Vaccines in the Pipeline: Norovirus and Respiratory Syncytial Virus (RSV)

Aron J. Hall, DVM, MSPH, Dipl ACVPM
(RSV slides courtesy of Sue Gerber, MD)
CDC Division of Viral Diseases

National Adult and Influenza Immunization Summit, Atlanta, GA
May 10, 2017

Annual Burden (Lifetime Risk) of Norovirus Disease in the United States

- 570–800 Deaths (1 in 5000–7000)
- 56,000–71,000 Hospitalizations (1 in 50–70)
- 400,000 Emergency Dept Visits (1 in 9)
- 1.7–1.9 million Outpatient Visits (1 in 2)
- 19–21 million Total Illnesses (~5)

Hall 2013 EID
Severe Norovirus-associated Disease Rates by Age

![Graph showing disease rates by age and cause](image)

Community Norovirus Incidence, Kaiser Permanente Member Populations, 2012-2013

![Graph showing community norovirus incidence by age and site](image)
Global Disease Burden of Norovirus

- WHO Foodborne Disease Burden Epidemiology Reference Group (FERG)
- Global and regional age-stratified estimates of illnesses, deaths, and DALYs caused by specific foodborne hazards
- Total norovirus burden annually:
  - 685 million illnesses and 212,489 deaths
  - 29% of illnesses and 26% deaths in children <5
  - 85% of illnesses and 99% of deaths in developing countries
  - Total societal cost of $60 billion

Age-based Target Groups for Norovirus Vaccines

<table>
<thead>
<tr>
<th>Target population</th>
<th>High disease burden</th>
<th>High transmission risk</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young children</td>
<td>Yes</td>
<td>Yes</td>
<td>• Highest overall norovirus incidence rate and hospitalization rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Globally, norovirus is leading cause of pediatric acute gastroenteritis requiring medical attention in countries using rotavirus vaccines</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Highest R₀ of any age group</td>
</tr>
<tr>
<td>Elderly</td>
<td>Yes</td>
<td>No</td>
<td>• Greatest burden of fatal disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Higher hospital charges per case compared with children</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Nursing homes have higher rates of deaths during norovirus outbreak periods</td>
</tr>
</tbody>
</table>
### Occupational Target Groups for Norovirus Vaccines

<table>
<thead>
<tr>
<th>Target population</th>
<th>High disease burden</th>
<th>High transmission risk</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| Healthcare workers| No                  | Yes                    | • Most common setting for norovirus outbreaks  
                          • Infected healthcare workers can propagate infection to vulnerable patient populations |
| Food handlers     | No                  | Yes                    | • Most foodborne illnesses in US with identified agent caused by norovirus  
                          • Implicated source in majority of foodborne norovirus outbreaks in US  
                          • Poor compliance with hand hygiene and exclusion while ill |
| Military          | Yes                 | No                     | • Norovirus common cause of acute gastroenteritis in deployed troops  
                          • Lost duty time, decreased reserve readiness |

Aliabadi 2015
Exp Rev Vac

### Specific Sub-population Target Groups for Norovirus Vaccines

<table>
<thead>
<tr>
<th>Target population</th>
<th>High disease burden</th>
<th>High transmission risk</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| Travelers         | Yes                 | No                     | • 9–16% of traveler’s diarrhea attributable to norovirus  
                          • Numerous leisure settings implicated |
| Immuno-compromised patients | Yes | Yes | • Suffer severe clinical complications  
                          • Persistent viral shedding, up to months or years  
                          • Potential reservoir for new strain emergence  
                          • Poor immune response likely limits efficacy of vaccination |

Aliabadi 2015
Exp Rev Vac
## Norovirus Vaccine Candidates

<table>
<thead>
<tr>
<th>Norovirus antigen</th>
<th>P particle</th>
<th>Transgenic plant-vaccine</th>
<th>Trivalent noro-rota combo</th>
<th>Bivalent VLP</th>
<th>Adenoviral vector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norovirus antigen</td>
<td>2-3 norovirus P domains</td>
<td>Norwalk virus (GI.1) VLP</td>
<td>GiL.4 and GiL.3 VLP</td>
<td>Gl.1 and Gl.4 consensus VLP</td>
<td>Gl.1 VP1</td>
</tr>
<tr>
<td>Other antigen</td>
<td>Rotavirus VP6</td>
<td>None</td>
<td>Rotavirus VP6</td>
<td>None</td>
<td>Adenoviral vector</td>
</tr>
<tr>
<td></td>
<td>Influenza,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatitis E</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Route of administration</td>
<td>Intranasal</td>
<td>Intranasal</td>
<td>Intramuscular and intranasal</td>
<td>Intramuscular, previously intranasal</td>
<td>Oral (pill)</td>
</tr>
<tr>
<td>Commercial partner</td>
<td>UMN Pharma</td>
<td>Takeda</td>
<td>Vaxart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status</td>
<td>Preclinical</td>
<td>Preclinical</td>
<td>Preclinical</td>
<td>Phase 2</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>

## Human Challenge Efficacy Trials of Norovirus Vaccines

**Gl.1 intranasal**

**Gl.1/GII.4 intramuscular**
### IN Monovalent (GI.1) Vaccine Challenge
#### Per Protocol Efficacy Analysis

<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>NV infection</td>
<td>60.5%</td>
<td>82.1%</td>
<td>26% (1%, 45%)</td>
</tr>
<tr>
<td>Viral AGE</td>
<td>36.8%</td>
<td>69.2%</td>
<td>47% (15%, 67%)</td>
</tr>
</tbody>
</table>

#### IM Bivalent (GI.1/GII.4) Vaccine Challenge
#### Per Protocol Efficacy Analysis

<table>
<thead>
<tr>
<th>Illness Severity Infected</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>
Current Human Clinical Trials of Norovirus Vaccines

- GI.1/GII.4 bivalent VLP vaccine
  - Phase II: Safety and Immunogenicity in an Elderly population
  - Phase II: Safety and Immunogenicity in Children
  - Phase IIb: Efficacy and Immunogenicity in Adults (Military recruits)

- GI.1 Adenoviral vectored vaccine
  - Reportedly met all safety and immunogenicity endpoints

Challenges for a Norovirus Vaccine

- Role of prior infection history?
- Duration of protection?
- Protection against multiple genotypes?
- Need to be updated to keep up with viral evolution?
- Need for different vaccine formulation for certain groups?
- Variation in human genetic susceptibility?

Respiratory Syncytial Virus (RSV)

- Common cause of acute respiratory infections
  - Most infected in 1st year of life
  - Virtually all children infected by 2 years of age
  - Repeat infections affect older children and adults

- Most common cause of lower respiratory tract infections among infants
  - Including bronchiolitis or pneumonia

RSV Clinical Manifestations – Primary Infection

- Most have upper respiratory tract symptoms
- 20–30% develop lower respiratory tract disease
  - Bronchiolitis and/or pneumonia
    - Symptoms can include tachypnea, cough, labored breathing, wheezing, crackles
    - Most do not require hospitalization
- Fever may be absent
- Young infants may present with apnea, irritability, poor feeding
- Relationship with subsequent development of recurrent wheezing unclear

Glezen 1986 AJDC
Nair 2010 Lancet
Hall 2009 NEJM
Jain 2015 NEJM
RSV in Adults

- Repeat infections affect adults
- Most often upper respiratory tract illnesses
  - Symptoms often more severe than common cold
  - Less fever and fewer systemic symptoms compared to influenza
- Lower respiratory tract illnesses can occur
  - Especially among immunocompromised, underlying cardiopulmonary disease, elderly
  - Manifests as pneumonia and exacerbations of asthma, COPD, and congestive heart failure

Burden of RSV in Older US Adults (≥65 years)

- Importance first recognized with outbreaks in long-term care facilities for older adults
- Estimated 177,000 hospitalizations and 14,000 deaths annually
  - Based on extrapolation from prospective study in Rochester, NY over 4 consecutive winter seasons
- Average annual RSV hospitalization rate of 15 per 10,000 residents
  - Prospective study over 3 winter seasons
  - 1 county (Davidson County, Nashville, TN)
  - Similar hospitalization rate for influenza
Conclusions

- Norovirus and RSV exact a substantial disease burden, prompting development of multiple vaccine candidates currently in clinical trials
- Multiple potential target groups for candidate vaccines
  - Norovirus: pediatric, elderly, specific occupational/risk groups
  - RSV: pediatric, elderly, maternal
- Considerations for potential use of norovirus vaccines
  - Incidence and disease severity
  - Transmission risk to others
  - Compliance and other programmatic challenges
Questions?

ajhall@cdc.gov

For more information, contact CDC
1-800-CDC-INFO (232-4636)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.