Rotavirus & Norovirus Vaccines

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Rotavirus is the leading cause of diarrhea hospitalizations in children <5 years globally.
Proportion of diarrhea hospitalizations due to rotavirus in the Asian Rotavirus Network

- China: 41%
- Korea: TBD
- Taiwan: 41%
- Vietnam: 60%
- Malaysia: 56%
- Myanmar: 56%
- Hong Kong: 29%
- Indonesia: 39%
First rotavirus vaccine licensed in 1998 in US
A setback – Vaccine withdrawn within 1 year because it caused intussusception

1 intussusception case per 10,000 vaccinated infants
Two new rotavirus vaccines licensed in 2006

<table>
<thead>
<tr>
<th>RotaTeq™ (Merck&amp;Co., Inc.)</th>
<th>Rotarix™ (GlaxoSmithKline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 oral doses beginning at 6 weeks</td>
<td>2 oral doses beginning at 6 weeks</td>
</tr>
</tbody>
</table>

- Large trials (~70,000 infants) in US, Europe, and South America
- *No increased risk of intussusception!*

Vesikari et al and Ruiz-Palacios et al, NEJM 2006
High Efficacy of Both Vaccines in Trials in High/Middle Income Countries

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Region</th>
<th>Efficacy (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotarix</td>
<td>Europe</td>
<td>96% (90%-99%)</td>
</tr>
<tr>
<td>Rotarix</td>
<td>Latin America</td>
<td>85% (72%-92%)</td>
</tr>
<tr>
<td>Rotarix</td>
<td>Asia</td>
<td>96% (85%-99%)</td>
</tr>
<tr>
<td>RotaTeq</td>
<td>Europe/US</td>
<td>98% (88%-100%)</td>
</tr>
</tbody>
</table>

Vesikari et al and Ruiz-Palacios et al, NEJM 2006
98 countries have implemented national rotavirus vaccination programs
How well will vaccines perform in routine use?
Impact on All-Cause and Rotavirus-Specific Gastroenteritis Hospitalizations in USA

Payne DC et al, unpublished data
Unexpectedly, reduction in AGE hospitalizations seen in older unvaccinated children and adults in the US

Lopman et al. JID 2011
Gastanaduy et al JAMA 2013
Effect of Rotavirus Vaccination on Death from Childhood Diarrhea in Mexico

Richardson et al, NEJM 2010
Reduced risk of childhood seizures associated with rotavirus vaccination

Vaccinated children had ~20% reduction in risk of seizures requiring hospitalization or ED care compared with unvaccinated children during the year following vaccination.
Success.

How well will vaccines protect against range of rotavirus strains?
Two outer capsid proteins (G and P) determine rotavirus strain type.
RotaTeq is pentavalent & Rotarix is monovalent

RotaTeq

G1

G2

P[8]

G3

G4

Five bovine-human rotavirus strains

Rotarix

G1P[8]

Single human rotavirus strain
Monovalent rotarix (G1P8) efficacy similar against vaccine & non-vaccine strains in Africa

Madhi et al. NEJM 2010
Increase in G2P4 after implementation of monovalent Rotarix (G1P8) in Brazil


*Gurgel et al, EID, 13(10), 2007

Rapid Communication

Apparent extinction of non-G2 rotavirus strains from circulation in Recife, Brazil, after the introduction of rotavirus vaccine

*Nakagomi et al, Arch Vir 153(3); 2008
Is increasing prevalence of G2P[4] in Brazil caused by vaccine pressure or is it just natural variation?

![Pie charts showing data from 2005, 2006, and 2007 for Brazil and El Salvador.](image)

- **2005**: P[8]G9 94%
- **2007**: P[8]G1 91%

El Salvador: Rotarix, 2006 (opposite of Brazil)

Patel et al. EID 2009
How well will live oral rotavirus vaccines work in the developing world?
The vast majority of the ~200,000 annual deaths from rotavirus occur in developing countries.

1 dot = 100 deaths
Moderate efficacy seen in trials in low income African and Asian countries

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<tr>
<th>Vaccine</th>
<th>Region</th>
<th>Efficacy (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RotaTeq</td>
<td>Africa</td>
<td>64% (40%-79%)</td>
</tr>
<tr>
<td>RotaTeq</td>
<td>Asia</td>
<td>51% (13%-73%)</td>
</tr>
<tr>
<td>Rotarix</td>
<td>Africa</td>
<td>62% (44%-73%)</td>
</tr>
</tbody>
</table>

Armah et al. Lancet 2010
Zaman et al. Lancet 2010
Madhi et al NEJM 2010
What does 50% efficacy mean?

Would you rather have 99% of my salary or 1% of Bill Gates’?
Despite lower efficacy, rotavirus vaccines prevent more disease in high burden settings.

Despite lower efficacy, rotavirus vaccines prevent more disease in high burden settings.

Madhi, NEJM 2010
Decline in rotavirus hospitalizations after vaccine implementation in Ghana

Rotavirus vaccine introduction, April 2012

50% RV+

Armah et al CID 2016
Impact of monovalent rotavirus vaccine on diarrhoea-associated post-neonatal infant mortality in rural communities in Malawi: a population-based birth cohort study

- Diarrhea-associated mortality declined by 31% (95% CI, 1%-52%)
- Vaccine effectiveness against diarrhea mortality 34% (95% CI, -28%-66%)
Rotavirus remains the leading cause of severe diarrhea in developing countries after rotavirus vaccine introduction.
How can we improve rotavirus vaccine performance in developing countries?
Multiple factors affect rotavirus vaccine efficacy

- Poor response to oral rotavirus vaccine
- Transplacental and breast milk rotavirus antibodies
- Gastrointestinal pathogens
- Intestinal microbiota
- Nutrition
- Environmental enteropathy
- Interference of OPV co-administration
Delaying 2-dose schedule or adding 3\textsuperscript{rd} dose slightly improved Rotarix vaccine response

Ali, 2014 (Pakistan)

Seroconversion %

6 + 10 weeks  10 + 14 weeks  6 + 10 + 14 weeks
Supplementing with both Zn and probiotics slightly improved vaccine response.
Antibiotic microbiome modulation alters RV immunogenicity

Harris et al, Cell Host Microbe, 2018
Like polio – Injectable rotavirus vaccine?

Safety and immunogenicity of a parenteral P2-VP8-P[8] subunit rotavirus vaccine in toddlers and infants in South Africa: a randomised, double-blind, placebo-controlled trial

Michelle J Groome, Anthonet Koen, Alan Fix, Nicola Page, Lisa Jose, Shabir A Madhi, Monica McNeal, Len Dally, Ikunsong Cho, Maureen Power, Jorge Flores, Stanley Czysz

Vaccine 36 (2018) 2233–2236

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Short communication

The future control of rotavirus disease: Can live oral vaccines alone solve the rotavirus problem? ⋆

Roger L. Glass a,b,c, Baoming Jiang b, Umesh Parashar b

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b Viral Gastroenteritis Branch (previously), Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA
Will new rotavirus vaccines cause intussusception?
Low risk of intussusception in several high & middle income countries (Mexico, US, Australia, UK)

• ~1-6 cases per 100,000 vaccinated

• Similar risk with both vaccines
## Benefits vs. Risks of Vaccination

<table>
<thead>
<tr>
<th></th>
<th>Diarrhea Hospitalizations (Deaths) Prevented</th>
<th>Intussusception Cases (Deaths) Caused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico</td>
<td>11,600 (663)</td>
<td>41 (2)</td>
</tr>
<tr>
<td>Brazil</td>
<td>69,600 (640)</td>
<td>55 (3)</td>
</tr>
<tr>
<td>Australia</td>
<td>7,000 (0)</td>
<td>6 (0)</td>
</tr>
<tr>
<td>US</td>
<td>53,000 (16)</td>
<td>48 (0)</td>
</tr>
</tbody>
</table>

*
No intussusception risk in large study in 7 low income African countries!
Who Will Supply Rotavirus Vaccine to the World?

Big Pharma
- Merck
- GSK

Emerging Manufacturers
- Brazil
- Indonesia
- Germany
- China
- India
Prime Minister Modi

“Government of India will provide a rotavirus vaccine to all Indian children”
Rotavac and RotaSIIL™ were pre-qualified by WHO in 2018

**ROTAVAC™**, Bharat Biotech
(derived from a single Indian neonatal strain of human rotavirus) G9P11

**RotaSIIL™**, Serum Institute
(Reassorted bovine-human rotavirus)
Genetically engineered vaccine consisting of 5 different strains to protect against the 5 most common human rotaviruses G1,2,3,4 & 9
Efficacy of various rotavirus vaccines similar in developing countries

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<tr>
<th>Vaccine</th>
<th>Efficacy (95% CI)</th>
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<tr>
<td></td>
<td>Asia</td>
</tr>
<tr>
<td>RotaTeq</td>
<td>51 (13-73)</td>
</tr>
<tr>
<td>Rotarix</td>
<td>--</td>
</tr>
<tr>
<td>Rotavac</td>
<td>56 (37-70)</td>
</tr>
<tr>
<td>Rotasiil</td>
<td>37 (11-54)</td>
</tr>
</tbody>
</table>
Global implementation of rotavirus vaccines
Norovirus Vaccines
Norovirus is the leading cause of AGE outbreaks

Chipotle Is Subpoenaed in Criminal Inquiry Over Norovirus Outbreak

Hundreds laid low after eating Valentine's Day oysters

57 sick; norovirus strikes Scottish swimmers

Love sick: Hundreds of couples who ate oysters around Valentine's Day contracted a winter vomiting bug (file photo)

Butterflies in your stomach this Valentine's? Or is that the norovirus?

Just imagine — it's Valentine's Day and you and your special someone are about to enjoy a nice dinner together. There's a little music playing, soft candles lit, and you even have butterflies in your stomach... or at least that's what you think they are, until you start feeling nauseated...
Norovirus is the leading cause of severe AGE in US children after rotavirus vaccine implementation

- 21% of severe AGE episodes caused by norovirus
- ~1 million annual pediatric medical care visits
  - $273 million in health care costs
Norovirus causes severe disease in both young children & the elderly

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**Graphs showing rates of ED Visits, Hospitalizations, and Deaths due to Norovirus by Age Group:**

- **ED Visits and Hospitalizations** (left graph):
  - Age Group: 0-4, 5-64, ≥65
  - Rates per 10,000

- **Deaths** (right graph):
  - Age Group: 0-4, 5-64, ≥65
  - Rates per 1,000,000

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Hall 2013 EID
Noroviruses are genetically diverse

GII
Human, Porcine

GII.4

GVIII
human

GVII
canine

GIII
Bovine, ovine

GI
Human

GV
Murine

GVI
canine

Tentative new:
GII.23, 24, 25

Noroviruses are genetically diverse
## Norovirus Vaccine Candidates in Human Trials

<table>
<thead>
<tr>
<th>Norovirus antigen</th>
<th>Bivalent VLP (Takeda pharma)</th>
<th>Adenoviral vector (Vaxart)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI.1 and GII.4 consensus VLP</td>
<td></td>
<td>GI.1 VP1</td>
</tr>
<tr>
<td>Route of admin</td>
<td>Intramuscular, previously intranasal</td>
<td>Oral (pill)</td>
</tr>
<tr>
<td>Status</td>
<td>Phase 2b</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>
Intra-nasal monovalent GI.1 VLP vaccine efficacy (Takeda)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine (N=43)</th>
<th>Placebo (N=41)</th>
<th>% Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norovirus infection</td>
<td>60.5%</td>
<td>82.1%</td>
<td>26% (1%, 45%)</td>
</tr>
<tr>
<td>Norovirus AGE</td>
<td>36.8%</td>
<td>69.2%</td>
<td>47% (15%, 67%)</td>
</tr>
</tbody>
</table>

Atmar 2011 NEJM
Intra-muscular bivalent GI.1, GII.4 vaccine efficacy (Takeda)

<table>
<thead>
<tr>
<th>Norovirus AGE Severity</th>
<th>Vaccine (N=50)</th>
<th>Placebo (N=48)</th>
<th>% Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>20.0%</td>
<td>37.5%</td>
<td>47% (-4%, 73%)</td>
</tr>
<tr>
<td>Mod-severe</td>
<td>6.0%</td>
<td>18.8%</td>
<td>68% (-11%, 91%)</td>
</tr>
<tr>
<td>Severe</td>
<td>0%</td>
<td>8.3%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Challenges for a norovirus vaccine

1. Whom to target – Children? Elderly?
2. Protection against multiple genotypes?
3. Need to be updated to keep up with viral evolution?
4. Need for different vaccine formulations for different age groups?

Replication of human noroviruses in stem cell–derived human enteroids

Khalil Ettayebi,1,6 Sue E. Crawford,1,6 Kosuke Murakami,1,6 James R. Broughman,1 Umesh Karandikar,1 Victoria R. Tenge,1 Frederick H. Nell,1 Sarah E. Blutt,1 Xi-Lei Zeng,1 Lin Qu,1 Baijun Kou,1 Antone R. Opekun,2,3,4 Douglas Burrin,3,4 David Y. Graham,1,2,7 Sasirekha Ramani,1 Robert L. Atmar,1,2 Mary K. Estes1,2,7

The major barrier to research and development of effective interventions for human noroviruses (HuNoVs) has been the lack of a robust and reproducible in vitro cultivation system. HuNoVs are the leading cause of gastroenteritis worldwide. We report the successful cultivation of multiple HuNoV strains in enterocytes in stem cell–derived, nontransformed human intestinal enteroid monolayer cultures. Bile, a critical factor of the intestinal milieu, is required for strain-dependent HuNoV replication. Lack of appropriate histoblood group antigen expression in intestinal cells restricts virus replication, and infectivity is abrogated by inactivation (e.g., irradiation, heating) and serum neutralization. This culture system recapitulates the human intestinal epithelium, permits human host-pathogen studies of previously noncultivatable pathogens, and allows the assessment of methods to prevent and treat HuNoV infections.

Human noroviruses (HuNoVs) are the most common cause of epidemic and sporadic cases of acute gastroenteritis worldwide, and are the leading cause of food-borne gastroenteritis (1–3). Since the introduction of rotavirus vaccines, HuNoVs have become the predominant gastrointestinal pathogen within pediatric populations in developed countries (4). HuNoVs are highly contagious, with rapid person-to-person transmission directly through the fecal-oral route.