

# **Rotavirus disease burden: worldwide**

**Leading cause of severe dehydrating  
diarrhea in infants and young children**

**>125 million cases/year in under-five  
children**

**500,000 deaths/year, mostly in  
developing countries**

# **Rotavirus disease burden: United States**

**During first 5 years of life:**

**4 of 5 will have RV gastroenteritis**

**1 of 7 will require physician visit**

**1 of 78 will require hospitalization**

**\$264 million/year in direct medical costs**

**\$1 billion/year in total costs to society**

# **Rotavirus Disease Burden: India**

**150,000 deaths in under-five children every year**

**18% of all hospitalizations due to diarrhea, approx 400,000 per year**

# Rotavirus Serotypes: Global

**VP4**

**VP7**

**P [8]**

**G1 53%**

**G3 14%**

**G4 5%**

**P [4]**

**G2 11%**

**96% of typable strains**

# Rotavirus Serotypes: India 1996-8

VP4	VP7	
P [8]	G1	15%
	G4	6%
	G9	5%
P [4]	G2	22%
P [6]	G2	10%
	G9	9%

*Multicenter study: AIIMS-CDC collaboration*

# **Evidence of expanding diversity: Implications for vaccine development?**

**G types other than G1 to G4:**

**Porcine G5 in Brazil**

**Bovine-like G8 in Malawi**

**G9 in India, Bangladesh, US, Europe**

**Bovine P [11] VP4 reassortants in India**

**Unusual G/P combinations**

# Immunogenicity of RRV-TV in developed & developing countries

	US multi-center	Venezuela	Bangladesh
IgA	56%	84%	
Neutralization: parent strain	90%	77%	
Neutralization: human RV	14-31%	10-45%	
Any test	92%	88%	87%

# Risk of IS Following RRV-TV

STUDY	AUTHOR	RISK
Preliminary data	Livengood et al	1 in 2,500
Case-series	Murphy et al	1 in 4,670
Case-control	Murphy et al	1 in 9,474
Retrospective cohort	Kramarz et al	1 in 11,073
Ecological studies	Chang et al	1 in 17,000
	Simonsen et al	1 in 28,000

**Consensus NIH meeting (Sep 2001): 1 in 10,000**



# Risks/Benefits of RRV-TV in developing countries

Mortality from RV diarrhea: 40 per 10,000  
Assume 50% vaccine efficacy in prevention  
of deaths: 20 per 10,000

1 case of IS per 10,000 vaccinees  
Assume 20% mortality: 0.2 per 10,000

Risk of dying from RV diarrhea is **100 times**  
the risk of dying from vaccine induced IS

**RRV-TV still unlikely to be acceptable**

# Some vaccines under Development

Human-bovine [UK] reassortant vaccine (Merck)

VP7 (human): G1, G2, G3, G4

Human rotavirus vaccine (GSK)

VP7: G1

Lamb rotavirus vaccine (Lanzhou Inst., China)

Neonatal-strain vaccines

*Australia:* P[2] G3

*India: Delhi* P[11] G9

*Bangalore* P[11] G10

# Comparison of two new rotavirus vaccines under evaluation with RRV-TV

	RRV-TV	Human G1 vaccine (89-12, GSK)	Bovine-human G1-G4 vaccine (UK, Merck)
Fever >38°C	15% excess	14% excess	None
Diarrhea	3% excess	8% excess	None
Antibody response	88%	90%	89%
Efficacy (all RV)	49-68%	89% (65%, 96%)	Not yet known
Efficacy (severe RV)	64-91%	78% (14%, 94%)	Not yet known

# Neonatal rotavirus vaccines: Indo-US collaboration

- Based on two natural bovine-human reassortant rotavirus strains
  - 116 E: 10 human + 1 bovine genes
  - 40% children 2-12 years of age had any type of immune response*
  - I 321: 9 bovine + 2 human genes
- Neonates infected with these strains asymptomatic and protected against future infections
- Currently in early stages of development

# Potential ways to reduce risk of IS with rotavirus vaccines

- Different routes of administration: intranasal, parenteral
- Different formulations: human, bovine, lamb
- Different schedules: newborn, 1 or 2 doses

# **Challenges for future trials of rotavirus vaccines**

**Should trials of new vaccines be designed to measure only efficacy or risk of intussusception as well?**

**How intense should (can) the surveillance for intussusception be?**

**Concurrent evaluation in developed and developing countries**