Age at rotavirus disease in children, and the impact of delayed vaccination.

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September 2012
Synopsis

• Estimating public health impact
  – Vaccine efficacy
  – Age at RVGE
  – Vaccination coverage and timeliness

• Data on age at RVGE

• Data on coverage and timeliness

• Estimates of the impact of delays
Age-specific coverage: an indicator of vaccine delay

ideal ‘survival’ curves with a 6, 10, 14 week schedule

coverage

age in weeks
Age-specific coverage in Malawi: ‘survival’ curves from survey data for DPT (n = 7359)

Source: DHS6

- 1 dose
- 2 doses
- 3 doses
RVGE in Blantyre, Malawi, 1997-2007:
% of all cases aged < 60m, by week of age  (n = 790)

Source: Turner
RVGE in Blantyre, Malawi, 1997-2007:
% of all cases aged < 60m, by week of age (n = 790)

Data and a fitted distribution

Source: Turner
Observed vs modelled distributions:

all East Med RO (n=12,339) & E&W 2005-7(n=37,267)

All EMRO cases

England & Wales: laboratory surveillance

Source: Atchison et al
Age at RVGE
Hospital admissions, Blantyre, Malawi 1997-2007

Source: Turner et al

2.5% of cases are aged < 6 weeks
39% of cases are aged < 6 months
Aim
to use these data to address 2 questions:

If, at the time of these studies, a rotavirus vaccination programme had been in place, administered at the same time as DTP:

1. What proportion of the children who got RVGE would have had 1 or more doses of vaccine in time to give them some direct protection?

2. What proportion of the cases of RVGE would have been prevented?
Assumptions for question 1

- the age distribution of *exposure* to infection is unchanged by introducing a vaccine; and
- children at higher risk of RVGE* are just as likely to be vaccinated at given age as children at lower risk

* with no vaccination programme
Estimating protection by 1, 2, 3 doses at different ages

Blantyre, Malawi 1997-2007: hospital admissions with RVGE

EPI coverage based on DTP in Malawi, 2004-6
Estimating protection by 1, 2, 3 doses at different ages

Blantyre, Malawi 1997-2007: hospital admissions with RVGE

EPI coverage based on DTP in Malawi, 2004-6
Malawi: age distribution for RVGE (in weekly and monthly slices) and coverage for DTP1

Source: Turner et al

"% of all cases of RVGE" — DTP1 coverage
Estimating protection by 1, 2, 3 doses at different ages

Blantyre, Malawi 1997-2007: hospital admissions with RVGE

EPI coverage based on DTP in Malawi, 2004-6

% of all cases aged <36m for different ages and doses.

0 doses

1 dose

0.0%
0.5%
1.0%
1.5%
2.0%
2.5%
3.0%

0% 20% 40% 60% 80% 100%

0 13 26 39 52 65 78 91 104

0 doses

1 dose

0.0%
0.5%
1.0%
1.5%
2.0%
2.5%
3.0%

0 13 26 39 52 65 78 91 104
Estimating protection by 1, 2, 3 doses: Malawi

Blantyre, Malawi 1997-2007: hospital admissions with RVGE

EPI coverage based on DTP in Malawi, 2004-6
Estimating protection by 1, 2, 3 doses: Malawi

Blantyre, Malawi 1997-2007: hospital admissions with RVGE

EPI coverage based on DTP in Malawi, 2004-6

Cumulative protection

% of all cases aged < 36m, by week

Cum % of all cases aged < 36m, by week

0 doses 1 dose 2 doses 3 doses

0 doses 1 dose 2 doses 3 doses

age in weeks
Assumptions for question 2: what % of cases would have been prevented?

• Indirect/herd protection excluded

• Vaccine efficacy is unrelated to
  – age at vaccine if > 6 weeks
  – vaccine interval if > 4 weeks

• Vaccine efficacy scenarios

<table>
<thead>
<tr>
<th></th>
<th>1 dose</th>
<th>2 doses</th>
<th>3 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid/higher</td>
<td>65%</td>
<td>75%</td>
<td>80%</td>
</tr>
<tr>
<td>Lower</td>
<td>45%</td>
<td>50%</td>
<td>55%</td>
</tr>
</tbody>
</table>

• No waning of protection
Malawi:
age distribution for RVGE, coverage for DTP1
and coverage x efficacy for dose 1

Source: Zaman et al
Estimating % of cases prevented at different ages

**Efficacy scenario:**

“Very severe RVGE in Africa”

Dose 1: 50%
Dose 2: 65%
Dose 3: 65%
RVGE in Malawi:
numbers of doses of vaccine protection, and cases prevented

Source: Turner
Data collection

Aim: in an as many countries as we can, to:

• compile data on distributions of age at *RVGE* in children in different populations pre-vaccine, using mainly surveillance data;

• compile data on the distributions of age at *vaccination* in national EPI programmes, using survey data.
Age at RVGE: studies in 43 populations

Selection criteria:

*included* if more than 100 subjects aged < 3 years

ages in bands of <=1 month up to 1 year

study period before introduction of rotavirus vaccine

From: AFRO 4, AMRO 3, EMRO 13, EURO 12, SEARO 5, WPRO 6

*Numbers of events (median, IQR)* 665 (380-1046)
Age at RVGE:
examples of earlier and later peaks

Blantyre, Malawi

Matlab, Bangladesh

% of all cases aged < 36m per week

Age in weeks
Age at vaccination: data from 69 countries

Representative population data from:

• 42 DHS surveys (rounds 5 & 6)
  – 2004-10   sample median (IQR) = 5,183 (3,491-6,750)

• 27 MICS surveys (round 3)
  – 2005-7   sample median (IQR) = 3,926 (2,355-5,879)

• AFRO 34, AMRO 10, EMRO 6, EURO 8, SEARO 5, WPRO 6
Variation in coverage by age: 6 countries

Egypt: Coverage from DHS5 2008

Thailand: Coverage from MICS3 2005

Bangladesh: Coverage from DHS5 2007

Iraq: Coverage from MICS3 2006

Lao: Coverage from MICS3 2006

India: Coverage from DHS5 2005-6
Estimating impact

1. For countries with both
   • survey data on coverage and
   • surveillance data on age at RVGE

2. For other countries we need
   • estimates of age-specific coverage (feasible); and/or
   • estimates of age distribution for RVGE (??)
% of cases prevented: links to timing & schedule: low efficacy scenario

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Kenya    Malawi    Bangladesh    India    Egypt    Iraq    Thailand

6, 10, 14w OT  2, 3, 4m OT  2, 4, 6m OT  actual
% of cases prevented: links to timing & schedule high efficacy scenario

- Kenya
- Malawi
- Bangladesh
- India
- Egypt
- Iraq
- Thailand

- 6, 10, 14w OT
- 2, 3, 4m OT
- 2, 4, 6m OT
- actual
Coverage by wealth quintile:
DPT3 in India 2003

Source: DHS5
The model

• Developed from QUIVER-approved ‘TriVac’ by Andy Clark at LSH&TM

• Analysis at country level, aggregated to WHO mortality strata

• Numbers of deaths in each country from WHO national estimates (total 453,000 in 2008)

• Assumes age distribution of RVGE mortality to be same as (hospital) morbidity.
Mortality vs morbidity: PNG and Sudan

PNG: RV deaths vs RV admissions

Sudan: RV deaths vs RV admissions

- Deaths fitted
- Deaths data
- Admissions fitted
- Admissions data

Graphs showing frequency density per week vs age in weeks for PNG and Sudan.
Model estimates: impact of vaccines on RVGE deaths/year for various schedules

- **Current timing**
- **All 2,4,6 m on time**
- **All 2,3,4 m, on time**
- **All 6,10,14 w, on time**
Conclusion

If the aim is to increase the % of children in age groups at risk who have at least *some* level of direct protection, earlier schedules are better.

*However*

shifting schedules only has a material impact in countries in which
• the distribution of ages at RVGE is young; and/or
• the distribution of ages at vaccination is old
  (poorer children tend to be at higher risk & have lower protection)

*and against this*

later schedules may offer more effective and durable protection.

Currently it is unclear where the balance between earlier and later schedules should lie, but it will vary between populations.

This matter needs further consideration.
Acknowledgements

Age at RVGE:
David Taylor, Brenda Bolanos, Andy Clark, Paul Fine
Support: IVR, WHO Geneva + all who provided data

Model estimates
Andy Clark, Manish Patel
Support: PAHO ProVac Initiative, BMG Foundation
% of all cases
aged < 36m occurring before age 4 months

RE pooled estimate
10.1% (8.6 to 11.6%)

Median (IQR):
10.0% (6.8 to 13.7%)

### Table: Proportion with a rotavirus event

<table>
<thead>
<tr>
<th>Source</th>
<th>country</th>
<th>type</th>
<th>n</th>
<th>Proportion (95% CI)</th>
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<td>African Region: 5 studies</td>
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<td>Nokes</td>
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<td>574</td>
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<td>436</td>
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<td>Seheri</td>
<td>S Africa ip</td>
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<td>Zaman</td>
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<td>Subtotal</td>
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<td>Grimwood</td>
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<td>Fox</td>
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<td>Fox</td>
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<td>0.08 (0.06, 0.09)</td>
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<td>Heterogeneity between groups:</td>
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<tr>
<td>Overall</td>
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<td>0.10 (0.08, 0.12)</td>
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</tbody>
</table>

Proportion (95% CI): 10.0% (6.8 to 13.7%)

Median (IQR): 10.0% (6.8 to 13.7%)
The impact of changes in timing and schedule

<table>
<thead>
<tr>
<th>Country</th>
<th>% of episodes before dose</th>
<th>episodes prevented efficacy</th>
<th>Country</th>
<th>% of episodes before dose</th>
<th>episodes prevented efficacy</th>
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<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Kenya</td>
<td>0%</td>
<td>1%</td>
<td>3%</td>
<td>79.5%</td>
<td>54.6%</td>
</tr>
<tr>
<td></td>
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<td>3%</td>
<td>8%</td>
<td>77.7%</td>
<td>53.3%</td>
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<td>11%</td>
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<tr>
<td></td>
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<tr>
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<td>6%</td>
<td>13%</td>
<td>76.1%</td>
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<td>Iraq</td>
<td>3%</td>
<td>9%</td>
<td>15%</td>
<td>76.7%</td>
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<tr>
<td></td>
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<td>14%</td>
<td>23%</td>
<td>71.1%</td>
<td>48.6%</td>
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<td>5%</td>
<td>79.0%</td>
<td>54.3%</td>
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<tr>
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<td>3%</td>
<td>5%</td>
<td>7%</td>
<td>76.9%</td>
<td>52.8%</td>
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</tbody>
</table>
## Determination of rotavirus

<table>
<thead>
<tr>
<th>Test</th>
<th>n</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>EIA/ELISA only</td>
<td>32</td>
<td>85%</td>
</tr>
<tr>
<td>RT-PCR only</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Latex agglutination (LA) only</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>RT-PCR or ELIZA</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>ELISA (65%) or electron microscopy or LA</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>ELISA or LA or PAGE</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>38</td>
<td>100%</td>
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</table>
Model estimates: impact of vaccines on RVGE deaths/year for various schedules

![Diagram showing the impact of vaccines on RVGE deaths/year for various schedules. The x-axis represents regions: America, Asia, and Africa, and the y-axis represents the number of RVGE deaths per year. The legend shows different vaccination schedules, including no vaccination, current timing, and schedules for different age groups.]
India: age-specific RVGE and vaccine coverage

Coverage based on DHS5 data: India

2005-6

Source: DHS

3 doses

Boost

RVGE in Trichy, Vellore, India & doses of vaccine

Source: Kang

0 doses

1 dose

2 doses

3 doses

Boost

% of all cases aged <36m, by week

age in weeks

% of all cases aged <36m, by week

age in weeks

% of all cases aged <36m, by week

age in weeks

% of all cases aged <36m, by week

age in weeks

Source: Kang

0 doses

1 dose

2 doses
RVGE in Egypt and Iraq

Egypt:
Coverage from DHS5 2008

RVGE & doses of vaccine

RVGE, doses of vaccine, and cases prevented (lower eff.)

Iraq:
Coverage from MICS3 2006

RVGE & doses of vaccine

RVGE, doses of vaccine, and cases prevented (lower eff.)