</th>
<th>Middle</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relative risk of infection following</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First infection</td>
<td>0.62</td>
<td>0.62</td>
<td>0.62</td>
</tr>
<tr>
<td>Second infection</td>
<td>0.37</td>
<td>0.37</td>
<td>0.48</td>
</tr>
<tr>
<td>Third infection</td>
<td>0.37</td>
<td>0.37</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Proportion of infections with SEVERE GE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First infection</td>
<td>0.13</td>
<td>0.13</td>
<td>0.17</td>
</tr>
<tr>
<td>Second infection</td>
<td>0.03</td>
<td>0.03</td>
<td>0.23</td>
</tr>
<tr>
<td>Third infection</td>
<td>0</td>
<td>0</td>
<td>0.24</td>
</tr>
<tr>
<td>Fourth infection</td>
<td>0</td>
<td>0</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Patel, PIDJ, 2010
Velazquez, NEJM, 1996
Gladstone, NEJM, 2011
Phillips, AJE, 2010
Natural immunity

Immunogenicity

Model

Vaccine efficacy
## Parameters: Immunogenicity

<table>
<thead>
<tr>
<th>Seroconversion (%)</th>
<th>High</th>
<th>Middle</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.86</td>
<td>0.74</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Patel, PIDJ, 2010  
Velazquez, NEJM, 1996  
Gladstone, NEJM, 2011  
Phillips, AJE, 2010
### Parameters: Local Incidence

<table>
<thead>
<tr>
<th>INCIDENCE*</th>
<th>High</th>
<th>Middle</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-23m</td>
<td>14</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>24-59m</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-11m</td>
<td></td>
<td></td>
<td>49</td>
</tr>
<tr>
<td>12-35m</td>
<td></td>
<td></td>
<td>12</td>
</tr>
</tbody>
</table>

*severe RV-GE per 100 years

- Patel, PIDJ, 2010
- Velazquez, NEJM, 1996
- Gladstone, NEJM, 2011
- Phillips, AJE, 2010
## Parameters

<table>
<thead>
<tr>
<th>NATURAL IMMUNITY</th>
<th>High</th>
<th>Middle</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of infections with any GE (severe GE)</td>
<td>First Primary</td>
<td>Primary All</td>
<td>Second</td>
</tr>
<tr>
<td></td>
<td>Third</td>
<td></td>
<td>Fourth infection</td>
</tr>
<tr>
<td>IMMUNOGENICITY</td>
<td>Most</td>
<td>Many</td>
<td>Some</td>
</tr>
<tr>
<td>INCIDENCE</td>
<td>Low</td>
<td>Middle</td>
<td>High</td>
</tr>
</tbody>
</table>
PREDICTED:
Vaccine Efficacy against severe RV-GE
6-23 month olds

<table>
<thead>
<tr>
<th>Level</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>93%</td>
</tr>
<tr>
<td>Middle</td>
<td>86%</td>
</tr>
<tr>
<td>Low</td>
<td>51%</td>
</tr>
</tbody>
</table>
Point estimates of Rotarix* and RotaTeq† vaccine efficacy

Nelson & Glass, Lancet 2010
Vaccine efficacy

**SEVERE RV-GE**

- High
- Mid
- Low

**ALL RV-GE**

- High
- Mid
- Low
Vaccine efficacy

SEVERE RV-GE

ALL RV-GE

Higher VE against severe disease
Vaccine efficacy

SEVERE RV-GE

ALL RV-GE

Reducing VE with age
## VE and age

<table>
<thead>
<tr>
<th>Setting</th>
<th>First year</th>
<th>Second Year</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>US, Europe</td>
<td>99%</td>
<td>95%</td>
<td>Vesikari et al</td>
</tr>
<tr>
<td>Latin America</td>
<td>83%</td>
<td>79%</td>
<td>Linhares et al</td>
</tr>
<tr>
<td>Africa</td>
<td>64%</td>
<td>20%</td>
<td>Armah et al</td>
</tr>
</tbody>
</table>
Potential for improvements in VE

Nelson & Glass, Lancet 2010

LOW: 51%

-GDP per head purchasing power parity US$ 2007

1-year efficacy %
Potential for improvements in VE

Improve IMMUNOGENICITY to middle income levels (+10%)

LOW: 51%

Nelson & Glass, Lancet 2010
Potential for improvements in VE

Nelson & Glass, Lancet 2010

LOW: 51%

MIDDLE: 86%

Improve NATURAL IMMUNITY to Mexico levels (25%)

LOW: 51%

Nelson & Glass, Lancet 2010
Potential for improvements in VE

Improve IMMUNOGENICITY to **high** income levels (7%)
Model consistently predicts:

• Gradient of efficacy: higher in high SES

• Higher VE against severe disease

• Provides an explanation of ‘waning immunity’
Potential areas for gains

• Improve IMMUNOGENICITY of vaccine
  • New vaccines
  • Withhold breastfeeding
  • Delaying administration

• Improve NATURAL IMMUNE RESPONSE
  • Probiotics
  • Micronutrient deficiency (Zn supplementation)
Conclusions

• Reduced vaccine efficacy can be explained by intrinsic immunological and epidemiological factors
• An explanation for ‘waning’ VE
• Modifying aspects of the vaccine or vaccination program may bring substantial improvements
• Cases prevented in low SES are greater than in high SES, despite lower VE
Models have helped us to understand

- Biennial pattern
- Seasonality
- Shifting age distribution
- Indirect benefits to unvaccinated

...IN HIGH INCOME SETTINGS
Acknowledgements

CDC
  – Manish Patel
  – John Glasser
  – Umesh Parashar

Princeton University, USA
  – Virginia Pitzer
  – Bryan Grenfell

LSHTM, UK
  – Christina Atchison
  – John Edmunds

Christian Medical College, Vellore, India
  – Rajiv Sarkar
  – Beryl Gladstone
  – Gagandeep Kang

Mexico National Institute of Medical Sciences and Nutrition
  – Guillermo Ruiz-Palacios
  – Lourdes Guerrero

Imperial College London/ CDC
  – Manoj Gambhir