Vaccines for gastro

*the good, the bad, and the remainder*

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Vaccines for gastro

the here and now, and the horizon
Gastro vaccines

- here and now (handbook)
  - cholera
  - rotavirus (the good, the bad, and the remainder)

- the horizon
  - norovirus
Cholera
Cholera

- profuse, watery diarrhoea
  - toxigenic *Vibrio cholerae*
  - serogroups O1 and O139
  - endemic in Africa, parts of Asia
  - contaminated water or food
Cholera

- globally: millions of cases
  ~100,000 deaths annually
- Australia: since 1991, 3 to 4 cases a year all returned travelers except for
  - 1 case of laboratory acquired disease\textsuperscript{1996}
  - 3 cases in Italian women aged >70 years in Sydney with no history of travel/contact with travelers\textsuperscript{2006}
Cholera

- globally: ~100,000 deaths annually
- Australia: since 1991, 3 to 4 cases a year all returned travelers except for
  - 1 case of laboratory acquired disease in 1996
  - 3 cases in Italian women in Sydney in 2006
  - whitebait imported from Indonesia
  - all women on proton pump inhibitors
  - all tasted batter/fish mix before cooking
CDC:

...the worst epidemic of cholera in recent history
Haiti

- Catastrophic earthquake, January 2010
  - 52+ aftershocks
  - 10M population, death toll 250K
  - severe infrastructure damage
Cholera outbreak in Haiti

- cholera not seen in Haiti for >century
- outbreak confirmed October 2010
- by August 2013:
  - 6+% of population infected
  - 400K+ hospitalised
  - 8,231 dead, CFR 1.2%
Figure 2. Cases of Cholera in Haiti during a 2-Year Period, According to Age.

Shown are the number of cases of cholera, as documented from the initiation of surveillance on October 20, 2010, through October 20, 2012, according to age (<5 years or ≥5 years) (left axis) and 7-day averages of the percentage of cases in children under the age of 5 years (right axis).
Cholera outbreak in Haiti

- vaccine a possible response
- concerns cold chain, logistics, setting
- 2012 demonstration exercise in rural Haiti:
  - used Indian produced BivWC vaccine
  - US$1.85 per dose
Cholera outbreak in Haiti

- Outcomes
  - cold chain maintained
  - >45,000 received at least one dose
  - 77-93% of targeted population
  - second dose delivered to >90% of first dose recipients
  - success
Haiti launches cholera vaccination campaign

Effort targets 200,000 people in three departments considered at high risk

Port-au-Prince, Haiti, 2 September 2014 (PAHO/WHO) – Haiti launched a cholera vaccination campaign last week that seeks to reach 200,000 people in three departments. The campaign is being led by the Ministry of Health and Population (MSPP) with support from the United Nations and a coalition of strategic partners, including the Pan American Health Organization/World Health Organization (PAHO/WHO).

The campaign has financing from the U.N. Central Emergency Response Fund (CERF) and is using vaccines from a global stockpile created at the request of the 2011 World Health Assembly as a tool to help control cholera outbreaks worldwide. WHO serves as secretariat for the global stockpile, which is also supported by the International Federation of Red Cross and Red Crescent Societies, Doctors without Borders, and UNICEF.

Last week’s campaign was carried out in Artibonite (Gonaives and Ennery), Central (Lascahobas, Saut d’Eau, Savanette and Mirebalais), and West (Arcahaie) departments, which are considered high-risk zones. A second phase is planned for mid-September to deliver a second dose of the vaccine.
VIRUS PARTICLES IN EPITHELIAL CELLS
OF DUODENAL MUCOSA FROM CHILDREN
WITH ACUTE NON-BACTERIAL
GASTROENTERITIS

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Summary
Electron microscopy of duodenal mucosa from nine children with acute non-bacterial gastroenteritis revealed virus particles in epithelial cells from six patients. The morphology of the virus particles was identical in each of the six children. The virus belonged to the orbivirus group. No virus particles were observed in duodenal mucosa obtained from three of these children after clinical recovery. This orbivirus is believed to have been an important cause of sporadic gastroenteritis in children in Melbourne during the 3 months of the survey.

Introduction
Most infants with acute non-bacterial gastroenteritis show histological abnormalities in the duodenal mucosa associated with depression of disacchari-

Thin-section electron micrograph of part of an intestinal epithelial cell in a biopsy specimen from a child with acute gastroenteritis.
This area includes numerous virus particles (V) in endoplasmic reticulum cisternae; arrows indicate enveloped particles. Parts of a reticulate inclusion (R, upper left) and of the apical surface of the cell with its microvilli (M) are also visible. Reduced to two-thirds from ×45,000.
RotaShield (the bad)

- Rhesus monkey-human reassortant vaccine
- Tetravalent: RRV-TV
- Licensed in US in August 1998
  - 27 trials
  - 10,054 vaccinated, 4,633 placebo
  - Intussusception imbalance (not significant)
RotaShield

- rhesus monkey-human reassortant vaccine
- tetravalent: RRV-TV
- licensed in US in August 1998
  - 27 trials
  - 10,054 vaccinated, 4,633 placebo
  - intussusception imbalance (not significant)
  - 5 cases in vaccine group: 0.05%
  - 1 case in placebo group: 0.02%
- identified as a condition of interest for post-marketing surveillance
RotaShield

- October 1998 to May 1999
  - 9 reports of intussusception to VAERS in RotaShield recipients
- July: recommendation to halt use
RotaShield

- October 1998 to May 1999
  - 9 reports of intussusception to VAERS in RotaShield recipients
- recommendation to halt use
- product withdrawn from market
- subsequent research
  - increased excess risk of intussusception was ~1 case of IS per 5,000-10,000 doses of vaccine
  - risk higher with first dose, older age at first dose
## New vaccines in clinical development

<table>
<thead>
<tr>
<th>Rotarix</th>
<th>RotaTeq</th>
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<tr>
<td>GSK</td>
<td>Merck/bioCSL</td>
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<td>oral liquid</td>
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<tr>
<td>- monovalent</td>
<td>5 human RV proteins:</td>
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<td>2 dose course</td>
<td>2 bovine RV proteins:</td>
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<td>G6 P[5]</td>
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<td>3 dose course</td>
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Rotarix
N = 63,225
1:1 randomisation
@31 days
IS in 6 RV1 and 7 placebo recipients

RotaTeq
N = 68,038
1:1 randomisation
@42 days
IS in 6 RV5 and 5 placebo recipients
Both vaccines

- registered for use in Australia in 2006
- added to the national immunisation program
- children born on or after 01 May 2007 were eligible for dose 1 on 01 July 2007
- strict time windows for administration to lessen risk of intussusception
Changes in hospitalisations for acute gastroenteritis in Australia after the national rotavirus vaccination program

Rotavirus gastroenteritis is the leading cause of severe acute gastroenteritis (AGE) in children aged less than 5 years; it results in over half a million deaths each year, most of which occur in developing countries.1 Most children worldwide are infected with rotavirus by the age of 5 years, with severe disease occurring most commonly between the ages of 6 months and 2 years.1

In Australia, before a rotavirus vaccination program was introduced, this virus was responsible for more than 10000 hospitalisations of children aged under 5 years annually, placing an enormous burden on paediatric hospitals.2-4 The burden of disease in Aboriginal and Torres Strait Islander children was much greater, with a hospitalisation rate about five times that of non-Indigenous children aged less than 12 months.5 Large outbreaks in Indigenous children occur on a

Abstract

Objective: To evaluate the impact of the Australian rotavirus vaccination program on both rotavirus and all-cause acute gastroenteritis (AGE) hospitalisations and to compare outcomes in Indigenous and non-Indigenous people.

Design and setting: Retrospective analysis of the Australian Institute of Health and Welfare National Hospital Morbidity database for hospitalisations coded as rotavirus and all-cause AGE, between 1 July 2001 and 30 June 2010.

Main outcome measures: Age-specific hospitalisation rates in Indigenous and non-Indigenous people, before and after the introduction of the vaccine program in July 2007.

Results: There was a 71% decline in rotavirus-coded hospitalisations of children aged < 5 years between periods before and after rotavirus vaccination (from 261 per 100 000 to 75 per 100 000). There was also a 38% decline in non-rotavirus coded AGE hospitalisations (from 1419 per 100 000 to 880 per 100 000). This represented more than 7700 hospitalisations of children aged < 5 years being averted in the financial year 2009–10. Reductions were also observed in the 5–19-years age group, suggesting that transmission of virus was reduced at a population level. Decreases in hospitalisations of Indigenous children were smaller than those for the general population, and fluctuated by location and year.

Conclusions: These data show a sustained and substantial decline in severe rotavirus disease and all-cause AGE since the introduction of rotavirus vaccination, most pronounced in the target age group, but with evidence of herd immunity. The impact of rotavirus vaccination in Indigenous children in hyperendemic settings was less remarkable.
Number of hospitalisations* coded as rotavirus gastroenteritis (all ages) and infant rotavirus vaccine coverage,† Australia, July 2001 to June 2010

![Graph showing the number of hospitalisations and vaccine coverage over time.](image)
Timeliness of other vaccines

- Pre-rota Indigenous: 52.2%
- Post-rota Indigenous: 56%
- Pre-rota non-Indigenous: 71.4%
- Post-rota non-Indigenous: 75.9%
• ~9-fold increased risk of IS in 7 days post dose 1
• ~2-fold increased risk post dose 2
• extra 14 cases of IS per year in Australia
  ▪ background of 200 cases per year
• vaccine now preventing ~7,000 hospitalisations per year
Rotavirus Immunisation
INFORMATION FOR PARENTS AND GUARDIANS

What is rotavirus and how serious is it?
Rotavirus is the most common cause of severe gastroenteritis in infants and young children in Australia and worldwide.

The severity of the illness ranges from mild, watery diarrhoea of limited duration to severe, dehydrating diarrhoea with vomiting, fever and shock. Rotavirus infections are often more severe than other causes of diarrhoea, are more likely to be associated with dehydration and are more likely to require treatment in hospital.

Prior to the introduction of rotavirus vaccination in Australia, almost every child was infected with rotavirus by the age of 5 years, and there was approximately 10,000 hospitalisations due to rotavirus in children less than 5 years of age each year. In addition to hospitalised children, an estimated 115,000 children under 5 years of age visited a GP, and 22,000 children required an emergency department visit. On average, there was one childhood death from rotavirus each year.

Children can be infected with rotavirus several times during their lives, and without vaccination almost every child will suffer from at least one infection by the age of 3 years. The disease is easily spread from one child to the next. Confirmation of rotavirus infection can only be made by laboratory testing of faecal specimens.

When is rotavirus vaccine given?
Rotavirus vaccination is only recommended for children up to 6 months of age. The first dose of vaccine is recommended to be given with your child’s 2 month old vaccines and it is most important that the vaccine is given on time. It is possible that the risk of intussusception, a rare side effect of vaccination discussed below, may be increased if the vaccine is delayed past the scheduled time. The vaccine is given orally (by the mouth).
Good vs Bad

- successful introduction of vaccines ✓
- intussusception: adverse event due to RV vaccines ✗
- coverage ok, timeliness requires improvement ~
- epidemiology shows reduction in any and severe disease with herd protection impacts ✓
- Australia researchers made a meaningful contribution to global safety assessments ✓
- risk-benefit still strongly in favour of vaccinating ✓
- typing not suggestive of undue vaccine pressure ✓
Norovirus

- “perfect human pathogen”
  - highly stable in the environment
  - infectious at low doses
  - shed in large quantities
  - moderately virulent
  - multiple strains
  - evolving
  - induces limited immunity after natural infection
Norovirus

- unpleasant, usually self-limiting gastro
- 270M cases, 200K deaths per year
- causes ~18% of all gastro
- vaccine development hard because
  - multiple strains
  - human noroviruses don’t replicate in cell culture
- vaccine may be cost effective even if modest efficacy, short-lived
Norovirus Vaccine against Experimental Human Norwalk Virus Illness

Norovirus VLPs

- double blind, placebo controlled RCT
- 98 healthy adults, 18 to 50y, 1:1
- active arm: 2 doses of GI.1, intranasal
  - nasal related adverse events, same in placebo
  - seroresponse in 70% of vaccine recipients
  - gastro: 69% placebo, 37% vaccine
  - severity score reduced: 35% lower
- vaccine strategy against norovirus possible
Gastro vaccines

- cholera vaccines
  - travel vaccines in Australia
  - significant role in global control of disease
- rotavirus vaccines
  - successfully implemented in Australia
  - ongoing need for effectiveness/safety monitoring
- norovirus vaccines
  - VLPs effective in human challenge
  - role in controlling outbreaks? wider use?