Update on Norovirus Vaccine Development

Commander Dennis J. Faix, MD, MPH
Military Population Health
Naval Health Research Center
San Diego, California, USA

Commander Mark S. Riddle, MD, MPH&TM, DrPH
Enteric Diseases Department
Naval Medical Research Center
Silver Spring, Maryland, USA

- The views expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.
- The study protocols of presenter’s data were approved research by the US Navy Institutional Review Boards in compliance with all applicable Federal regulations governing the protection of human subjects.
- This work was supported only by internal Department of Defense funding and the presenter has no financial/non-financial conflicts of interest to disclose. The US Navy has agreements with Takeda Vaccines to conduct epidemiology and clinical vaccine development.
Outline

• Acute consequences of NoV in Military Populations
  – Deployment settings
  – Garrison/training settings

• Chronic consequences of NoV

• Military vaccine value / demand

• NoV vaccine development update
Norovirus Burden (US)

http://www.cdc.gov/norovirus/php/illness-outbreaks-figure.html
NoV is an important health concern to military forces: Ashore, Underway & Deployed

**ORIGINAL PAPERS**

**VIRAL GASTROENTERITIS OUTBREAKS IN DEPLOYED BRITISH TROOPS DURING 2002-7**

MS Bailey, CI Gallimore, LD Lines, AD Green, BA Lopman, JJ Gray, DWG Brown

Waldir et al. BMC Infectious Diseases
http://www.biomedcentral.com/1471-2334/10/90

**RESEARCH ARTICLE**

Food-borne norovirus-outbreak at a military base in Germany, 2009

Marie Waldir, Kathrin Scheeren, Stine Nielsen, Sabine Diedrich, Lüppo Ellerbroek, Christina Frank, Renate Gatter, Marina Hoehne, Reimar Johne, Günter Klein, Judith Koch, Jörg Schulenberg, Uta Thielbein, Klaus Staub, Helen Bernard

Gastroenteritis in US Marines during Operation Iraqi Freedom

Scott A. Thornton, Sterling S. Sherman, Tibor Farke, Weiming Zhong, Pete Torres, and Xi Jiang

**BMC Gastroenterology**

Epidemic infectious gastrointestinal illness aboard U.S. Navy ships deployed to the Middle East during peacetime operations – 2000–2001

Mark S Riddle, Bonnie L Smoak, Scott A Thornton, Joseph S Breeze, Dennis J Faix, and Shannon D Putnam

**FIGURE**

Acute gastroenteritis outbreak due to norovirus infection in a French military parachuting unit, April 2011 (n=138 cases)

^ With known date of symptom onset

^ The cook presented only subjective symptoms and did not meet the case definition, but was added to the curve for a better understanding of the outbreak.

**RESEARCH ARTICLE**

**Noroviruses : a Challenge for Military Forces.**

H Delacour, P Dubrous, JL Koeck

1Beigain Hospital, Department of Biology, 69 avenue de Paris, 94 163 Saint Mandé Cedex, France, 2Robert Picqué Hospital, Department of Biology, 331, route de Toulouse, CS 80002 33882 Villeneuve d'Ornon Cedex, France

**FIGURE**


- Destroyer
- Aircraft Carrier
- Amphibious Assault/Combat Support
Global snapshot of AGE risk and etiology among deployed US (~8% due to norovirus) (Riddle et al. AJTMH 2005)

- Moderate-risk: 8-20% attack rates per month
- High-risk: 30-50% attack rates per month

- ETEC
- EAEC
- Campylobacter
- NoV
- Shigella
- Salmonella
- Rotavirus
- Unknown

(Riddle et al. AJTMH 2005)
AGE Surveillance among US Military Recruits
Naval Health Research Center – Enteric Disease Surveillance Program

- EDSP - established in 2011 with support of Ligocyte with DoD funding
- 4 Active Sites
- Standardized case definition/eligibility criteria
- All specimens tested at NHRC Enterics Lab
  - Standard bacterial culture
  - Molecular methodologies
    - NoV & other enteric viruses
    - Multiplex Path. E. coli

Slide courtesy of Dr. Shan Putnam, NHRC
AGE Attack Rate and Norovirus Positivity Among U.S. Military Recruits, All Sites, 08/2011 - 12/2014

Slide courtesy of Dr. Shan Putnam, NHRC
“Don’t Worry it’s Just a Viral Gastroenteritis”

Postinfectious Gastrointestinal Disorders Following Norovirus Outbreaks

Chad K. Porter,1 Dennis J. Faix,2 Danny Shiau,3 Jennifer Espiritu,4 Benjamin J. Espinosa,4 and Mark S. Riddle1

1Naval Medical Research Center, Silver Spring, Maryland; 2Naval Health Research Center, San Diego, California; 3Naval Bureau of Medicine and Surgery, Falls Church, and 4Naval Environmental Preventive Medicine Unit 2, Norfolk, Virginia

Growing evidence of potential chronic long term health consequences of acute enteric infection (Verdu & Riddle, Am J Gastro, 2012)

Prior studies associating increased risk of IBS after viral gastroenteritis

– 7-fold increase risk of IBS at 3 months, resolving by one year (Marshall, Clin Gastroenterol Hepatol, 2007)
– 11-fold increase risk of IBS at 12 months (Zanini, Am J Gastro, 2012)
Reflux disease and constipation, but not IBS associated with confirmed NoV outbreaks

- Risk varies by outbreak (genotype/strain variation?)
- Dysfunction in gastric accommodation and delayed gastric emptying identified in PI-dyspepsia (Tack, 2002; Futagami, 2010)
- Study underway evaluating biomarkers which may predict long-term health outcomes

Note: aRR, adjusted relative risk; *p<0.05
What about norovirus and the value of a vaccine?

Norovirus and FGD Risk

• Cohort Study (DMSS data)
  ➢ 3 confirmed NoV outbreaks
  ➢ 3:1 matched non-exposed
  ➢ Medical encounter record f/u

Recruit hypothetical NoV Cost Benefit Analysis (unpublished)

• Cost-benefit economic analysis
• Acute and chronic consequences
• Seasonal vs. year round vaccination strategies vs. no intervention
• Does not consider benefit against NoV post-training/during deployment

Porter & Riddle, CID, 2012
Relative cost-effectiveness of a norovirus vaccine in the deployed military setting compared to a vaccine against *Campylobacter* sp., ETEC, and Shigella sp.☆,☆☆

Aaron Tallant, Chad K. Porter, Shannon D. Putnam, David R. Tribble, Tomoko I. Hooper, Mark S. Riddle

**Highlights**

– NoV vaccine equivalent to Shigella, but not as favorable as ETEC or Campy vaccines.

– The absolute value of NoV vaccine appears favorable.

– Added value in preventing domestic infxn not considered.

– Research needed for uncertain & influential inputs.
Functional GI disorders have been linked to dysbiosis (Krogius-Kurikka L, 2009; Carroll IM, 2012; Si JM, 2004).

This study aimed to explore the effect of NoV on the microbiome:
- 38 NoV infected cases (~1.5 days after illness onset)
- 22 healthy controls
- 16S rRNA-encoding gene sequence data from DNA isolated from the fecal samples of NoV-infected patients

Limitations up front (cross-sectional study):
- NO baseline, NO long term follow-up, NO link with disease severity
1 of 5 had loss of diversity and increased Proteobacteria
Takeda Norovirus (NoV) vaccine candidate

Bivalent virus-like particle (VLP)-based adjuvanted injectable vaccine candidate

**VLPs**
- Conformationally correct representation of the virus capsid
- Contains no genetic material (cannot cause infection)
- Can be readily manufactured in cell culture on large scale
- Are protective in other vaccines (e.g. HPV)
- GI.1 and GII.4 VLPs
  - GI.1 and GII.4 have demonstrated cross-reactivity in vivo
  - GII.4 antigen is a consensus sequence of 2002, 2006(a), 2006(b) GII.4 strains
  - GII.4 is currently the dominant circulating NoV type worldwide

**Adjuvants**
- Aluminium hydroxide [Al(OH)₃]
- Formulations with / without 3-O-desacyl-4′ monophosphoryl lipid A (MPL)

*Noroviruses have been classified into 6 different genogroups (GI–GVI) and multiple genotypes*

GII.4 is currently dominant type worldwide\(^1\)

NoV genotype distributions

- **US** (1994-2006)\(^{3}\)
- **Brazil** (2005-2008)\(^{6}\)
- **Germany** (2001-2009)\(^{4}\)
- **England and Wales** (2011-2014)\(^{5}\)
- **China** (1999-2011)\(^{2}\)
- **Japan** (2008)\(^{7}\)
- **Global** \(^{1}\)

4. Bernard H Epi Infect 2014;
5. PHE 2014;

*Slide courtesy of Takeda Vaccines*
Selection of Vaccine Antigens

- GI.1 VLPs broadly cross-react with other GI strains
  - Selected as GI antigen in Takeda vaccine
- GII.4 is the natural choice for a GII antigen due to its current dominance worldwide
- Takeda developed a consensus VLP from three relevant GII.4 strains
  - 2002 (Houston)
  - 2006a (Yerseke)
  - 2006b (Den Haag)


_Slide courtesy of Takeda Vaccines_
Norovirus Vaccine Clinical Development Plans (Efficacy)

- Two Phase III efficacy trials are in the planning stages – in adults aged 18 to 49 years and infants aged 2 months of age.
- Licensure in other age groups will be supported by immunogenicity bridging and post-licensure studies.
Previous Experience in Humans - Trial LV03-104

**Design**

- Safety and immunogenicity study
- Phase I, randomized, double blind, placebo-controlled, dosage- and age-escalation:
  - Doses: 5/5; 15/15; 50/50 and 150/150 µg VLP per dose, adjuvanted with 50 µg MPL and Al(OH)$_3$
  - Healthy adults (N=102), 18-49 years of age (Cohorts A and D), adults 50-64 (Cohort B) and adults 65-85 years of age (Cohort C)
- Two doses, 28 days apart

**Results (N=102)**

- Sero-response rates (% subjects with ≥4-fold rise in serum antibody levels)
- Geometric mean fold ratios (GMFRs)
- Lower responses for the GII.4 VLP compared with the GI.1 VLP
- All dosages equally well tolerated
- Five SAEs reported; none were vaccine-related


*Slide courtesy of Takeda Vaccines*
Previous Experience in Humans - Trial LV03-104

- Increases in serum antibodies to each of the VLPs (GI.1 and GII.4)
- **Immune responses were already observed at Day 7** (the first time point measured)
- A second dose of vaccine at Day 28 did not have an impact on titer values for either VLP
- **Serum antibodies persist 12 months after vaccination**
- Similar response by age group to the selected 50/50 µg dosage

*Treanor et al. JID 2014;210:1763-71.*

*Slide courtesy of Takeda Vaccines*
Solicited AEs

- No dose-related effect
- No increase after Dose 2
- Headache* was the most frequent solicited systemic AE
- Tenderness* and pain* were the most frequent solicited local AE
- AEs were primarily mild or moderate in severity

Previous Experience in Humans - Trial LV03-104

**Breadth of Response**

- Vaccination with 50µg/50µg Alum and MPL intramuscular vaccine with in humans induces broad functional Ab responses
  - Vaccination induces HBGA blocking antibody response against strains and types not included in vaccine
  - Consensus GII.4 antigen induced antibody response against Sydney 2012 GII.4 strain that emerged 1-2 years later

Lindesmith LC et al, PLoS Med. 2015 Mar 24;12(3) e1001807
Study NOR-201: Design

• Phase II - Safety and Immunogenicity study
• Randomized, placebo-controlled, double-blind
• Recruitment at 10 U.S. sites – N ≈ 450 subjects
• 18-49 years of age, general U.S. population ≈ 150 subjects per arm
  • Randomized 1:1:1 to receive on Day 1 one IM injection of either
    – 15/50 μg Norovirus Vaccine, adjuvanted with 50 μg of MPL and 500 μg of Al(OH)$_3$ = “15/50/50”
    – 50/50 μg Norovirus Vaccine, adjuvanted with 50 μg of MPL and 500 μg of Al(OH)$_3$ = “50/50/50”
    – Saline Placebo
  • Blood draws Days 1, 3, 5, 7-10, 28, 180, 365
  • All participants will receive one additional dose of 15/15 μg NoV vaccine without MPL on Day 365 and additional blood draws will be made on Days 365, 368, 372 and 393
• 98% compliance at interim analysis - 28 days post dose one
Study NOR-201: Immunogenicity

Pan-Ig: Geometric Mean Titres by Visit (PPS)

Error bars represent a 95% confidence interval
NOR-201 Interim Conclusions

- The two candidate VLP vaccine formulations were generally well tolerated with acceptable safety profiles up to Day 28 – assessment is ongoing
- Both formulations elicited rapid and robust immune responses
- Slightly higher responses to a higher dose of GI.1 led to lower responses to GII.4
- As GII.4 is currently responsible for most human infections the VLP (GI.1 / GII.4) 15/50 µg formulation has been selected for subsequent vaccine candidate development in adults

Next steps:
- Additional dosage finding study with/without MPL
- Phase IIb studies/efficacy
Previous Experience in Humans - Trial LV03-105

Design

• Safety, immunogenicity, and efficacy study
• Phase I/II randomized, double blind, multi-center, placebo-controlled
• Healthy adults (N=132), 18-50 years of age:
• Two doses of NoV vaccine (50/50 µg per VLP), 28 days apart
• Challenge on study day 56

Results

• Vaccination Stage, with post-vaccination follow-up
  – 127/132 subjects received both doses of vaccine/placebo
  – 5 subjects did not receive their second dose, not related to any AE
• Challenge Stage, with post-challenge follow-up
  – 109 vaccinees given oral live GII.4 NoV (strain 031693) challenge
• No SAEs reported

Bernstein et al. JID 2015;211:870-8.
## Previous Experience in Humans - Trial LV03-105

<table>
<thead>
<tr>
<th>Gastroenteritis Symptom (post-hoc analysis)</th>
<th>Vaccine (%) N = 50</th>
<th>Placebo (%) N = 48</th>
<th>Rate Difference (95% CI)</th>
<th>% Reduction (95% CI)</th>
<th>p value (Fisher’s Exact)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe vomiting AND/OR diarrhea</td>
<td>0 (0.0%)</td>
<td>4 (8.3%)</td>
<td>-8.3 (-16.2, -0.5)</td>
<td>100% (-,-)</td>
<td>0.054</td>
</tr>
<tr>
<td>Moderate or severe vomiting AND/OR diarrhea</td>
<td>3 (6.0%)</td>
<td>9 (18.8%)</td>
<td>-12.8 (-25.6, 0.1)</td>
<td>68% (-11.2, 90.8)</td>
<td>0.068</td>
</tr>
<tr>
<td>Mild, moderate or severe vomiting AND/OR diarrhea</td>
<td>10 (20.0%)</td>
<td>20 (41.7%)</td>
<td>-21.7 (-39.5, -3.8)</td>
<td>52% (8.3, 74.9)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

- **2° endpoint met:** severity of illness by modified Vesikari score reduced in subjects receiving vaccine vs placebo *(p=0.002)*
- **Composite 1° endpoint not met,** informs design of efficacy trial
  - illness definitions and serum and stool assays to confirm illness by norovirus to be refined for Phase III studies

*Bernstein et al. JID 2015;211:870-8.*

*Slide courtesy of Takeda Vaccines*
Virus shedding:

- Fewer vaccine recipients were found to shed virus at day 10 post-challenge compared with placebo recipients (22% vaccine vs 36% placebo, NS p=0.179)
- Mean viral load in positive stool samples following illness was lower in vaccine recipients (not tested for infectivity)

Mean viral load in PCR-positive stool samples, Study LV03-105

Bernstein et al. JID 2015;211:870-8.
Summary - Next Steps

- Challenge studies indicate that vaccination against norovirus can have a meaningful clinical impact
- Efficacy studies need to be conducted to fully assess protection levels at the community level
- Modeling efforts are being initiated to develop tools to assess impact of vaccination and cost-effectiveness
- Epidemiology studies will continue to quantify burden of illness, particularly severe disease
Thank you / Questions?

• AFHSC-GEIS, Maryland
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• Takeda Vaccines