

THE ROTAVIRUS VACCINE PIPELINE AND PRIORITIES FOR DEVELOPMENT

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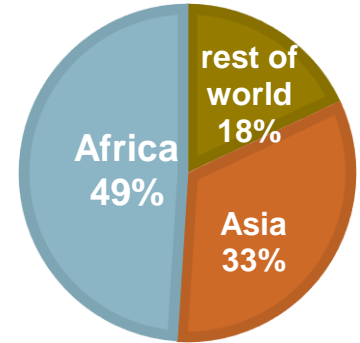
PRESENTATION OUTLINE

1. Background of rotavirus disease
2. Current vaccine efforts:
 - live oral rotavirus vaccines & non-replicating rotavirus vaccines
3. Challenges to ongoing vaccine success
 - Vaccine effectiveness
 - Duration of protection
4. Can we improve performance?
 - Schedule changes

ROTAVIRUS DISEASE

- Rotavirus is the leading cause of severe diarrhea among all children below 5 years of age worldwide (20-40%)
- Significant impact on child health, disease burden:
 - >100 million cases of diarrhea annually
 - 215,000 deaths (197-233,000) deaths in 2013 ¹
 - (declined from >500,000 in 2000).

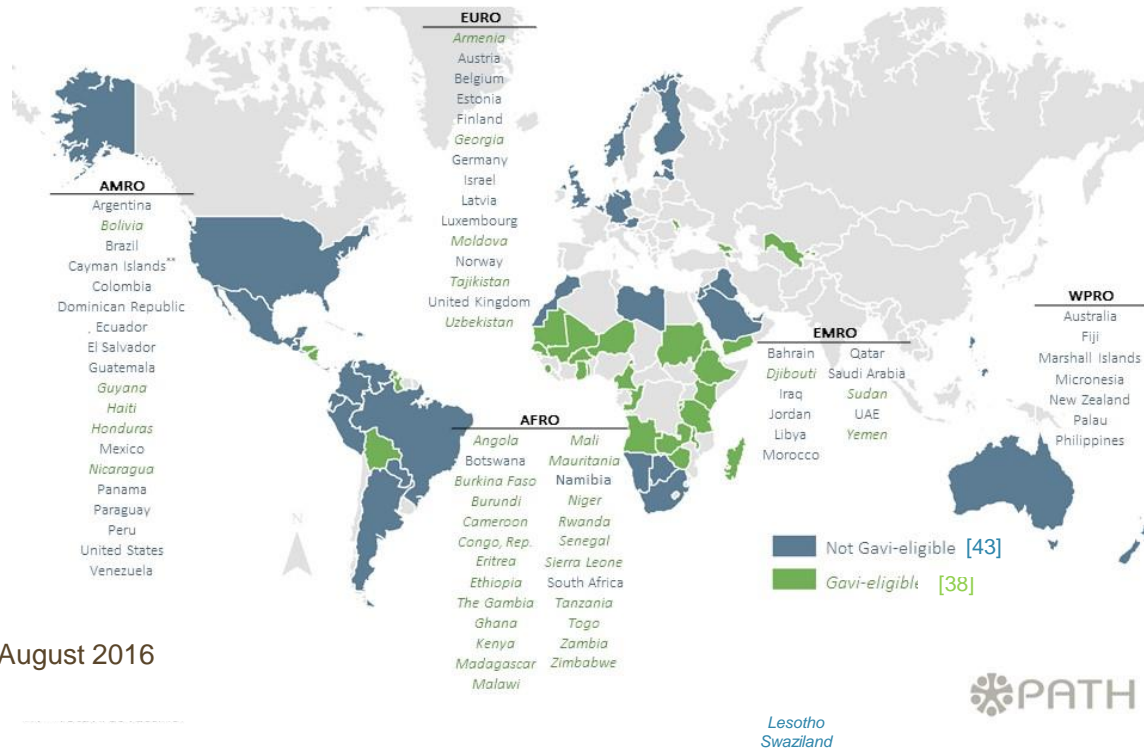
WORLDWIDE DEATHS



- Two live attenuated oral rotavirus vaccines (Rotarix, GSK; RotaTeq; Merck)
 - WHO pre-qualified & commercially available, vaccination is now well established worldwide
- All settings observed a real impact (high, middle and low income settings)
 - significant reduction in rotavirus related mortality, severe rotavirus diarrhea and all cause diarrhea in countries that have introduced the vaccine.

1. Tate et al CID 2016.

ROTAVIRUS VACCINES – National Introduction



* August 2016

81 countries have introduced rotavirus vaccine into their national immunization programs, including 38 Gavi eligible countries:

- 25 sub-Saharan Africa
- 5 Americas
- 5 Europe
- 3 E. Mediterranean/Middle East
- 31/47 countries in AFRO

Three countries have regional introduction: India, Canada & Philippines. Five have GAVI approval but not introduced (Nigeria, Pakistan, Central African Republic, Cote d’Ovoire & Sao Tome & Principe).

Thus, rotavirus vaccine has been introduced in >50 Gavi-eligible countries and LMICs

But gaps remain in Asia.



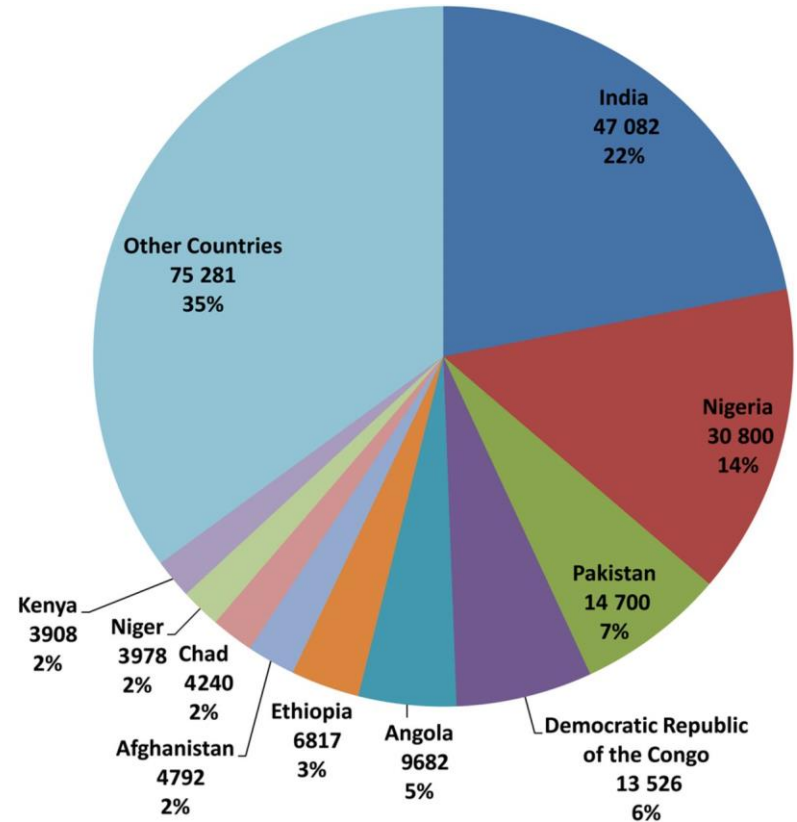
OPPORTUNITY FOR IMPACT OF ROTAVIRUS VACCINE

Four countries: India, Nigeria, Pakistan, & DRC, accounted for 49% of all rotavirus deaths (2013 estimates).

Ten countries account for 65% of rotavirus deaths.

Of these:

- only Ethiopia and Angola have introduced vaccine
- India has introduced a staged regional program (2016),
- Pakistan & Nigeria plan introduction 2017/2018
- So vaccination can still impact child health



VACCINE DEVELOPMENT

ROTAVIRUS VACCINE PIPELINE

Why continue to develop new rotavirus vaccines?

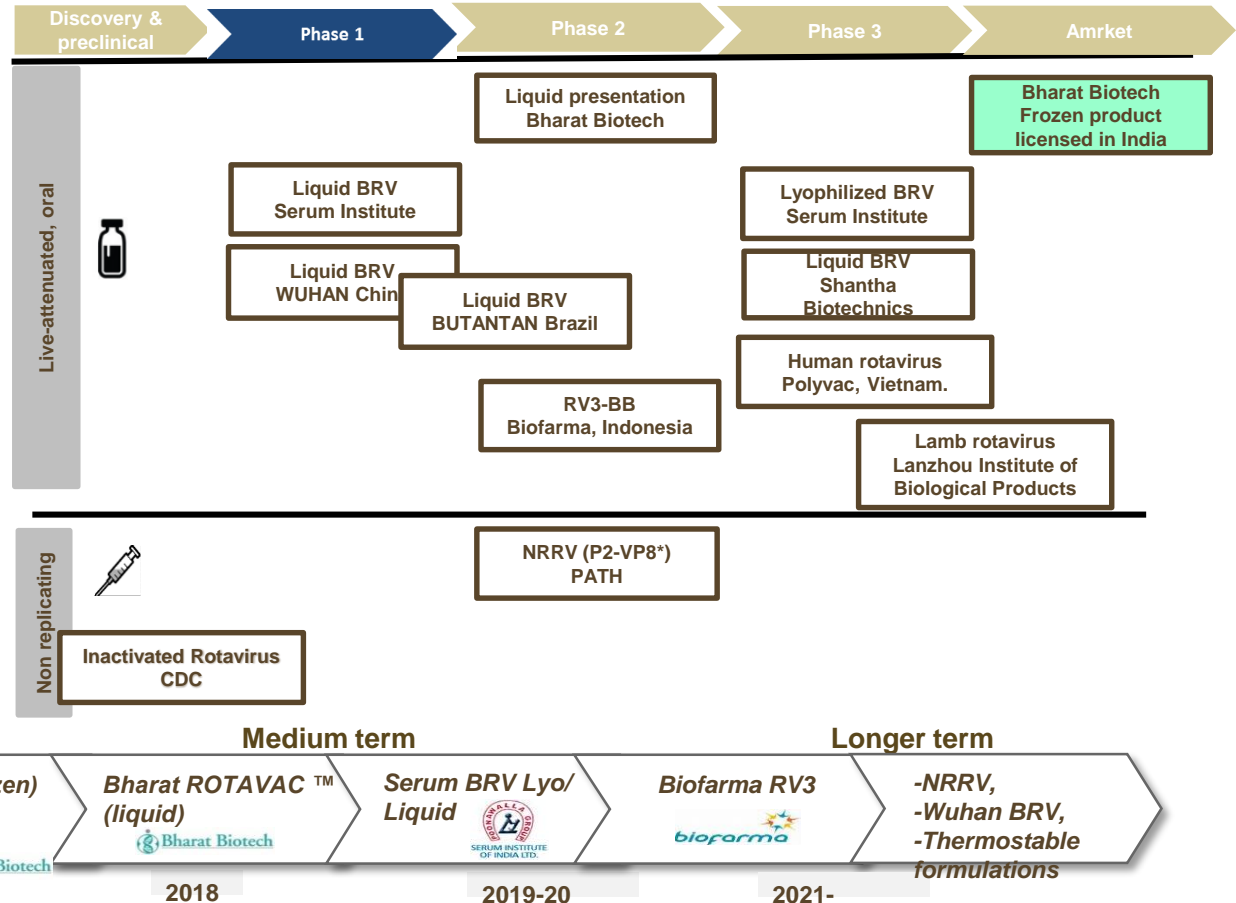
- Two live attenuated oral rotavirus vaccines (Rotarix, RotaTeq):
 - WHO pre-qualified & commercially available and used across the globe.
- New rotavirus vaccines:
 - ensure an adequate global vaccine supply and vaccine diversity,
 - market pressure will assist to lower cost
 - May improve effectiveness and impact in low income settings
 - Country preference for own indigenous vaccine (India, Vietnam & Indonesia)
- Ensure adequate supply of acceptable presentations of rotavirus vaccines for use in Gavi-eligible countries and LMICs.
 - Packaging & presentation in Cold chain

ROTAVIRUS VACCINE CANDIDATE PIPELINE

Vaccine development:

- oral live attenuated
- non-replicating candidates
- DCVM:

BBIL
SII
Shanta
Wuhan
Butantan
BioFarma
Polvac
Lanzhou
SK



ROTAVIRUS VACCINES UNDER CURRENT CLINICAL DEVELOPMENT:

Highlights

Candidate	Producer	Strain	Characteristics	Route	Recent Findings
RotaVac (116E)	Bharat Biotech, India	Human G9P[11]	frozen formulation licensed. Ongoing evaluation of a liquid presentation.	Oral	Phase 3 efficacy completed: 56.3% efficacy 1 st year of life. Licensed in India. Submitted to WHO for PQ
BRV-human Reassortant	Serum Institute of India	Pentavalent combination G1-4, G9 with P[5] VP4	First presentation is lyo, Ongoing evaluation of liquid presentation	Oral	Phase 3 efficacy of lyo (n=7,500) India/Niger - completed. Phase 3 non-inferiority study completed (n=1,200)
RV3-BB	BioFarma, Indonesia MCRI, Melbourne	Human neonatal G3P[6]	Frozen presentation, ongoing evaluation of a liquid product.	Oral	Phase 2a immuno 76% (New Zealand) Phase 2b immuno & efficacy underway in Indonesia. Neonatal dose, no porcine trypsin
P2-VP8* (NRRV)	PATH	Trivalent, truncated VP8* of P[4], P[6] and P[8]	NIH developed the constructs, and provided license for use.	Parenteral	Phase 2a immunogenicity of monovalent. Ongoing Phase 2 of trivalent construct in South Africa

POST VACCINE INTRODUCTION STUDIES

IMPACT OF ROTAVIRUS VACCINES

Large body of evidence demonstrates the impact of rotavirus vaccines (>30 studies):

- Significant reduction in diarrheal deaths, rotavirus hospitalizations, and all cause diarrhea.
- Resulted in saved lives and improved child health globally.

However; issues still remain:

- Vaccine effectiveness is lower in low income settings, where burden is highest
 - Duration beyond first year of life
-

IMPACT OF ROTAVIRUS VACCINES: vaccine effectiveness

Vaccine introduction has been an enormous success, however, vaccine effectiveness is not consistent across the globe.

- Different vaccine effectiveness rates (VE) observed in high and low income countries
- A lower protection has been observed in emerging countries in Asia and Africa over the first year of life

Developed setting (US/Finland): 75-95% VE against severe RVGE hospitalisation

Australia	Rotarix, RotaTeq	45-88%
Belgium	Rotarix, RotaTeq	50-80%
Finland	RotaTeq	78%
USA	Rotarix, RotaTeq	55-94%

Developing settings (Africa/ SE Asia): 50-70 % VE against severe RVGE hospitalisation

Ghana	Rotarix	60% (first 3yrs)
Botswana	Rotarix	54%
Rwanda	RotaTeq	75%
Nicaragua	RotaTeq	45%

IMPACT OF ROTAVIRUS VACCINES: protection beyond first year of life

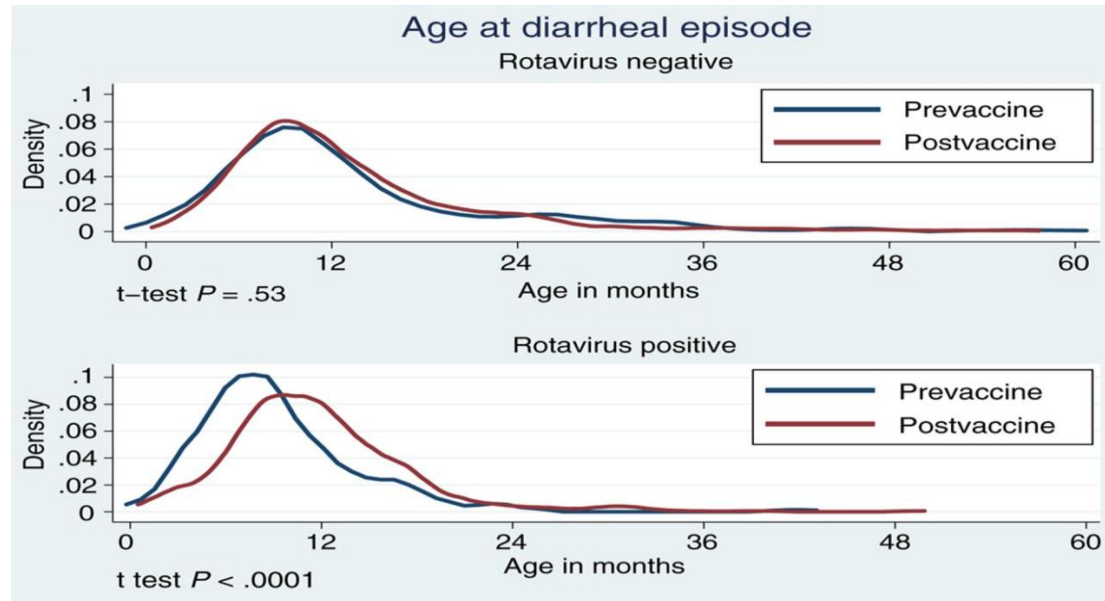
In many settings, protection is similar in first and second year of life.

However, there are several lines of evidence suggest vaccine protection is not as enduring/ complete as predicted.

Country	Vaccine/year introduced	VE against RV hospitalisation (full course) (Vesikari >11)
Bolivia	2008 – Rotarix	Overall VE all – 59% (37-73%) (2-59 mo) 2-11mo – 76% (50-89%) >12mo – 45% (0-70%)
Malawi	2012 – Rotarix	Overall VE all- 58.3% (20-78%) (0-59 mo) [G1P8 – 82.1 (44-94); G2P4 – 34.9% (-135-82%)] <12mo – 70.6% (33-87%) 12-23mo – 31.7% (-140 -80%) 24-31mo – 28.8% (-147-79%)
Moldova	2012 – Rotarix	Overall VE all – 79% (62-88%) (6-59mo) 6-11mo – 84% (67-92%) 12-23mo – 46% (-16-75%)

IMPACT OF ROTAVIRUS VACCINES: Age of diarrhea by rotavirus status

- In Malawi: age of diarrhea episodes before and after rotavirus vaccine introduction.
- Evidence suggest age of disease has changed post vaccine introduction
 - Shift to later disease, older infants



IMPACT OF ROTAVIRUS VACCINES

Thus despite 10 yrs since vaccine introduction; questions still remain.

- Vaccine effectiveness is lower in low income settings, where burden is highest
- Vaccine protection is not as enduring/complete as predicted beyond first year of life.
- Multiple factors may contribute to these reduced vaccine effectiveness:
 - maternal antibodies
 - environmental enteropathy
 - gut microbiome
 - host genetics (Lewis secretor status/HBO)
 - Cross protection
 - emerging diversity of rotavirus strains
 - Genotype G2P4, novel equine-like G3P8, antigenic variants,

CAN WE IMPROVE VACCINE EFFECTIVENESS AND PROTECTION?

CAN WE IMPROVE VACCINE PERFORMANCE?

Alterations in delivery schedule may be an approach to improve effectiveness & impact

- *Additional dose*
- *Booster dose*

We know that Rotarix is provided as a 2 dose product, administered at 6 and 10 weeks

- It has demonstrated excellent effectiveness in high and middle income settings, but less protection in low income settings:
 - Studies have shown some definite improvements in IgA seroconversion and trends to improved efficacy in some settings with 3 doses course versus the 2 dose course.
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ADDITIONAL VACCINE DOSE: PAKISTAN & GHANA

Country	Vaccine/ schedule	IgA Seroconversion	GMC (U/ml)
Pakistan	2 dose 6/10	36.1% (29-43.9)	24.0
	10/14	38.5% (31.2-46.3)	
	3 dose 6/10/14	36.7% (29.8-44.2)	25.8
Ghana	2 dose 6/10	28.9% (22.1-36.8)	22.1 (17.4-28.12)
	10/14	37.4% (29.8-45.7)	26.5 (20.7-34.0)
	3 dose 6/10/14	43.4% (35.5-51.6)	32.6 (24.4-43.2)

Ali et al. JID 2016; Armah et al. JID 2016

Studies have investigated potential benefit of three doses of Rotarix.

Same study protocol:

2 dose 6/10 weeks or 10/14 weeks

3 dose 6/10/14 weeks

Pakistan: no difference in IgA seroconversion rates or GMC in 2 or 3 dose schedule.

However, in Ghana, significantly more infants seroconverted in the 3 dose regime, when compared to 2 dose schedule.

ADDITIONAL VACCINE DOSE SOUTH AFRICA & MALAWI

Country	Vaccine Schedule 2 dose: 10/14 wks 3 dose: 6/10/14	IgA Seroconversion	Vaccine efficacy (2 seasons)
South Africa	2 dose	57.1%	72.2
	3 dose	66.7%	81.5
	Pool	-	76.9
Malawi	2 dose	47.2%	49.2
	3 dose	57.1%	49.7
	Pool	-	49.4

Additional dose studies in South Africa and Malawi:

study protocol:

2 dose 10/14 weeks

3 dose 6/10/14 weeks

- later start start to vaccination

In South Africa: the 3 dose schedule shows a distinct trend to being more immunogenic and provides higher efficacy.

In Malawi, no difference in vaccine efficacy over 2 seasons between 2 or 3 dose schedule.



CAN WE IMPROVE VACCINE PERFORMANCE

Other strategies to improve performance:

Booster dose at 9 months:

A strategy to overcome observed waning of immunity in second year of life may be to provide an additional dose later in life – 9 months (either live oral or inactivated parental).

Neonatal delivery:

Does initial immunization prior to maternal antibody interference, help stimulate immune responses.

SUMMARY

- Rotavirus vaccine have achieved a significant and substantial improvement in child health globally
- Current live attenuated oral rotavirus vaccines provide excellent effectiveness in developed countries, however, the effectiveness is less in developing settings.
- New rotavirus vaccine (eg live attenuated & non replicating) continue to be developed with aim to improve effectiveness & impact,
 - Many DCVM partners,
 - Ensure supply security, vaccine diversity and assist in reducing cost.
- Need to continue to ensure ongoing success of vaccines:
 - Alternative dosing schedules (additional/ booster dose).

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