Noroviruses

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Global norovirus burden

- Globally, norovirus is associated with 18% (95% CI: 17-20%) of diarrhoeal disease
- Estimated to cause approximately:
  - 1 billion episodes annually
  - 200,000 deaths annually, about >70,000 of which are among children in developing countries.
- Disease occurs across the age range in all settings, but incidence is highest in young children.
- Noroviruses are transmitted by multiple routes
  - Person-to-person spread predominates
  - Foodborne transmission is estimated to account for approximately 15% of disease
Estimates of norovirus mortality

<table>
<thead>
<tr>
<th>Year</th>
<th>ROTAVIRUS DEATH ESTIMATES</th>
<th>NOROVIRUS DEATH ESTIMATES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>877,000 25%</td>
<td>212,000 12%</td>
</tr>
<tr>
<td>1994</td>
<td>440,000 22%</td>
<td>90,000 13%</td>
</tr>
<tr>
<td>2004</td>
<td>527,000 29%</td>
<td>71,000 9.9%</td>
</tr>
<tr>
<td>2008</td>
<td>453,000 37%</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>197,000 28%</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>173,000 26%</td>
<td></td>
</tr>
</tbody>
</table>

- Total diarrhea deaths (Millions)
- Mid-point of Study Period
Norovirus detection is common amongst healthy controls

1) True asymptomatic infection
2) Shedding of virus in stool continues long after the resolution of symptoms
3) Ingested virus may even transit the gut without replicating

- For this combination of reasons, norovirus can frequently be detected using RT-qPCR in stools from healthy individuals.
- However, norovirus is clearly a pathogen
- Complicates interpretation of etiological studies including MAL-ED or GEMS
Norovirus illness and infection rates in children in community based cohort studies

A) Norovirus illness

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Incidence per 100 child years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 yrs</td>
<td>17</td>
</tr>
<tr>
<td>0-5 m</td>
<td>29</td>
</tr>
<tr>
<td>6-11 m</td>
<td>79</td>
</tr>
<tr>
<td>12-23 m</td>
<td>84</td>
</tr>
</tbody>
</table>

B) Norovirus infection

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Incidence per 100 child years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 yrs</td>
<td>23</td>
</tr>
<tr>
<td>0-5 m</td>
<td>21</td>
</tr>
<tr>
<td>6-11 m</td>
<td>188</td>
</tr>
</tbody>
</table>

Equador, Peru, Nicaragua, England, Lopman, Saito
Molecular re-analysis of MAL-ED

A total of 8,508 diarrhoeal and 24,238 control stools were tested for a broad range of enteropathogens in the primary analysis; 2,182 diarrhoeal and 3,244 control stools from approximately 60 children per site were re-analyzed by qPCR assays in TAC

Figure 2. Overall adjusted attributable fractions derived for conventional diagnostic work-up (red) and TAC re-analysis (blue)
Challenges to Estimating Global Norovirus Burden

• Little routine testing performed in ongoing surveillance platforms; or in developing countries
• Sensitive assays have only recently been widely available, and are not available for most settings
• Community-based studies are expensive and challenging
• Some norovirus acute gastroenteritis cases do not present with diarrhoea, only vomiting
• Challenges in interpretation of diagnostic results

➢ Birth cohort study in Vellore, India
➢ Leveraging the global rotavirus networks with TAC assays
Norovirus: basic virology

- Noroviruses are a highly diverse group of ssRNA viruses.
- GII.4 norovirus:
  - is the most common genotype causing cases and outbreaks across the age range
  - evolves in a boom-and-bust cycling of epochal evolution and escape population immunity with new variants emerge every 2-4 years
  - cause more severe disease and affect both young and elderly vulnerable populations.
- Real time RT-PCR is
  - the gold standard for norovirus diagnostics
  - exquisitely sensitive and frequently detects virus in the stool of healthy individuals
- Uncultivable, but there has been important recent progress in *in vitro* cell culture for norovirus.
Norovirus vaccines

- A number of noroviruses vaccines being developed.
- Based on the expression of VP1 leading to the production of VLPs or P particle subunit in various expression systems.
- Preclinical and early human studies of various concentrations of monovalent or bivalent norovirus antigens, with and without adjuvants, and various routes of immunization have shown safety and immunogenicity.
## Norovirus vaccine candidates

<table>
<thead>
<tr>
<th>Norovirus vaccine</th>
<th>Norovirus P particle and combination vaccines</th>
<th>Trivalent norovirus/rotavirus combination vaccine</th>
<th>Bivalent norovirus VLP vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Principal inventor</strong></td>
<td>Charles Arntzen, PhD Arizona State University</td>
<td>Xi Jason Jiang, PhD Cincinnati Children's Hospital</td>
<td>Timo Vesikari, MD PhD University of Tampere, Finland</td>
</tr>
<tr>
<td><strong>Norovirus antigen(s) (all based on VP1)</strong></td>
<td>Norwalk virus (GI.1) VLP</td>
<td>Two to three noroviruses P domains representing different GI and GII strains</td>
<td>GII-4 and GI-3 VLP</td>
</tr>
<tr>
<td><strong>Other antigen(s)</strong></td>
<td>None</td>
<td>Chimeric norovirus P-rotavirus VP8* particle, experimental formulations include influenza, Hepatitis E</td>
<td>Rotavirus VP6</td>
</tr>
<tr>
<td><strong>Adjuvant(s)</strong></td>
<td>gardiquimod or none when delivered with GelVac</td>
<td>5 mg chitosan, 50 µg MPL, and TNC buffer 24920797</td>
<td>None, but some evidence that the RV VP6 component adjuvant effect</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Intranasal by GelVac dry powder and oral by ingestion of raw potato</td>
<td>Intranasal</td>
<td>Intramuscular and intranasal</td>
</tr>
<tr>
<td><strong>Commercial partner</strong></td>
<td>UMN Pharma (Japan).</td>
<td></td>
<td>Takeda Pharmaceuticals</td>
</tr>
</tbody>
</table>
Human efficacy data from challenge studies

• The only products with human efficacy data are being developed by Takeda Pharmaceuticals.
  – An intranasal monovalent formulation was shown to be effective against infection and disease following GI.1 challenge.
    • 47% (95% CI, 15%–67%) against AGE
    • Norwalk virus infection by 26% (95% CI, 1%–45%)
  – An IM bivalent formulation showed a degree of protection against disease following GII.4 challenge sufficient to warrant further clinical development.
    • Non-significant reduction in AGE (26.0% among vaccinees; 33.3% among placebo recipients)
    • Reductions of more severe disease and diarrhoea and vomiting in vaccine recipients following GII.4 challenge
Critical questions for a norovirus vaccine

• Can a vaccine elicit broad protection against multiple genotypes?
• What will be the duration of protection from vaccination?
• Will a norovirus vaccine have to be regularly updated in order to keep up with natural evolution of the virus?
• How will prior norovirus infection history affect vaccine immunogenicity and effectiveness?
• Will the same vaccine formulation be effective in all population groups, including in infants or low-income settings?
• How will the variation in human genetic susceptibility affect vaccine outcomes?
<table>
<thead>
<tr>
<th>Target Groups</th>
<th>Incidence</th>
<th>Health care utilization</th>
<th>Hospitalization</th>
<th>Deaths</th>
<th>Societal costs</th>
<th>Healthcare costs</th>
<th>Role/risk in transmission</th>
<th>Challenges in vaccinating: immunological</th>
<th>Challenges in vaccinating: programmatic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children (&lt;5 years)</strong></td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Med</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Naïve: may need multiple doses</td>
<td>Interaction with other routine immunizations</td>
</tr>
<tr>
<td><strong>Older children (5-14 years)</strong></td>
<td>Med</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Med</td>
<td>Low</td>
<td>Med</td>
<td>History of exposure</td>
<td></td>
</tr>
<tr>
<td><strong>Younger adults (15-64 years)</strong></td>
<td>Med</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Med</td>
<td>Low</td>
<td>Med</td>
<td>History of exposure</td>
<td>Generally low coverage</td>
</tr>
<tr>
<td><strong>Older adults (≥65 years)</strong></td>
<td>Low</td>
<td>Med</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>History of exposure immune senescence</td>
<td>Generally low coverage</td>
</tr>
</tbody>
</table>
Specific sub-population target groups for vaccination

• Healthcare workers
• Travelers
• Military personnel
• Immunocompromised patients
• Food service workers

Each group has unique epidemiological, economic and programmatic considerations
Specific roles for WHO in 2016-2017

• Study design to help quantify incidence and burden, particularly in developing countries

• Call for better epidemiology data on norovirus
  – Birth cohort studies
  – Regional norovirus surveillance networks with standardized protocols
  – Development / optimization of diagnostics for use in etiology and clinical studies

• Development of preferred product characteristics; TPPs
  – Different population targets will likely have different TPPs

• Confirmation of currently proposed immune correlates of protection; validation in different populations
THE WORK IS COMPLICATED. WHY WE DO IT, IS NOT