The human impact of rotavirus vaccine in Malawi

Naor Bar-Zeev
Malawi-Liverpool-Wellcome Trust Clinical Research Programme
College of Medicine, University of Malawi

Centre for Global Vaccine Research
Institute of Infection & Global Health, University of Liverpool
Conflicts of interest

Supported by

PATH

CDC

Wellcome Trust

GlaxoSmithKline
Malawi’s VacSurv Programme
Malawi’s VacSurv Programme

Methods

• Population demographic surveillance
• Large scale cohort studies
• Sentinel surveillance
• Case control studies
• Costing studies
• Household transmission studies
Malawi’s VacSurv Programme

Morbidity impact & effectiveness

Cost-effectiveness

Mortality impact & effectiveness
Rotavirus hospitalisation

Rotavirus monthly cases by age

- **infants <12mth**
- **children 1-4 yrs**

2015 vs 2012 reduction in infants: 54% (95% CI, 33%, 69%)
Age at rotavirus hospitalisation

Age at diarrhoeal episode

**Rotavirus negative**

- Pre-vaccine
- Post-vaccine

- t-test $p=0.53$

**Rotavirus positive**

- Pre-vaccine
- Post-vaccine

- t-test $p<0.0001$
Efficacy & effectiveness

**Vaccine trial efficacy**

49% (95%CI 19, 68)

**Vaccine effectiveness**

64% (95%CI 24, 83)

58% (95%CI 20, 78)
Cost-effectiveness

- Prospective cohort N=530
- Household & Societal perspective
  - Itemised household expenditures
  - Post-discharge home visit
  - Detailed socioeconomic data
- Government perspective
  - Detailed costing of individual healthcare actually received
  - Illness >1 mth income in 9% OP & 17% IP
  - For 2015 birth cohort: avert 54,000 cases of RVGE and 281 deaths
  - US$19 per DALY averted
Mortality: methods

Data Collection

- Prospective cohort from March 2012
- Pregnancies, births and deaths registered by key informants
- Children followed at 4 months and 1 year to ascertain vaccine status
- Under-5 deaths followed up for verbal autopsy (VA)

Analysis

- Cluster-level population impact (Poisson Regression)
- Individual level survival analysis (Cox Proportional Hazards)

Vaccine 2015a

Vaccine 2015b
Mortality: Cohort recruited (post introduction)

Live births registered: 36,065
- Births not followed = 621 (2%)
- DOB unknown = 10 (0.1%)

1 year follow-ups completed: 35,434
- Migrated = 5,648 (16%)
- HH not found = 391 (1%)
- No consent = 33 (0.1%)
- Data error = 1168 (3%)

Included in analysis:
- Surviving = 28,194
- Deceased = 2,163
- Deceased 10-52wks = 327
- Deceased diarrhoea 10-52wks = 92

Deaths registered: 2,640
- Deaths not followed = 192 (7%)
- DOB unknown = 4 (0.1%)

Verbal autopsies completed: 2,444
- Migrated = 228 (9%)
- HH not found = 45 (2%)
- No consent = 8 (0.3%)
- Data error = 0
Mortality impact: pre-post

Poisson regression - A reduction of:
Unadjusted: 48% (95% CI 23, 65), P=.001, N=34,264
SES adjusted: **49% (95% CI 24, 66)**, P=.001, N=34,151

<table>
<thead>
<tr>
<th>10-week survivors</th>
<th>Pre</th>
<th>Post</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survived 52 weeks</td>
<td>5,708</td>
<td>28,431</td>
<td>34,139</td>
</tr>
<tr>
<td>Diarrhoeal death &lt;52 weeks</td>
<td>35</td>
<td>92</td>
<td>125</td>
</tr>
<tr>
<td>Rate per 1,000</td>
<td>6.2</td>
<td>3.2</td>
<td></td>
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</tbody>
</table>
Mortality per cluster by coverage

2-dose RV coverage and diarrhoea mortality over time
Clustered by RCT Zone

RV coverage

- Oct2012-Mar2013
- Apr2013-Sept2013
- Oct2013-Mar2014
- Apr2014-Sept2014

Diarrhoea-related mortality

- Oct2012-Mar2013
- Apr2013-Sept2013
- Oct2013-Mar2014
- Apr2014-Sept2014

unadjusted IRR: 0.97 (95% CI 0.93, 1.0)
Mortality impact: “dose-response”
### Mortality effectiveness: Cox PH model

<table>
<thead>
<tr>
<th>10-week survivors</th>
<th>Survived 52 weeks</th>
<th>Died &lt;52 weeks</th>
<th>HR</th>
<th>adjHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 doses</td>
<td>6%</td>
<td>10%</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2 doses</td>
<td>92%</td>
<td>82%</td>
<td>0.56</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.28, 1.13)</td>
<td>(0.29, 1.17)</td>
</tr>
<tr>
<td>Total</td>
<td>28241 (100%)</td>
<td>92 (100%)</td>
<td>28172 (87 deaths)</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted 2-dose VE **42% (-17, 71)**, P=.13
Mortality effectiveness: Royston-Parmar model

VE changes as the underlying risk changes!
VE can apparently drop with no change in immunobiology
Summary

Rotarix in Malawi:
✓ Reduces rotavirus hospitalisation burden
✓ Effective individual protection
✓ Highly cost-effective
✓ Halving of population diarrhoea-mortality, coverage-dependent
✓ Reduces individual mortality hazard by 42%

• Ongoing work:
  • Viral evolution (K. Jere)
  • Vaccine indirect effects (A. Bennett)
  • Vaccine failures (L. Pollock)
  • Impact of the microbiome (M. Iturriza-Gomara)
  • Rotavirus and impoverishment (N. Hendrix & C. Pecenka)
Carina King, James Beard, Tambosi Phiri, Sonia Lewycka, Hazzie Mvula, Amelia C Crampin, Richard Wachepa, Caroline Mwale, Ellen Heinsbroek, Lester Kapanda, Jean Chikafa, Clint Pecenka, Deborah Atherly, Aisleen Bennett, Louisa Pollock, Khuzwayo Jere, Miren Iturriza-Gomara, Osamu Nakagomi, Charles Mwansambo, Anthony Costello, Jacqueline E Tate, Umesh D Parashar, Robert S Heyderman, Neil French, Nigel A Cunliffe

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