Rotavirus Policy Review

- No immediately ‘pressing’ policy issues

- 2013 WHO Position Paper still valid

- Possible WHO SAGE review in October 2017
  - Coverage and impact (including strain dynamics, economic impact)
  - Improvement of efficacy (schedules, supplementation)
  - Safety (GACVS review)
  - RVGE surveillance
WHO Position Paper 2013

- RV to be included in all national immunization programmes
- RV part of comprehensive strategy to control diarrhoeal diseases (e.g. water, sanitation, ORS, breastfeeding, zinc treatment)
- Ensure timely administration of doses (first dose as soon as possible after 6 weeks of age with DTP) before RVGE occurs
- Inform health staff of risks and benefits
- Monitor safety of RV vaccines:
  - Enhance routine AEFI reporting and management system
  - Establish baseline rate of natural IS before vaccine introduction
  - Conduct self-controlled case-series studies, where appropriate
- Monitor epidemiological impact of rotavirus vaccination through high-quality surveillance in selected countries
Countries with Rotavirus vaccine in the national immunization programme; and planned introductions in 2016

Data source: WHO/IVB Database, 27 June 2016
Map production Immunization Vaccines and Biologicals (IVB), World Health Organization

* Includes partial introduction

- Introduced* to date (86 countries or 44.3%)
- Planned introductions in 2016 (5 countries or 2.6%)
- Not WHO Member States or Not Introduced/No Plans (103 countries or 53.1%)
- Not applicable

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. ©WHO 2016. All rights reserved.
Global rotavirus vaccine uptake

- Slower than expected uptake in large countries
- Gavi 73 countries behind 2011-2015 targets
- Country concerns related to:
  - Declining all-cause diarrhoea mortality
  - Vaccine price and concerns about sustainability
  - Questions about sustainable supply
  - Vaccine safety concerns
  - Country readiness (e.g. cold chain capacity)
  - Competing vaccine introductions (e.g. IPV)
- Countries to make hard cost-benefit decisions on rotavirus vaccines vs. other interventions – especially those nearing Gavi graduation
Large Countries in Asia

- **Pakistan:** Gavi approved application for phased introduction, Punjab initiating roll-out in 2016, followed by other provinces

- **Bangladesh:** Gavi application submitted in September 2016 for introduction in 2018

- **India:** RotaVac™ introduction in March 2016 in Andhra Pradesh, Haryana, Himachal Pradesh and Odisha
  - Strong Leadership of Deputy Commissioner MOHFW (Dr Haldar)
  - Vaccine presentation apparently well accepted:
    - -20°C cold chain need (similar to OPV)
    - Removal of stopper and fixing of dropper (dropper mix-up)
    - 10-dose vial with VVM2 on cap (30 - 70% wastage)
## Reduction in rotavirus hospitalizations

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>VACCINE USED</th>
<th>REDUCTION IN HOSPITALIZATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Rotarix, RotaTeq</td>
<td>45-88%</td>
</tr>
<tr>
<td>Austria</td>
<td>Rotarix, RotaTeq</td>
<td>74-79%</td>
</tr>
<tr>
<td>Belgium</td>
<td>Rotarix, RotaTeq</td>
<td>50-80%</td>
</tr>
<tr>
<td>Bolivia</td>
<td></td>
<td>70%</td>
</tr>
<tr>
<td>Finland</td>
<td>RotaTeq</td>
<td>78%</td>
</tr>
<tr>
<td>Malawi</td>
<td></td>
<td>64% in &lt;5yo</td>
</tr>
<tr>
<td>Nicaragua</td>
<td></td>
<td>60% (severe RVGE)</td>
</tr>
<tr>
<td>USA</td>
<td>Rotarix, RotaTeq</td>
<td>55-94%</td>
</tr>
<tr>
<td>South Africa</td>
<td></td>
<td>54 – 58% in &lt;5yo</td>
</tr>
</tbody>
</table>

*Studies vary in time period and age group, and therefore are not directly comparable. However, when taken together, they demonstrate the significant impact of the vaccine.

Source: Rota Council 2016
### Reduction in all-cause diarrhoea deaths

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>INTRODUCTION YEAR</th>
<th>REDUCTION IN ALL-CAUSE GE DEATHS AMONG CHILDREN UNDER AGE 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolivia</td>
<td>2008</td>
<td>36-43%</td>
</tr>
<tr>
<td>Brazil</td>
<td>2006</td>
<td>22%</td>
</tr>
<tr>
<td>El Salvador</td>
<td>2006</td>
<td>0-36%</td>
</tr>
<tr>
<td>Honduras</td>
<td>2009</td>
<td>16-20%</td>
</tr>
<tr>
<td>Mexico</td>
<td>2007</td>
<td>43-55%*</td>
</tr>
<tr>
<td>Panama</td>
<td>2006</td>
<td>50%**</td>
</tr>
<tr>
<td>Venezuela</td>
<td>2006</td>
<td>57-64%</td>
</tr>
</tbody>
</table>

*Measured from 2009-2011. While methodologies differ, and some studies aren’t directly comparable, it is clear the vaccine has had a significant impact.

**Among children age 0-4

Source: Rota Council 2016
Indirect Effects: Reductions in RV-related hospitalizations among vaccinated and unvaccinated

<table>
<thead>
<tr>
<th>COUNTRY (NATIONWIDE)</th>
<th>AGE-ELIGIBLE</th>
<th>NOT AGE-ELIGIBLE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>El Salvador</td>
<td>79-86%</td>
<td>41-81%</td>
</tr>
<tr>
<td>Austria</td>
<td>76-79%</td>
<td>35%</td>
</tr>
<tr>
<td>USA**</td>
<td>74-96%</td>
<td>41-92%</td>
</tr>
<tr>
<td>Belgium</td>
<td>65-80%</td>
<td>20-64%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COUNTRY (REGIONAL)</th>
<th>AGE-ELIGIBLE</th>
<th>NOT AGE-ELIGIBLE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia***</td>
<td>50-89%</td>
<td>30-100%</td>
</tr>
<tr>
<td>Sao Paulo, Brazil</td>
<td>56-69%</td>
<td>24%</td>
</tr>
</tbody>
</table>

NOTE: All studies vary in time period and age group and therefore are not directly comparable. However, when taken together, they clearly demonstrate the significant impact of the vaccine.

* Typically 2-5 years old, but varies by country  ** Combines three national studies  *** Combines three regional studies

Source: Rota Council 2016
Intussusception and rotavirus vaccines

- Association between IS and RotaShield™ vaccine identified after vaccine was introduced in the United States in 1998
- Attributable risk: 1 case / 10,000 vaccine recipients
- RotaTeq™ / Rotarix™ RCTs (> 60,000 infants) did not detect similar risk
- RotaTeq™ / Rotarix™ initially recommended for use by WHO with age restrictions
- Post-marketing safety assessments:
  - Mexico: Increased IS risk 1-7 days after first dose; 3-4 additional IS cases / 100,000 vaccinated infants
  - Brazil: Increased IS risk 1-7 days after second dose, not after first dose
  - US and Australia: 1 to 5 (US) or 6 (Australia) cases / 100,000 vaccinated after first or second dose
- Insufficient data from Asia and Africa (high mortality settings)
Age restrictions ‘lifted’ by WHO SAGE in 2013

- Age restrictions may have prevented vaccination of many vulnerable children in settings where the DTP doses are given late (i.e. after 15 wks for DTP1 or after 32 wks for DTP2 or DTP3)

- By allowing infants to receive rotavirus vaccine together with DTP, immunization programmes will be able to reach children who were previously excluded from the benefits of rotavirus vaccines

- However, 60% (52/86) of countries are still administering vaccine with age restrictions today (WHO Repository, 7/2016)
Vaccine safety monitoring

- Available data support that benefits exceed risks, and WHO continues to support vaccination.
- Continuous need to assess how countries are adopting vaccine.
- Ongoing evaluations of vaccines in Africa with respect to intussusception.
- Monitoring intussusception risk in Asia important, given regional differences in rates and epidemiology of intussusception.
- Need for specific risk analysis in MICs given lower rotavirus mortality.
- GACVS review in late 2017 to inform future recommendations.
Rotavirus vaccines and breastfeeding

- Results of effect of withholding breast feeding during administration of oral RV vaccines are considered conclusive

- Four separate studies demonstrated that breast feeding has no impact on the immune responses to RV vaccines

- No further clinical research is considered needed at this point in time to evaluate impact of breastfeeding on immune responses to rotavirus vaccines
Surveillance and impact monitoring in WHO coordinated GRSN

- Critical to continue global rotavirus networks as vaccines are rolled out.
- Measuring impact and effectiveness across a range of locations and settings will encourage countries to adopt and sustain vaccine use.
WHO Global Framework for RV Implementation Evaluation (March 2015)

- Comparative modelling of rotavirus mortality estimates and impact assessment: For 2013, global rotavirus disease deaths of under-5s were estimated to be 215,757 (WHO/CDC); 157,398 (CHERG); and 122,322 (IHME).

- Update existing tools and guidelines (surveillance, impact monitoring)

- Systematic review of available impact evidence

- Monitor strain dynamics in different settings periodically

- Evaluate available data on economic impact on health system and wider economic relevance, e.g. out-of-pocket expense, household impact, affordability, savings through establishing herd immunity etc.

- Review data on alternative methods to improve efficacy, e.g. alternate schedules, supplementation with probiotics, zinc or Vit A.

- Review data on any new WHO prequalified rotavirus vaccines to inform WHO SAGE review
UNICEF accompanies vaccine introductions in Gavi-eligible countries around 11 ‘healthy actions’ for pneumonia and diarrhoea prevention in line with ‘Framework for New Vaccine Introduction and Child Survival’

2014: 12/22 new vaccine introductions included collateral messaging about pneumonia and diarrhoea in mass communication activities or key messages for HCWs or CHW

Biggest obstacle to integration appears to be vertical structure of EPI, varying interest in different regions in integration
BMGF grants for policy development and country support

- Global Framework for Rotavirus Vaccines (WHO)
- ROTA Council – advocacy and communications (JHU)
- RAVIN – support to country decision making and implementation (JHU)
- Cost effectiveness and evidence generation for countries (PATH)
- Understanding the performance of rotavirus vaccines (PATH)
- Impact assessment of vaccine (US CDC)
- Intussusception surveillance for rotavirus vaccines (US CDC)
Overview of Gavi rotavirus programme

Gavi financial support since 2009

39 country introductions and 5 approvals to introduce in 2016-17

Estimated number of children immunised*: > 21 million

Gavi73 2014 coverage*: 15%

2014 coverage for countries with programmes in steady state*: 88%

*WUENIC Rev 2014
Gavi policies, strategies and procedures for country support

Crosscutting policies: Fragility and Immunisation, Transparency and Accountability, Risk, and Gender
Rotavirus vaccine market

- Global market for RV reached approximately 1.3 billion USD in 2015, 7% for Gavi countries (87 million)
- RV1 represents 77% of global volume
- Market growth to 2025 expected at 130% to >100 million courses/year
- Up to four new vaccines may enter market between 2017 and 2020
- Weighed average price for Gavi USD 4.80/course (Rotarix™ 4.17 USD/course; RotaTeq™ 10.50/course)
Rotavirus vaccine

Updated: 25 August 2016
# V3P rotavirus vaccine - Data description

## V3P database, 2016

<table>
<thead>
<tr>
<th>Years with available data</th>
<th>2013, 2014, 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of countries reporting price info in 2016</td>
<td>50</td>
</tr>
<tr>
<td>Number of countries per region reporting price information</td>
<td>AFR (11), EMR (1), EUR (29), SEAR (2), WPR (7)</td>
</tr>
<tr>
<td>Number of countries per income group reporting price information</td>
<td>LIC (2), LMIC (16), UMIC (16), HIC (16)</td>
</tr>
</tbody>
</table>

## V3P rotavirus vaccine specific information, 2016

<table>
<thead>
<tr>
<th>Data collection year</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data year</td>
<td>2015</td>
</tr>
<tr>
<td>Number of countries reporting price info in 2016</td>
<td>19</td>
</tr>
<tr>
<td>Number of countries self-procuring the vaccine (%)</td>
<td>11 (52%)</td>
</tr>
<tr>
<td>Number of procurement records from countries (and over the last 3 years)</td>
<td>21 (39)</td>
</tr>
<tr>
<td>Number of countries per region reporting Rota price information</td>
<td>AFR (8), EMR (1), EUR (9), SEAR (0), WPR (1)</td>
</tr>
<tr>
<td>Number of countries per income group reporting Rota price information</td>
<td>LIC (0), LMIC (9), UMIC (6), HIC (4)</td>
</tr>
<tr>
<td>List of presentations registered in the database</td>
<td>1-dose (plastic tube of applicator)</td>
</tr>
<tr>
<td>Number of products*</td>
<td>2</td>
</tr>
<tr>
<td>Number of manufacturers</td>
<td>2</td>
</tr>
<tr>
<td>Min/average/max price per dose in USD - pool procurement</td>
<td>2.06/2.13/2.47 **</td>
</tr>
<tr>
<td>Min/average/max price per dose in USD - self procurement</td>
<td>3.70/15.32/61.00</td>
</tr>
<tr>
<td>Min/median/max volume procured by countries</td>
<td>1,200/70,500/2,938,500</td>
</tr>
</tbody>
</table>

*Product defined as the combination of presentation and manufacturer

** Variation in price can be due to exchange rate fluctuations. UNICEF/Gavi price for the GSK Rota product is 1.88 EUR (~ 2.08 USD).

Quick market overview

**SUPPLY**
Share of countries procuring through different available suppliers

- **Merck**
  - 5.26%, 1 country(ies)

- **GSK**
  - 94.74%, 18 country(ies)

**DEMAND**
Procurement method used by countries to purchase Rotavirus vaccine in 2015

- **HIC**
  - 100.00%

- **UMIC**
  - 16.67%
  - 83.33%

- **LMIC**
  - 22.22%
  - 77.78%

- Procurement through UNICEF
- Self-procurement

- Only two manufacturers of Rotavirus vaccines.
- GSK Rotarix as clear market leader, with 95% of countries* purchasing this product.
- Many countries procure through UNICEF (42%, 8 countries: all Gavi-eligible or in transition), while all non-eligible UMICs and HICs (11 countries) self-procure the vaccine.

* Countries with registered price information for rotavirus vaccine in the V3P database (19 countries)

Source: V3P database - [www.who.int/immunization/v3p](http://www.who.int/immunization/v3p)
Income level and procurement method influence price of rotavirus vaccine

- Gavi-eligibility allows countries to access Rota at the lowest global price of 1.88€ per dose (~2.08 USD).
- PAHO gets the vaccine at 6.50 USD.
- MICs with the lowest prices are high-volume countries.
- Prices seem to be tiered by income level with some overlap between income groups. Regional location may also influence pricing.

Weighed Average Price (WAP*) of rotavirus vaccine in non-Gavi eligible countries, 2015 (in USD per dose)

- PAHO price, 2015: $6.50 (regardless of country income level)
- Lowest Gavi/UNICEF price, 2015: $2.08 (for Gavi-eligible countries only)

* WAP by volume / ** 3-dose schedule

Note: Difference in price may be due to exchange rate fluctuations
Source: V3P database - www.who.int/immunization/v3p

"Source: V3P database - www.who.int/immunization/v3p"
Rotavirus vaccine is priced high compared to most vaccines

Weighed Average Price (WAP)* of selected vaccines by income group, 2015
In USD per dose

- WAP for the vaccine ranges from 2.47 USD per dose in LMICs to 17.48 USD per dose in HICs.
- Across all income groups, RV is one of the most expensive vaccines purchased by countries.
- However, its price is consistently lower than other vaccines considered as “newer”, such as aP-containing vaccines, HPV or PCV.

Source: V3P database - [www.who.int/immunization/v3p](www.who.int/immunization/v3p) (extract on 25 August 2016).
Information drawn from V3P can be used to inform countries & stakeholders

1. Identify price ranges and budget spending
   - Rota vaccines price range: $2.06-$61.
   - Important share of most countries’ budget.

2. Understand the market and what factors influence prices
   - Rota prices seem to be influenced by income level and regions. Duopoly.

3. Compare prices with similar countries on a more even footing
   - UMICs pay between 6.25 and $11 for Rota vaccine

4. Make the vaccine market more transparent
   - 19 / 50 countries have shared Rota prices

To facilitate country planning and budgeting
- To understand possible factors behind the price a country pays
- To make informed decisions regarding prices a country is able and willing to pay
- To measure progress toward goals of transparency and affordability
For more information:

WEB: www.who.int/immunization/v3p
EMAIL: v3p-project@who.int
The Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea
A multi-pronged approach

- Pneumonia and diarrhoea are caused by multiple pathogens and **no single intervention** will address the entirety of the problem.

- **Multiple interventions of proven effectiveness exist**, which are complementary but not implemented in a coordinated fashion.

- Establishing **better coordination between existing programmes** can lead to **synergies and efficiencies** that will maximise the benefits of the individual interventions.

- Focus on **Protection, Prevention and Treatment**
Strategies for preventing and treating pneumonia and diarrhoea

Diarrhoea
- Vitamin A supplementation
- Vaccination: rotavirus
- Safe water & improved sanitation
- Low-osmolarity ORS, zinc & continued feeding

Pneumonia
- Vaccination (PCV, Hib, pertussis)
- Reduced household air pollution
- Antibiotics for pneumonia
- Oxygen therapy (where indicated)

Many interventions and treatment strategies are identical.
Protect, Prevent, Treat: a useful framework for an integrated approach

**PROTECT**
Children by establishing good health practices from birth
- Exclusive breastfeeding for 6 months
- Adequate complementary feeding
- Vitamin A supplementation

**PREVENT**
Children becoming ill from pneumonia and diarrhoea
- Vaccines: pertussis, measles, Hib, PCV and rotavirus
  - Handwashing with soap
  - Safe drinking-water and sanitation
  - Reduce household air pollution
  - HIV prevention
- Cotrimoxazole prophylaxis for HIV-infected and exposed children

**TREAT**
Children who are ill from pneumonia and diarrhoea with appropriate treatment
- Improved care seeking and referral
- Case management at the health facility and community level
- Supplies: Low-osmolarity ORS, zinc, antibiotics and oxygen
- Continued feeding (including breastfeeding)
Acknowledgements

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