The Oral Rotavirus Vaccine

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Interactive Session.....

1. Which age group has the highest incidence of confirmed rotavirus disease?
   • <1, 1-4, 5-14, 15-24, 25-44, 45-64, 65+

2. Which age group has the highest number of cases of confirmed rotavirus disease?
   • <1, 1-4, 5-14, 15-24, 25-44, 45-64, 65+ y

3. Where do adults get rotavirus from? Who are these adults?

4. Where do toddlers (1-4 year-olds) get rotavirus from?

5. Where do infants (<1 year-olds) get rotavirus from?
Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis

Rotavirus vaccines (United States)

Source: Rha et al., 2014

Figure 1. Number of positive and total rotavirus tests from 25 continuously reporting National Respiratory and Enteric Virus Surveillance System laboratories, by week of year and region, June 2000-July 2012, 3-week moving average.
Rotavirus vaccines (Australia)

Source: Dey et al., 2012
Indirect impact on older children

<table>
<thead>
<tr>
<th>Age</th>
<th>Decline in rotavirus hospitalization rate (2008 vs. 2006)</th>
<th>Rotavirus vaccine coverage in 2008 (≥1 dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>66%</td>
<td>56%</td>
</tr>
<tr>
<td>1 - &lt;2 years</td>
<td>95%</td>
<td>44%</td>
</tr>
<tr>
<td>2 - &lt;3 years</td>
<td>85%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

This age cohort was NOT eligible to receive rotavirus vaccine.
Indirect impact of rotavirus vaccine in other age groups
Risk of IS in infants following Rotashield vaccination in the US

Murphy et al., N Engl J Med 2001; 344: 564:72
Intussusception and rotavirus infection

Table 1: Seasonal Distribution of Rotavirus Disease and Intussusception in children < 3 yrs old (WHO Conference, 2000)
Intussusception Risk and Disease Prevention Associated With Rotavirus Vaccines in Australia’s National Immunization Program

- Relative risk of IS for Rotarix® was
  - **6.8** (95% CI, 2.4–19.0; P<0.001) @ 1-7 days after first dose
  - **3.5** (95% CI, 1.3-8.9; P=0.01) @ 8-21 days after first dose
  - **2.8** (95% CI, 1.1-7.3; P=0.03) @ 1-7 days after second dose

- Relative risk of IS for Rotateq® was
  - **9.9** (95% CI, 3.7-26.4; P<0.001) @ 1-7 days after first dose
  - **6.3** (95% CI, 2.8-14.4; P<0.001) @ 8-21 days after first dose
  - **2.8** (95% CI, 1.2-6.8; P=0.03) @ 1-7 days after second dose

- Excess of 14 annual IS cases and >6500 fewer gastroenteritis hospitalizations

- Vaccine attributable risk for IS was
  - **4.3** (95% CI, 0.8–23.3) cases/100,000 infants vaccinated (Rotarix)
  - **7.0** (95% CI, 1.5–33.1) cases/100,000 infants vaccinated (Rotateq)
Rotavirus in the UK
Rotavirus: burden

- In England and Wales, in children <5 years of age:
  - 90-133,000 GP consultations (25% of GP consultations for gastroenteritis)
  - 37,000 NHS Direct calls (27% of NHS direct calls for gastroenteritis)
  - 30,000 A&E attendances
  - 14,000 hospital admissions (45% of gastroenteritis admissions)

**Estimated annual cost of £14.8 million**
Rotavirus: Seasonal Variation

Number of Reports

0 1000 2000 3000 4000

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60

Vaccination Against Rotavirus
Admissions attributable to each organism
Episodes coded as “infectious intestinal disease”
Rotavirus infection: age in months

Number of reports

Age in months

Vaccination Against Rotavirus
The UK infant immunisation schedule *(changes in 2013)*

- **2 months**  
  DTaP/IPV/Hib + PCV13 + Rotarix

- **3 months**  
  DTaP/IPV/Hib + MenC + Rotarix

- **4 months**  
  DTaP/IPV/Hib + MenC + PCV13

- **12/13 months**  
  MMR + Hib/Men C + PCV13

- **Pre-school**  
  DTaP-IPV (polio) + MMR

- **12-13 years**  
  HPV (girls)

- **13-18 years**  
  Td/IPV(polio)
We found that the incidence of intussusception associated with the first dose of vaccine increased with age.

First dose: 6-15 weeks

Second dose: <24 weeks
Coverage of Rotavirus Vaccination in infants

- Immunisation coverage:
  - CPRD data – MHRA (Jan 2014, 6% E&W population)
    - 89% by 3 months and 93% by 4 months: received at least one dose
    - 78% by 4 months, 81% by 5 months and 93% by 6 months: received two doses
  - Automated extracts from GP systems in England via ImmForm website (Feb 2014, 49% of GP practices in England)
    - 93% by 25 weeks: received one dose
    - 88% by 25 weeks: received two doses
Weekly rate of laboratory-confirmed rotavirus infections (per 1,000,000)
England and Wales, 2000-2014
Weekly rate of laboratory-confirmed rotavirus infections (per 1,000,000) by age group
England and Wales, 2000/01-2012/13 (mean) vs. 2013/14

- **Age <1 years**
- **Age 1 year**
- **Age 2-4 years**
- **Age 5+ years**
Weekly rate of AGE hospitalisations (per 1,000,000) by age group
England and Wales, 2000/01-2012/13 (mean) vs. 2013/14
Case Reduction by Age Group
(Average 2002/03-2012/13 vs. 2013/14)

Vaccination Against Rotavirus
Case Reduction by sample source

(Average 2002/03-2012/13 vs. 2013/14)

- GP
  - N=5,514
  - n=1,334
  - Proportional Reduction: -0.76

- A&E
  - N=729
  - n=134
  - Proportional Reduction: -0.82

- In-patient
  - N=4,014
  - n=681
  - Proportional Reduction: -0.83
### Laboratory-confirmed rotavirus infections

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Mean 2000-01 to 2012-13 (minimum)</th>
<th>2013-14</th>
<th>RR (95% CI)</th>
<th>p value</th>
<th>Number averted</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>6,041 (5,310)</td>
<td>1,402</td>
<td>0.23 (0.16-0.32)</td>
<td>&lt;0.0001</td>
<td>4,810</td>
</tr>
<tr>
<td>1</td>
<td>5,417 (4,895)</td>
<td>2,083</td>
<td>0.34 (0.23-0.50)</td>
<td>&lt;0.0001</td>
<td>4,026</td>
</tr>
<tr>
<td>2</td>
<td>1,696 (1,402)</td>
<td>604</td>
<td>0.36 (0.24-0.52)</td>
<td>&lt;0.0001</td>
<td>1,087</td>
</tr>
<tr>
<td>3</td>
<td>617 (534)</td>
<td>207</td>
<td>0.34 (0.23-0.50)</td>
<td>&lt;0.0001</td>
<td>405</td>
</tr>
<tr>
<td>4</td>
<td>316 (257)</td>
<td>112</td>
<td>0.35 (0.23-0.52)</td>
<td>&lt;0.0001</td>
<td>210</td>
</tr>
<tr>
<td>≥5†</td>
<td>788 (652)</td>
<td>343</td>
<td>0.50 (0.37-0.67)</td>
<td>&lt;0.0001</td>
<td>246</td>
</tr>
<tr>
<td>All ages</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10,884</td>
</tr>
</tbody>
</table>

### All-cause AGE hospital admissions

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Mean 2007-08 to 2012-13 (minimum)</th>
<th>2013-14</th>
<th>RR (95% CI)</th>
<th>p value</th>
<th>Number averted</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>20,663 (20,131)</td>
<td>15,101</td>
<td>0.74 (0.65-0.84)</td>
<td>&lt;0.0001</td>
<td>5,256</td>
</tr>
<tr>
<td>1</td>
<td>14,678 (14,019)</td>
<td>10,078</td>
<td>0.67 (0.54-0.82)</td>
<td>&lt;0.0001</td>
<td>4,648</td>
</tr>
<tr>
<td>2</td>
<td>6,108 (5,760)</td>
<td>4,524</td>
<td>0.73 (0.61-0.88)</td>
<td>&lt;0.0001</td>
<td>1,565</td>
</tr>
<tr>
<td>3</td>
<td>3,490 (3,074)</td>
<td>2,986</td>
<td>0.81 (0.69-0.94)</td>
<td>&lt;0.0001</td>
<td>710</td>
</tr>
<tr>
<td>4</td>
<td>2,490 (2,197)</td>
<td>2,402</td>
<td>0.88 (0.77-1.00)</td>
<td>0.006</td>
<td>333</td>
</tr>
<tr>
<td>5-14</td>
<td>11,426 (10,446)</td>
<td>11,782</td>
<td>0.92 (0.87-0.98)</td>
<td>&lt;0.0001</td>
<td>1,020</td>
</tr>
<tr>
<td>15-44</td>
<td>64,381 (56,408)</td>
<td>70,781</td>
<td>0.92 (0.90-0.94)</td>
<td>&lt;0.0001</td>
<td>6,043</td>
</tr>
<tr>
<td>45-64</td>
<td>64,734 (53,920)</td>
<td>71,082</td>
<td>0.88 (0.86-0.90)</td>
<td>&lt;0.0001</td>
<td>9,484</td>
</tr>
<tr>
<td>≥65</td>
<td>133,468 (121,978)</td>
<td>134,079</td>
<td>0.86 (0.83-0.90)</td>
<td>&lt;0.0001</td>
<td>21,368</td>
</tr>
<tr>
<td>All ages</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50,427</td>
</tr>
</tbody>
</table>
Laboratory-confirmed rotavirus disease
England & Wales (up to 10 March 2016)

Seasonal comparison of laboratory reports of rotavirus (England and Wales)

*Comparison is made with this ten year period as it is prior to the vaccine introduction.
The risk of intussusception following monovalent rotavirus vaccination in England: self-controlled case-series

Julia Stowe, Nick Andrews, Shamez Ladhani, Elizabeth Miller

<table>
<thead>
<tr>
<th>Dose</th>
<th>Risk period (days)</th>
<th>Cases in risk period</th>
<th>RI (95% CI*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-7</td>
<td>15</td>
<td>13.81 (6.44-28.32)</td>
</tr>
<tr>
<td>8-21</td>
<td></td>
<td>5</td>
<td>1.59 (0.34-3.75)</td>
</tr>
<tr>
<td>1-21</td>
<td></td>
<td>20</td>
<td>3.94 (2.03-6.69)</td>
</tr>
<tr>
<td>2</td>
<td>1-7</td>
<td>5</td>
<td>2.20 (0.50-5.02)</td>
</tr>
<tr>
<td>8-21</td>
<td></td>
<td>14</td>
<td>2.77 (1.36-5.32)</td>
</tr>
<tr>
<td>1-21</td>
<td></td>
<td>19</td>
<td>2.48 (1.34-4.50)</td>
</tr>
</tbody>
</table>
The risk of intussusception following monovalent rotavirus vaccination in England: self-controlled case-series

Julia Stowe, Nick Andrews, Shamez Ladhani, Elizabeth Miller

<table>
<thead>
<tr>
<th>Feature</th>
<th>1-7 days post first dose n/N (%)</th>
<th>Out of risk period-baseline** n/N (%)</th>
<th>Odds ratio (95%CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiological</td>
<td>8/15 (53.3%)</td>
<td>30/56 (53.6%)</td>
<td>0.96 (0.24-3.91)</td>
</tr>
<tr>
<td>Surgical</td>
<td>7/15 (46.7%)</td>
<td>22/56 (39.3%)</td>
<td>1.58 (0.38-6.59)</td>
</tr>
<tr>
<td>Days from onset to admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same day</td>
<td>5/15 (33.3%)</td>
<td>29/56 (51.8%)</td>
<td>1.04 (0.24-4.60)</td>
</tr>
<tr>
<td>Mean (range) in days</td>
<td>0.71 (0-4)</td>
<td>0.77 (0-4)</td>
<td></td>
</tr>
<tr>
<td>Duration of admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 days</td>
<td>9/15 (60.0%)</td>
<td>32/56 (57.1%)</td>
<td>0.44 (0.11-1.85)</td>
</tr>
<tr>
<td>Mean (range) in days</td>
<td>0.33 (0-8)</td>
<td>0.50 (0-12)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10/15 (66.7%)</td>
<td>37/56 (66.1%)</td>
<td>0.54 (0.11-2.58)</td>
</tr>
</tbody>
</table>
The risk of intussusception following monovalent rotavirus vaccination in England: self-controlled case-series

Julia Stowe, Nick Andrews, Shamez Ladhani, Elizabeth Miller

<table>
<thead>
<tr>
<th>Country</th>
<th>Period post dose 1</th>
<th>Period post dose 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-7 days</td>
<td>8-21 days</td>
</tr>
<tr>
<td>Australia</td>
<td>6.76 (2.40-19.01)</td>
<td>3.45 (1.33-8.94)</td>
</tr>
<tr>
<td>Mexico</td>
<td>5.30 (3.00-9.30)</td>
<td>0.99 (0.52-1.91)</td>
</tr>
<tr>
<td>Singapore</td>
<td>8.36 (2.42-28.96)</td>
<td>0.00</td>
</tr>
<tr>
<td>England</td>
<td>13.81 (6.44-28.32)</td>
<td>1.59 (0.34-3.75)</td>
</tr>
<tr>
<td>Pooled^</td>
<td>7.50 (5.07-11.09)</td>
<td>1.41 (0.87-2.30)</td>
</tr>
</tbody>
</table>
Rotavirus & Seizures

Data on 250,601 infants, including 186,502 children fully vaccinated (74.4%) and 64,099 (25.6%) not vaccinated with rotavirus vaccine.

After adjusting for covariates, a statistically significant protective association was seen between a full rotavirus vaccination course vs no vaccination:

- First-ever seizures: risk ratio [RR] = 0.82; 95% CI, 0.73–0.91
- All seizures (RR = 0.79; 95% CI, 0.71–0.88).

Conclusions: rotavirus vaccination was statistically associated with an 18%–21% reduction in risk of seizure requiring hospitalization or A&E care in the year following vaccination,
Impact of Rotavirus Vaccination on Childhood Hospitalization for Seizures

Jacobo Pardo-Seco,*† Miriam Cebey-López,*† Nazareth Martinón-Torres, MD, PhD,*† Antonio Salas, PhD,*†† Jose Gómez-Rial, MSc, † Carmen Rodríguez-Tenreiro, PhD,*† José María Martinón-Sánchez, MD, PhD,*† and Federico Martinón-Torres, MD, PhD*†

The Pediatric Infectious Disease Journal • Volume 34, Number 7, July 2015
Rotavirus Vaccine in the UK: Summary of the programme

1. The **oral** rotavirus vaccine (Rotarix®) was introduced into the UK national infant immunisation programme on 01 July 2013
2. All infants born from 01 May 2013 onwards are eligible
3. Aim was to protect as many infants as possible before the next rotavirus season (January-April 2014)
4. No catch-up programme for older infants and children
5. First dose must be given between 6 and 15 weeks chronological age
6. Second dose must be given before 24 week chronological age (<6 mths)
7. Surveillance data indicate a massive impact on disease burden across all age groups
1. Stool samples in 2 & 3 MONTH olds coming to A&E with Diarrhoea

2. Small but significant increase is the risk of intussusception after both doses, but especially in the first 7 days after the first dose of vaccine

3. Suspect early → refer quickly → radiological reduction

4. Previous intussusception is a contra-indication to rotavirus vaccination – 10 infants with IS were vaccinated, no complications
Acknowledgements:

- Immunisation, Hepatitis and Blood Safety Department, Public Health England: Mary Ramsay, Sarah Collins, Nick Andrews, Julia Stowe, Rashmi Malkani, Joanne White, Christina Atchison
- Gastrointestinal Emerging and Zoonotic Infections Department, Public Health England: John Harris, Natalie Adams
- PHE Virus Reference Department: David James Allen, Sameena Nawaz, David Brown
- Medicines and Healthcare Products Regulatory Agency: Katherine Donegan
- PHE Sentinel Sites
- GP surgeries
Rotavirus Surveillance: England & Wales

- Laboratory-confirmed cases through LabBase2
- Linkage of HES and LabBase2: nosocomial infections
- Molecular epidemiology of rotavirus isolates and impact of routine vaccination (hospital laboratories & PHE VRD)
- **Vaccine Effectiveness**: using cases reported through LabBase2 and isolates submitted to PHE VRD
- Data sources for GP consultations: GPRD, RCGP, etc.
- Safety using data linkage: intussusception
The risk of intussusception following monovalent rotavirus vaccination in England: self-controlled case-series

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<table>
<thead>
<tr>
<th>Historical cases for age effect</th>
<th>Dose</th>
<th>Risk period (days)</th>
<th>Cases in risk period</th>
<th>RI (95% CI*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>1</td>
<td>1-7</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>8-21</td>
<td>5</td>
<td>1.18 (0.28-3.99)</td>
</tr>
<tr>
<td></td>
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<td>1-21</td>
<td>20</td>
<td>3.00 (1.48-6.44)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1-7</td>
<td>5</td>
<td>1.74 (0.37-5.16)</td>
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<td></td>
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<td>8-21</td>
<td>14</td>
<td>2.74 (1.22-5.89)</td>
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<tr>
<td></td>
<td></td>
<td>1-21</td>
<td>19</td>
<td>2.33 (1.23-4.75)</td>
</tr>
</tbody>
</table>
Global Burden of Rotavirus infection (2008)

- 610,000 deaths
- 2.4 million inpatient visits
- 24 million outpatient visits
- 114 million episodes

Countries with highest burden:
- India (21.9%) - 98,621
- Nigeria (30.8%) - 41,057
- Pakistan (39.5%) - 39,144
- Congo (46.7%) - 32,653
- Ethiopia (52.6%) - 28,218
- Afghanistan (58.6%) - 25,423
- Uganda (60.9%) - 10,637
- Indonesia (63.1%) - 9,970
- Bangladesh (65.2%) - 9,857
- Angola (67.2%) - 8,788
Rotavirus mortality in children younger than 5 years, 2008
Vaccination Against Rotavirus

**RotaShield® Story**

- **FDA approves RotaShield**
  - August 1998

- **RotaShield is universally recommended for US infants**
  - October 1998

- **CDC reports preliminary data suggesting association with intussusception**
  - July 1999

- **CDC presents data confirming association with intussusception**
  - October 1999
  - Universal recommendation rescinded
  - Vaccine withdrawn from market
### Infant Rotavirus Vaccination May Provide Indirect Protection to Older Children and Adults in the United States

**Ben A. Lopman, Aaron T. Curns, Catherine Yen, and Umesh D. Parashar**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Median 2000–2006 (minimum)</th>
<th>2008</th>
<th>RR (95% CI)</th>
<th>Admissions averted,(^b) thousands (95% CI)</th>
<th>Median 2000–2006 (minimum)</th>
<th>2008</th>
<th>RR (95% CI)</th>
<th>Admissions averted,(^b) thousands (95% CI)</th>
<th>Median costs (2008 USD)(^d)</th>
<th>Median length of stay (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>78,930 (75,924)</td>
<td>50,519</td>
<td>0.61 (0.52–0.71)</td>
<td>30.8 (22.8–37.6)</td>
<td>32,086 (^f) (23,548)</td>
<td>9,852</td>
<td>0.22 (0.14–0.34)</td>
<td>25.0 (21.4–27.6)</td>
<td>2,897</td>
<td>2</td>
</tr>
<tr>
<td>5–14</td>
<td>24,946 (23,179)</td>
<td>17,884</td>
<td>0.71 (0.65–0.78)</td>
<td>7.2 (5.4–8.8)</td>
<td>1801 (^f) (1,274)</td>
<td>747</td>
<td>0.29 (0.19–0.45)</td>
<td>1.28 (0.99–1.46)</td>
<td>3,750</td>
<td>2</td>
</tr>
<tr>
<td>15–24</td>
<td>20,306 (^f) (18,073)</td>
<td>21,769</td>
<td>0.92 (0.86–0.98)</td>
<td>1.6 (1.36–2.7)</td>
<td>127 (^f) (81)</td>
<td>70</td>
<td>0.35 (0.15–0.82)</td>
<td>0.08 (0.023–0.108)</td>
<td>5,925</td>
<td>2</td>
</tr>
<tr>
<td>25–64 (^e)</td>
<td>146,000 (^f) (132,729)</td>
<td>174,568</td>
<td>0.99 (0.95–1.03)</td>
<td>288 (^f) (231)</td>
<td>279</td>
<td>0.74 (0.47–1.16)</td>
<td>7,481</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\geq65)</td>
<td>118,332 (^f) (108,917)</td>
<td>147,906</td>
<td>1.03 (0.96–1.1)</td>
<td>266 (^f) (168)</td>
<td>390</td>
<td>0.79 (0.49–1.26)</td>
<td>10,260</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td></td>
<td></td>
<td>39.6 (28.5–49.1)</td>
<td></td>
<td>26.4 (22.4–29.2)</td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>
Decline in Childhood Diarrhoea Deaths After Rotarix Introduction, Mexico

![Graph showing the decline in childhood diarrhoea deaths after Rotarix introduction in Mexico.](image-url)

- **Vaccine Introduction (May 2007)**
- **2008**
- **2009**

**Legend**:
- Age ≤11 months
- Age 12-23 months
- Age 24-59 months

**Graph Description**:
- The graph displays the number of diarrhea deaths from 2003 to 2009, categorized by age groups.
- A significant decline in diarrhea deaths is observed after the introduction of the Rotarix vaccine in May 2007.

**Data Source**:
- Vaccination Against Rotavirus
Exceptionally low rotavirus incidence in the Netherlands in 2013/14 in the absence of rotavirus vaccination

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Weekly rotavirus detections (August 1999–August 2014) and general practice gastroenteritis consultation rate for children under five years old (August 2006–August 2014), the Netherlands
Stool sample testing rates

- Sentinel site reports of samples tested & numbers positive
Confirmed rotavirus reports by age in months
England & Wales

![Graph showing confirmed rotavirus reports by age in months for England & Wales from 2008/09 to 2013/14, with peaks occurring in the first few months of life and a decline thereafter. Each year is represented by a different line color: 08/09, 09/10, 10/11, 11/12, 12/13, and mean 08/09-12/13. The 13/14 data is highlighted in red.](image-url)