Systematic review of economic evaluations of rotavirus vaccines

Raymond Hutubessy PhD
(hutubessyr@who.int)

Initiative for Vaccine Research
World Health Organization
Geneva, Switzerland
Evidence elements considered

1. RV vaccines: introduction, coverage, characteristics and operational
   • Introduction and operational challenges
   • Characteristics
   • Coverage and timeliness of vaccination

2. BoD and epidemiology
   • WHO RV Global Surveillance Network and surveillance guidelines
   • Age distribution of RV infection
   • Burden of diarrhoeal diseases in children

3. Vaccine efficacy
   • Efficacy against all cause mortality and disease outcomes by number of doses, age at first dose, interval, co-administration
   • Duration of protection

4. Vaccine effectiveness
   • Effectiveness in routine programmes
   • Effect on RV hospitalization and reduction in AGE hospitalization and mortality

5. Safety
   • Safety profile of RV vaccines

6. Risk - benefit analysis
   • Estimated benefits of mortality reduction vs risk of fatal IS

7. Operational issues: thermostability
   • Analysis of the thermostability of RV vaccines

8. Economic considerations
   • Systematic review of economic analyses (CEA and budget impact analyses)
   • CE in 73 Gavi countries
   • CEA of nationally licensed RV vaccines

Global Framework for Rotavirus Vaccines Implementation Research – Ad Hoc Consultation, 2-3 October 2017, Geneva, Switzerland
Take home messages

1. Need for Cost-Effectiveness Analysis (CEA) of current & new rotavirus vaccines in LMICs. Current CEA studies show value for money in LICs/Gavi countries.

2. Society’s willingness to pay (WTP) for value for money should be based on national values.

3. Vaccine procurement costs are an important CEA driver of new vaccines. However, operational/delivery costs are equally important.

4. Need for Budget impact analysis (real financial consequences on national budgets) in LMICs.
Main policy questions

• How to sustain programmatically?
  – Current standard EPI program?
  – Adding new vaccines more expensive such as RV, PCV and HPV?

• How to sustain financially?
  – LMICs gear towards UHC and prepare for UMIC status (*Gavi graduation/most unvaccinated in MICs*)
Economic Evaluations for UHC

- Increasing pressure for health systems to adopt strategic purchasing strategies that explicitly assess interventions for inclusion in benefit or entitlement policies
  - Role for economic evaluations to play in services to cover

Rotavirus vaccines contribute towards universal health coverage in a mixed public-private healthcare system (example of Malaysia)

<table>
<thead>
<tr>
<th>Type of economic evaluation</th>
<th>Question to be addressed</th>
<th>Economic tool available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Economic burden</td>
<td>What is the VPD burden in economic terms?</td>
<td>Cost-of-Illness study</td>
</tr>
<tr>
<td>Affordability</td>
<td>What are the short- and long term impact on national budgets?</td>
<td>Budget Impact Analysis study</td>
</tr>
<tr>
<td>Value for money</td>
<td>What is the cost per immunized child, case, death or DALY?</td>
<td>Cost-effectiveness study</td>
</tr>
<tr>
<td>Broader economic impact</td>
<td>What is the macroeconomic impact of VPDs?</td>
<td>General equilibrium models</td>
</tr>
</tbody>
</table>
Reasons for conducting CEAs

- Advocacy – making the case for securing internal and/external financial resources
- Selecting the right mix of interventions to optimise the health care budget
- Informing tender negotiations between purchasers and vaccine manufacturers
- Ex-post appraising the value for money of past decisions
Global systematic review CE RV

104 studies identified from January 2000–November 2015
Geographic distribution and study quality

Most studies from European region
Only 6 studies from LICs

Overall reporting meets WHO Guide
VE varied from 21-100% from all RVGE severities
Only 2 studies used dynamic model

Table 1
Geographic distribution of all included studies using World Bank income groups and WHO regions.

<table>
<thead>
<tr>
<th>World Bank income groups</th>
<th>Number of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>LICs</td>
<td>6</td>
</tr>
<tr>
<td>LMICs</td>
<td>22</td>
</tr>
<tr>
<td>UMICs</td>
<td>18</td>
</tr>
<tr>
<td>HICs</td>
<td>6</td>
</tr>
<tr>
<td>Cannot be categorized (Multiple countries)</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 3
Extent to which included studies met standard economic evaluation guidelines.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Yes/No</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynamic transmission</td>
<td>3/104</td>
<td>3%</td>
</tr>
<tr>
<td>Perspective specified</td>
<td>104/104</td>
<td>100%</td>
</tr>
<tr>
<td>Time horizon specified</td>
<td>102/104</td>
<td>100%</td>
</tr>
<tr>
<td>Used discounting for costs/outcomes (if study period was &gt;1 year)</td>
<td>83/104</td>
<td>83%</td>
</tr>
<tr>
<td>Currency and price date reported</td>
<td>92/104</td>
<td>92%</td>
</tr>
<tr>
<td>Calculated and reported ICER or BCR or Net saving</td>
<td>104/104</td>
<td>100%</td>
</tr>
<tr>
<td>Performed uncertainty analysis</td>
<td>95/104</td>
<td>95%</td>
</tr>
<tr>
<td>Disclosed funding source(s)</td>
<td>70/104</td>
<td>70%</td>
</tr>
</tbody>
</table>

ICER, incremental cost-effectiveness ratio; BCR, benefit-cost ratio; 
*In which the recommendation is applicable.*

## Results

103 (99%) studies comparing RV1 or RV5 vaccine vs no vaccination  
51 (52%) studies reported RV is cost-effective  
- In Gavi eligible countries as a result of subsidized vaccine prices  
- In most LMICs no local CE thresholds (CET)  

In high income countries RV not cost-effective due to high vaccine price  

Drivers of CE: vaccine price, VE and CFR  

Incorporation of herd immunity could change results  

---

**Kotirum et al. Vaccine 35 (2017) 3364–3386**
How to define “value for money”? 

- Widely used CMH CET*: 
  - 3x GDP per capita “cost-effective” 
  - 1x GDP per capita “very cost-effective” 
- Not always useful from a country perspective

WHO-CHOICE used CMH CET for normative sector-wide and international comparisons of interventions (see WHR 2003)

---

*CMH: Commission on Macroeconomics and Health. 
CET: Cost-Effectiveness Thresholds 

New WHO recommendation on use of CETs

• Benchmark CE results against the least cost-effective health interventions already funded by relevant jurisdictions

• Use CET not in isolation but in context specific process for decision making supported by issues like:
  – Broader benefit package of interventions
  – Legislation
  – Stakeholder buy-in
  – Fairness

• Focus on budget impact

* CET: Cost-Effectiveness Thresholds
Budget impact analysis (BIA)

- BIA: real financial consequences of introducing a new intervention with in a defined budget and budgetary period

- In many HICs require BIA information alongside CEA when making policy decisions on adoption of vaccines
Affordability in LMICs (1)

- Systematic review on rotavirus vaccines BIA\(^1\) in LMICs showed
  - Only 6 BIAs against 60 CEAs in 2000-2017
  - Quality BIA methods against generic ISPOR Guides\(^2\)
    - model validation
    - justification time horizon
    - providing undiscounted financial streams

---

1. Carvalho, Jit, Cox, Yoong, Hutubessy. Pharmacoeconomics. 2017 Sep 13
2. International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Taskforce recommendations
Affordability in LMICs (2)

- Basis for vaccine specific WHO BIA Guide/Checklist
  - Guidance on how to extend existing CEA to capture BIA considerations

1. Carvalho, Jit, Cox, Yoong, Hutubessy. Pharmacoeconomics. 2017 Sep 13
2. ISPOR Taskforce recommendations
<table>
<thead>
<tr>
<th>No</th>
<th>Scale-up scenarios</th>
<th>No. of children vaccinated</th>
<th>Financial costs³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Global society perspective (Total vaccination program costs)</td>
</tr>
<tr>
<td>1</td>
<td>Base-case rollout scenario (Table 2)</td>
<td></td>
<td>(US$, million)</td>
</tr>
<tr>
<td></td>
<td>Vaccine efficacy based on the SAGE approach</td>
<td></td>
<td>5,879</td>
</tr>
<tr>
<td></td>
<td>Vaccine immunity waning (14% annually)</td>
<td>281.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Base-case rollout scenario (Table 2)</td>
<td></td>
<td>5,879</td>
</tr>
<tr>
<td></td>
<td>Vaccine efficacy based on the SAGE approach</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No vaccine immunity waning</td>
<td>281.8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Base-case rollout scenario (Table 2)</td>
<td></td>
<td>5,879</td>
</tr>
<tr>
<td></td>
<td>Vaccine efficacy adjusted for serotype distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vaccine immunity waning</td>
<td>281.8</td>
<td></td>
</tr>
</tbody>
</table>

Kim et al. BMC Public Health 2010, 10:253
## Procurement vs delivery costs routine immunization

<table>
<thead>
<tr>
<th>Region</th>
<th>Cost/Capita</th>
<th>Cost/Dose</th>
<th>Cost/Child</th>
<th>Cost/DTP3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine Cost</td>
<td>$0.36</td>
<td>$0.72</td>
<td>$12.33</td>
<td>$14.29</td>
</tr>
<tr>
<td>Non-Vaccine Cost</td>
<td>$0.31</td>
<td>$0.61</td>
<td>$10.36</td>
<td>$12.06</td>
</tr>
<tr>
<td>Total (n=40)</td>
<td>$0.67</td>
<td>$1.34</td>
<td>$22.68</td>
<td>$26.27</td>
</tr>
</tbody>
</table>

Need for detailed delivery costs

Table 5
Total financial and economic costs of three vaccine introductions in Rwanda in 2012 US$.  

<table>
<thead>
<tr>
<th></th>
<th>Prevnar</th>
<th>RotaTeq</th>
<th>Gardasil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target number of children to be vaccinated</td>
<td>376,202</td>
<td>394,473</td>
<td>91,317</td>
</tr>
<tr>
<td><strong>Financial costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Startup</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micro-planning</td>
<td>$4612</td>
<td>$4607</td>
<td>$13,197</td>
</tr>
<tr>
<td>Training</td>
<td>$23,959</td>
<td>$12,231</td>
<td>$44,283</td>
</tr>
<tr>
<td>Social Mobilization</td>
<td>$30,170</td>
<td>$30,170</td>
<td>$53,125</td>
</tr>
<tr>
<td>Information, Education, and Communication (IEC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-total</td>
<td>$58,741</td>
<td>$47,008</td>
<td>$110,605</td>
</tr>
<tr>
<td>Recurrent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Service delivery</td>
<td>–</td>
<td>–</td>
<td>$735,009</td>
</tr>
<tr>
<td>Vaccines/injection supplies</td>
<td>$565,366</td>
<td>$673,207</td>
<td>$156,503</td>
</tr>
<tr>
<td>procurement</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Monitoring &amp; evaluation (M&amp;E), Supervision</td>
<td>$55,767</td>
<td>$61,902</td>
<td>$59,873</td>
</tr>
<tr>
<td>Waste management</td>
<td>$46,253</td>
<td>$4694</td>
<td>$36,139</td>
</tr>
<tr>
<td>Sub-total</td>
<td>$667,386</td>
<td>$739,803</td>
<td>$987,524</td>
</tr>
<tr>
<td>Capital: cold chain</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>$726,127</td>
<td>$786,812</td>
<td>$1,098,129</td>
</tr>
</tbody>
</table>

**Economic costs**

|                      |         |         |          |
| Startup               |         |         |          |
| Micro-planning        | $59,543 | $56,151 | $84,146  |
| Training              | $111,412| $52,293 | $107,628 |
| Social Mobilization/IEC | $34,885 | $34,885 | $79,745  |
| Sub-total             | $205,840 | $178,214 | $271,519 |
| Recurrent             |         |         |          |
| Service delivery      | $243,662 | $239,557 | $904,918 |
| Vaccines/injection    |         |         |          |
| Sub-total             | $243,662 | $239,557 | $904,918 |

A cost comparison of introducing and delivering pneumococcal, rotavirus and human papillomavirus vaccines in Rwanda

Fidèle Ngabo a, b, Ann Levin b, 1, Susan A. Wang c, Maurice Gatera d, Celse Rugambwa a, Celestin Kayonga a, Philippe Donnen e, Philippe Lepage b, Raymond Hutubessy c, *  

a Rwanda Ministry of Health, Kigali, Rwanda  
b Independent Consultant to WHO, 6414 Holton Dr., Bethesda, MD 20817, United States  
c Department of Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland  
d Rwanda Biomedical Center, Kigali, Rwanda  
e WHO Rwanda Office, Kigali, Rwanda  
f Kigali Institute of Education, Kigali, Rwanda  
g Université Libre de Bruxelles/École de Santé Publique, Brussels, Belgium  
h Hôpital Universitaire des Enfants Réne Dabatola (HURED), Université Libre de Bruxelles, Brussels, Belgium  

ARTICLE INFO 

ABSTRACT
### IVIR Advisory Committee

Advises WHO on implementation research related to vaccines and immunization programs. Provides guidance on quantitative methods useful to vaccine research.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Minimize barriers</strong> and improve coverage of vaccines currently in use</td>
</tr>
<tr>
<td>2</td>
<td>Conduct <strong>impact evaluation</strong> of vaccines in use</td>
</tr>
<tr>
<td>3</td>
<td>Improve methods for <strong>monitoring</strong> of immunization programmes</td>
</tr>
</tbody>
</table>

- Modeled evidence for recommendations not relying on one model only
- WHO Guide on model comparisons under development
- Valuation issues for COI (productivity losses) and CBA (VSL)
WHO's VPD and Vaccine Economic analysis value chain

- **Decision to introduce immunization programs**
  - Disease burden analysis
  - Economic burden analysis
  - Cost-effectiveness analysis

- **Operational Costing of scaling up**

- **Planning roll out (informing cMYP)**

- **Development of Guidelines and Tools**
  - ECONOMIC ANALYSIS VALUE CHAIN
    - INFLUENZA VACCINES
    - HUMAN PAPILLOMA VACCINES
    - CHOLERA AND TYPHOID VACCINES
    - MALARIA AND DENGUE VACCINES

WHO Guidance documents on economic evaluations

- **WHO-CHOICE**
  - Sector-wide priority setting

- **WHO IVB Guides**
  - Guidelines for estimating costs of introducing new vaccines into the national immunization system (2002)
  - WHO guide for standardization of economic evaluations of immunization programmes (2009)

- **Health Systems Financing**
  - Broader economic impact
Conclusions

1. Different economic policy/research questions require different economic tools/analysis

2. Need for Cost-Effectiveness Analysis (CEA) of current & new rotavirus vaccines in LMICs. Most studies show value for money in LICs/Gavi countries.

3. Society’s willingness to pay (WTP) for value for money should be based on national values

4. Vaccine procurement costs are an important CEA driver of new vaccines. However, operational/delivery costs are equally important

5. Need for Budget impact analysis (real financial consequences on national budgets) in LMICs.
References


