

RotaTeq™: The Pentavalent Rotavirus Vaccine

Clinical Update and New Data



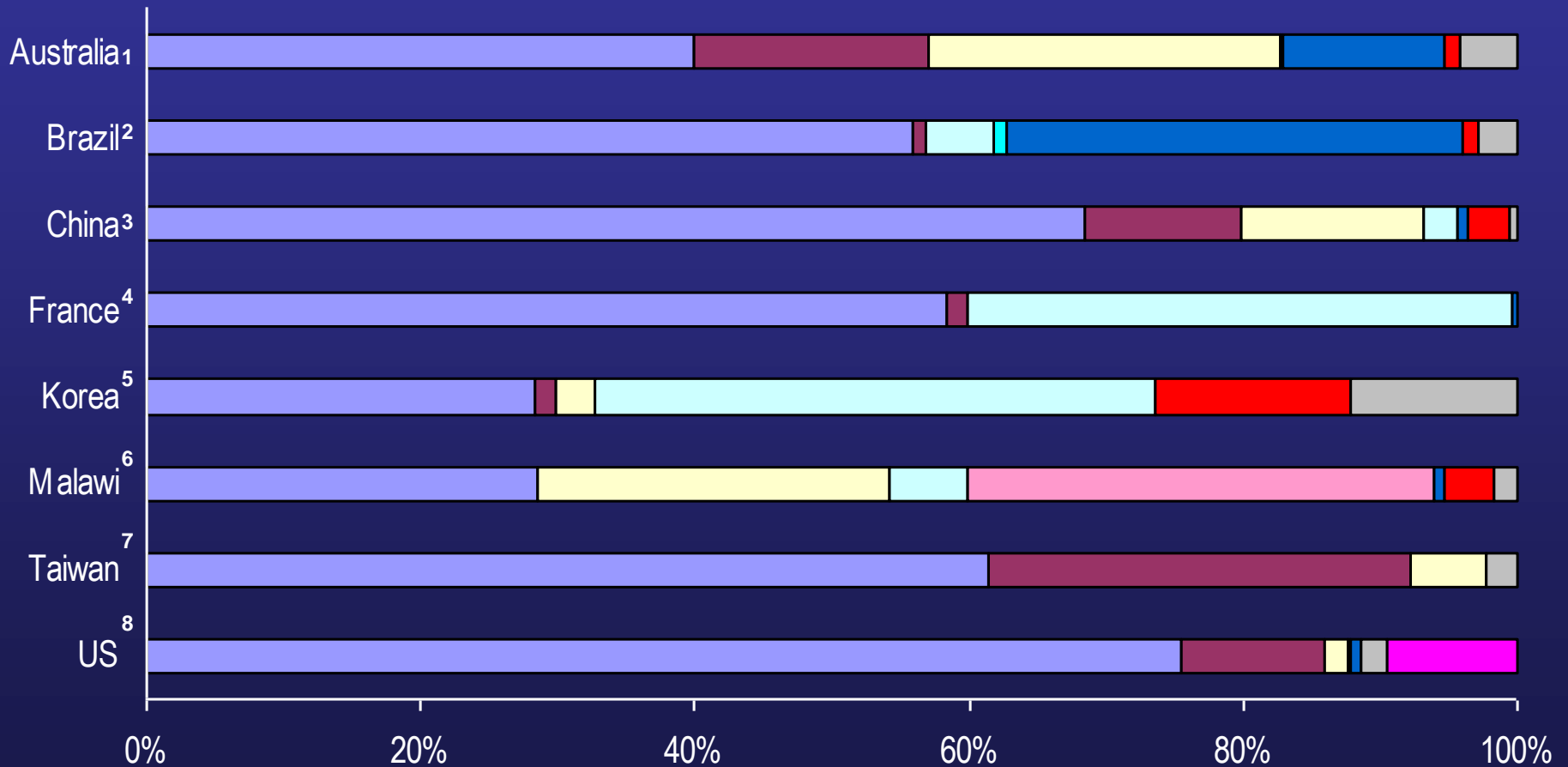
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Central East Europe, Middle East, Africa and, Canada
Tel Aviv, Israel – June 17th 2009

Merck's Strategy around Rotavirus Vaccine Development

To develop a vaccine against rotavirus that would:

- 1) Be able to effectively respond to the variable and unpredictable nature of circulating rotavirus (*from year to year and region to region*)
- 2) Be at least as effective with respect to the degree of protection against disease that follows natural infection.
- 3) Prevent the full scope of the burden caused by rotavirus disease

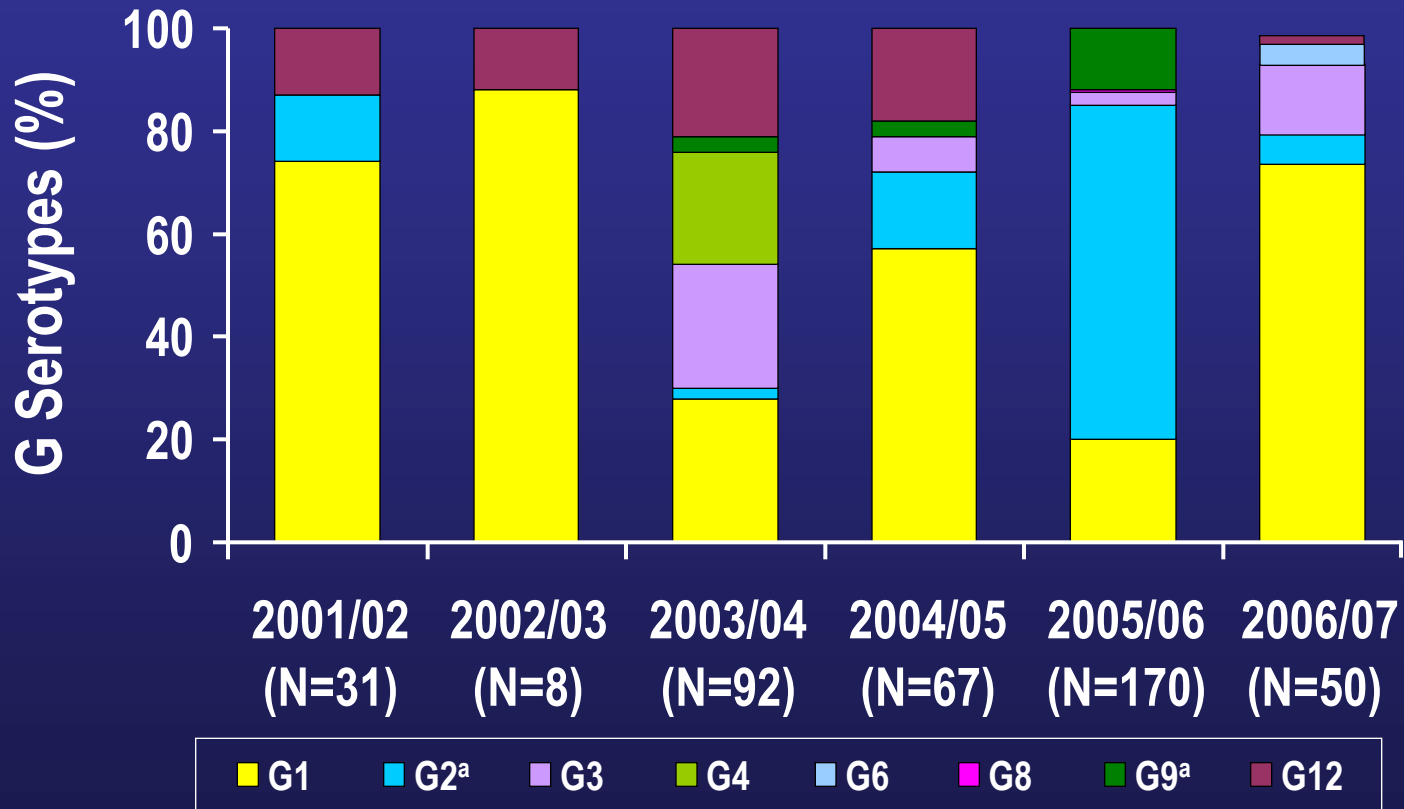
Global Prevalence of Rotavirus Serotypes



1. Kirkwood C, et al. *Commun Dis Intell.* 2004;28:481–485. 2. Gurgel RQ, et al. *J Clin Virol.* 2008;43:1–8. 3. Fang Z-Y, et al. *J Clin Microbiol.* 2002;40:1875–1878. 4. Bon F, et al. *J Clin Microbiol.* 2000;38:1681–1683. 5. Song M-O, et al. *J Med Virol.* 2003;70:324–332. 6. Cunliffe NA, et al. *J Clin Microbiol.* 2001;39:836–843. 7. Tsai C-H, et al. *Pediatr Int.* 2000;42:411–414. 8. Hull J, et al. Presented at the International Conference on Emerging Infectious Diseases (ICEID); March 16–19, 2008; Atlanta, GA.

Variations in Rotavirus G Serotypes Over Time – Children’s Hospital of Philadelphia (2001– 2007)

Rotavirus Surveillance at Children’s Hospital of Philadelphia (2001–2007)



^aAmong the typeable samples, G2 and G9 were associated with more than 1 P type. G2 was associated with P[4], P[6], and P[8] and G9 was associated with P[6] and P[8]. All other G types were only found with P[8] during the surveillance period.

G and P Serotype Combinations of Human Rotaviruses



| G Serotype | P Serotype [Genotype] | | | | | | | | | | | |
|------------|-----------------------|-------|--------|-------|------|-------|-------|------|--------|--------|--------|--------|
| | 1A[8] | 1B[4] | 2A[6] | 2C[6] | 3[9] | 4[10] | 5A[3] | 6[1] | 8[11] | 11[14] | 12[19] | [25] |
| 1 | Red | Cyan | | Cyan | Cyan | | Cyan | | | Cyan | | |
| 2 | Cyan | Red | | | | | | | | | | |
| 3 | Red | Cyan | Yellow | | Cyan | | Cyan | | Cyan | Cyan | | |
| 4 | Red | Cyan | Yellow | | Cyan | Cyan | | Cyan | Cyan | | | |
| 5 | Yellow | | Cyan | | | | | | | | | |
| 6 | | | Cyan | | Cyan | | | | | Yellow | | |
| 8 | Cyan | Cyan | Yellow | | | Cyan | | Cyan | | Yellow | | |
| 9 | Red | Cyan | Yellow | | | Cyan | | | Yellow | | Cyan | |
| 10 | Cyan | | | | | | | | Yellow | Yellow | | |
| 11 | | Cyan | | | | | | | | | | Yellow |
| 12 | Yellow | Cyan | Cyan | | Cyan | | | | | | | |



Globally Common



Regionally Common

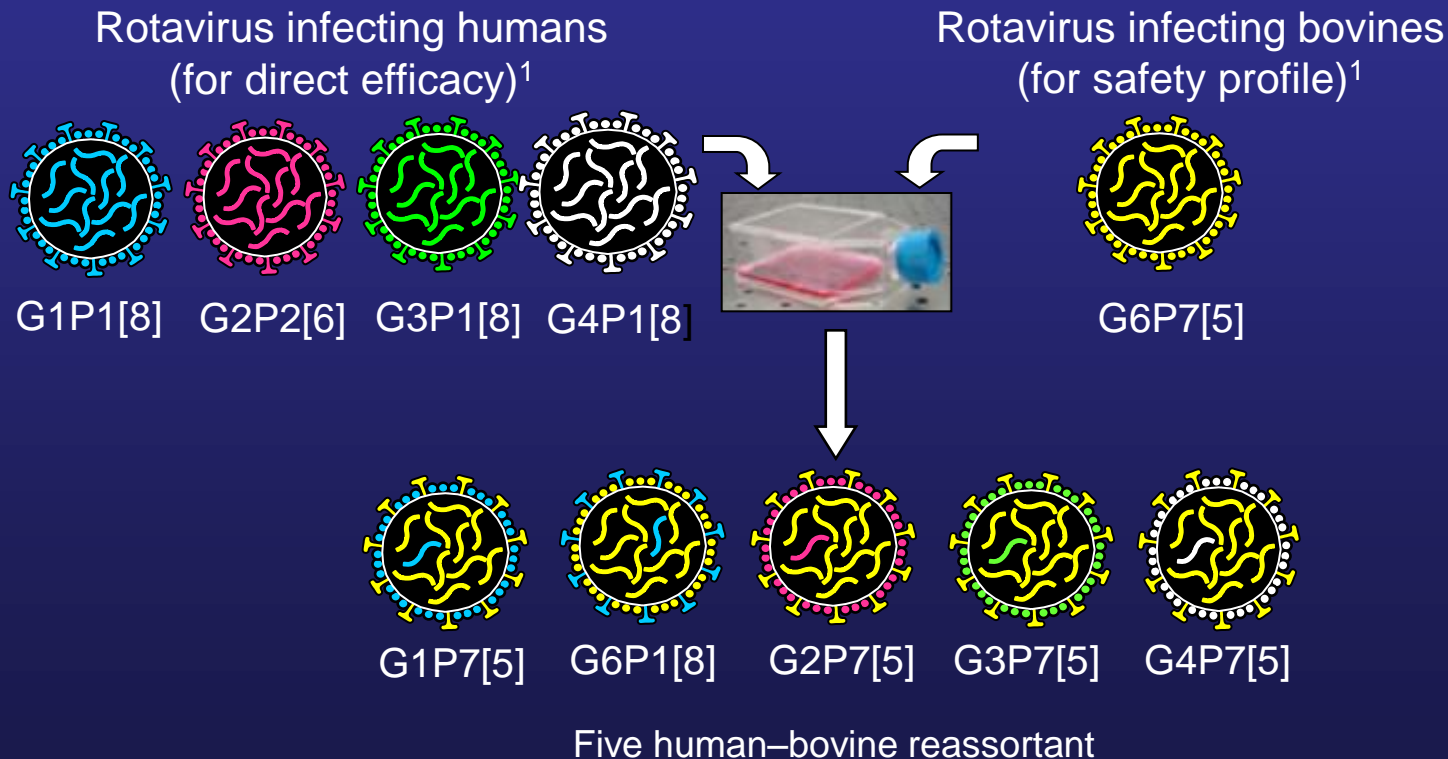


Uncommon

RV5 matches 29 (58%) circulating G/P combinations

RotaTeq[®]: Reassortment Process

- The bovine rotavirus strain is naturally attenuated for humans¹
- The human–bovine strains undergo a natural reassortment process^{1,2}



1. Offit PA, Clark HF. *Pediatr Ann.* 2006;35:29–34.

2. Heaton P, et al. *J Infect Dis.* 2005;192(Suppl 1):S17–S21.

Merck's Strategy around Rotavirus Vaccine Development

To develop a vaccine against rotavirus that would:

- 1) Be able to effectively respond to the variable and unpredictable nature of circulating rotavirus (*from year to year and region to region*)
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- 3) Prevent the full scope of the burden caused by rotavirus disease

Basis for Developing a Multidose, Pentavalent Rotavirus Vaccine

- Infants and young children have multiple rotavirus (RV) infections in first few years of life
- Wild-type rotavirus infection induces immunity against subsequent rotavirus gastroenteritis (RGE); immunity increases with number of infections

| # of Previous RV Infections | % Efficacy (95% CI) by Disease Severity | |
|-----------------------------|---|--------------------|
| | Any | Moderate-to-Severe |
| 1 | 77 (60, 88) | 87 (55, 96) |
| 2 | 83 (64, 92) | 100 |
| 3 | 92 (44, 99) | 100 |

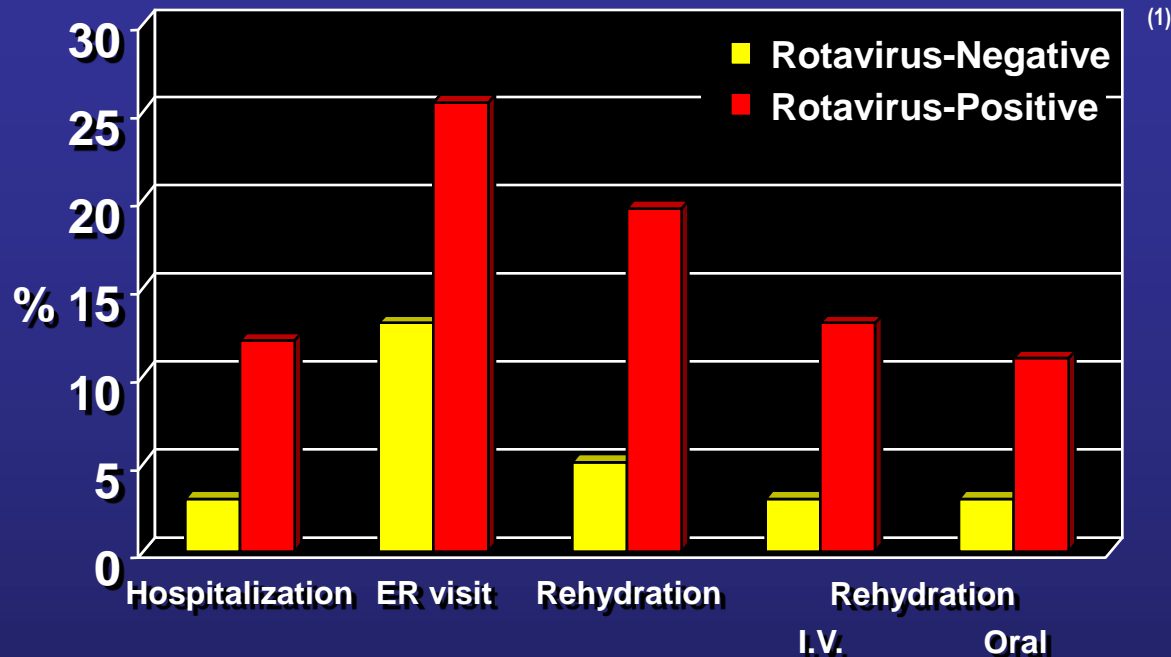
- Natural immunity largely serotype-specific, particularly with first infection
 - Second illness caused by the same G-serotype uncommon in Mexico study (n=22)

Merck's Strategy around Rotavirus Vaccine Development

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Rotavirus Related Burden of Illness



Work Lost (1)

For 56% of families, at least one parent had to miss work because of the RGE episode
These families lost an average of 4.8 work days
For hospitalized RGE cases, 67% of families missed, on average, 7.4 work days

QoL (2)

Our estimates of the QALY-lost per episode of RGE (2 to 7 per 1,000 episode) are very similar to those for children with chickenpox (4 per 1,000 episode), pneumonia (4 to 6 per 1,000 episode) and otitis media (5 per 1,000 episode)

(1) Can J Infect Dis Med Microbiol. 2008 Nov;19(6):397-404

(2) The Pediatric Infectious Disease Journal. In Press Jan 2010

RotaTeq™ Demonstrated Reductions in Hospitalizations/ED^a Visits for G1, G2, G3, and G4 RGE^b Consistent Across Regions in REST^c

Reductions in the combined incidence of hospitalizations/ED visits for RGE up to 2 years after vaccination¹:

~95% reduction in the overall study population (n=68,038)

in Post-hoc Analyses of REST^{1,2}:

~95% reduction in Europe (n=28,002)

~95% reduction in United States (n=24,463)^d

~93% reduction in Native American Nations (n=581)²

~90% reduction in Latin America/Caribbean (n=4,489)

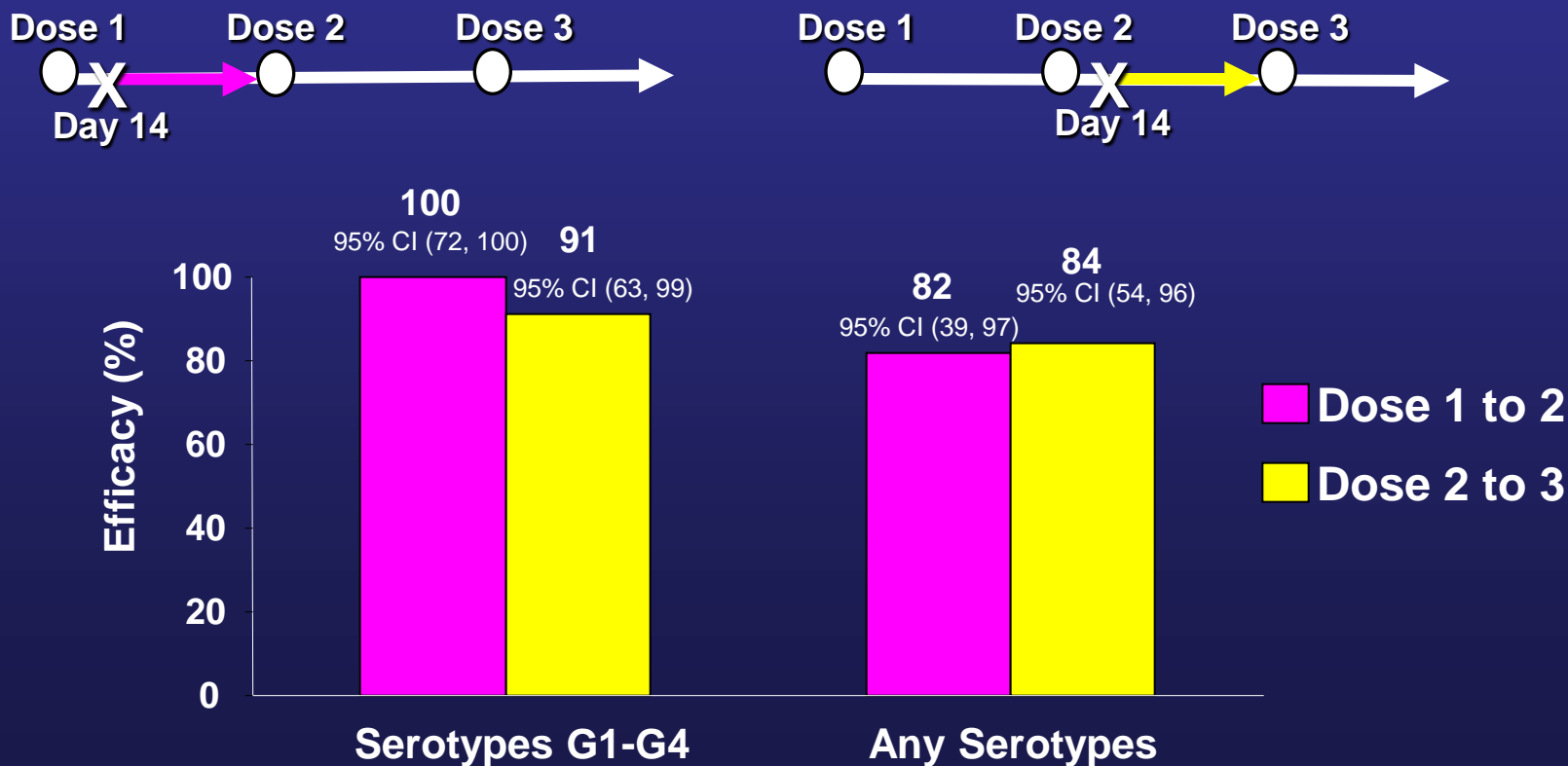
^aED=emergency department; ^bRGE=rotavirus gastroenteritis; ^cREST=Rotavirus Efficacy and Safety Trial; ^dUnited States data reported with Native American data.

1. Vesikari T, et al. *Int J Infect Dis.* 2007;11(Suppl 2):S29–S35.

2. Data on file, MSD _____.

RotaTeq™: Efficacy Between Doses

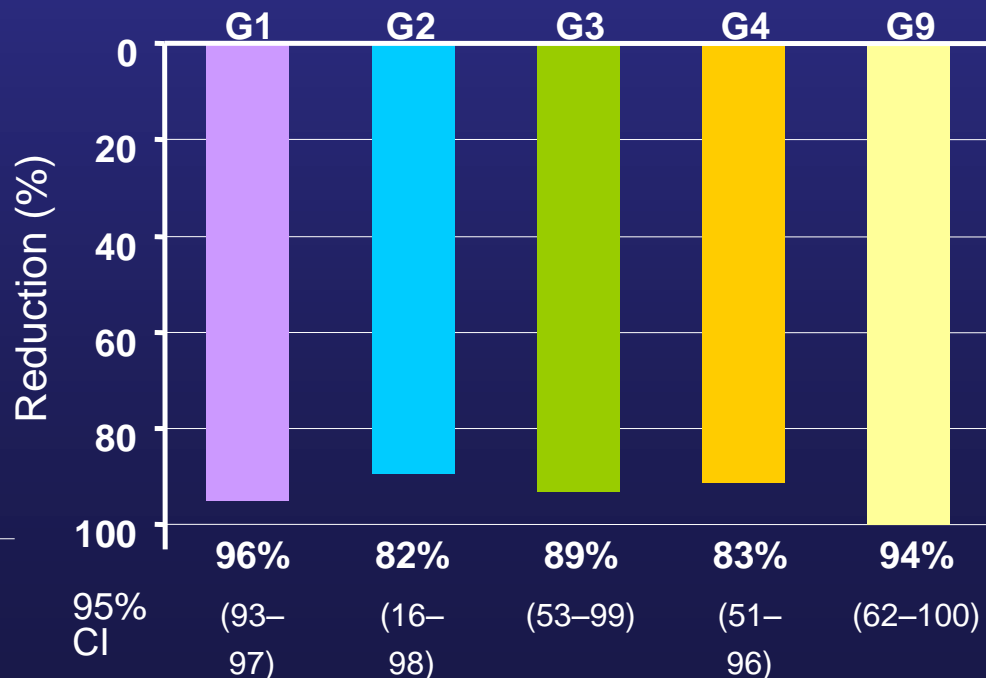
- More than 80% protection against hospitalisation & ED visits after the first dose¹
- Three doses must be given for complete administration of vaccine



RotaTeq™: High, Long-Lasting Protection up to 3 Years Postvaccination

- In the Finnish Extension Study (FES),¹ nearly 21,000 infants were followed for up to 3.1 years after their third dose in REST

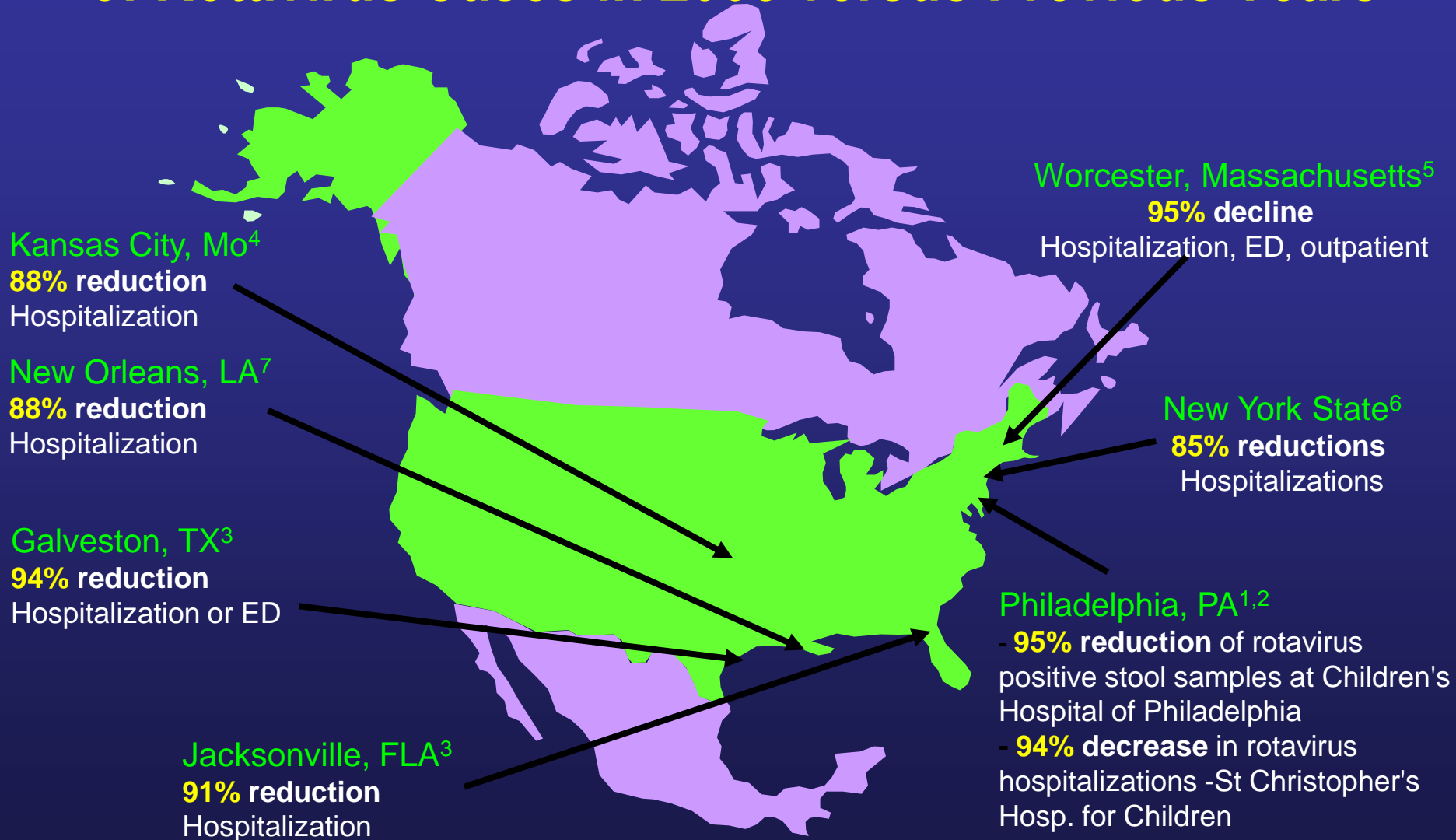
Durable Efficacy in Reducing RVGE-Associated Health Care Encounters (Combined hospitalizations and ED Visits), Regardless of Rotavirus Serotype, for up to 3.1 Years



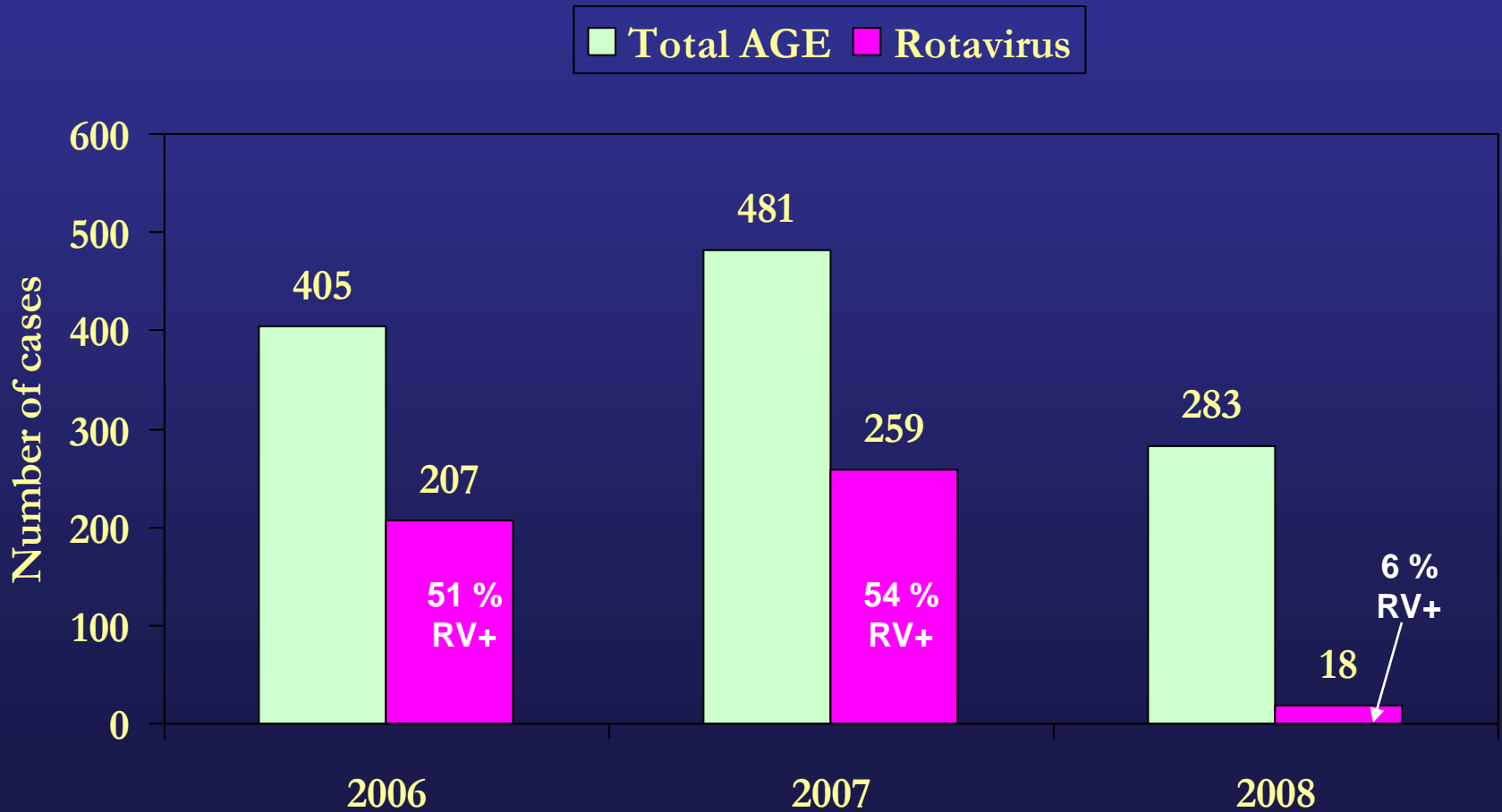
**Routine Use of RotaTeq[®]
Provides Positive Public Health
Impact against Rotavirus**

**New Evidence from the Post-licensure
RotaTeq[™] Experience**

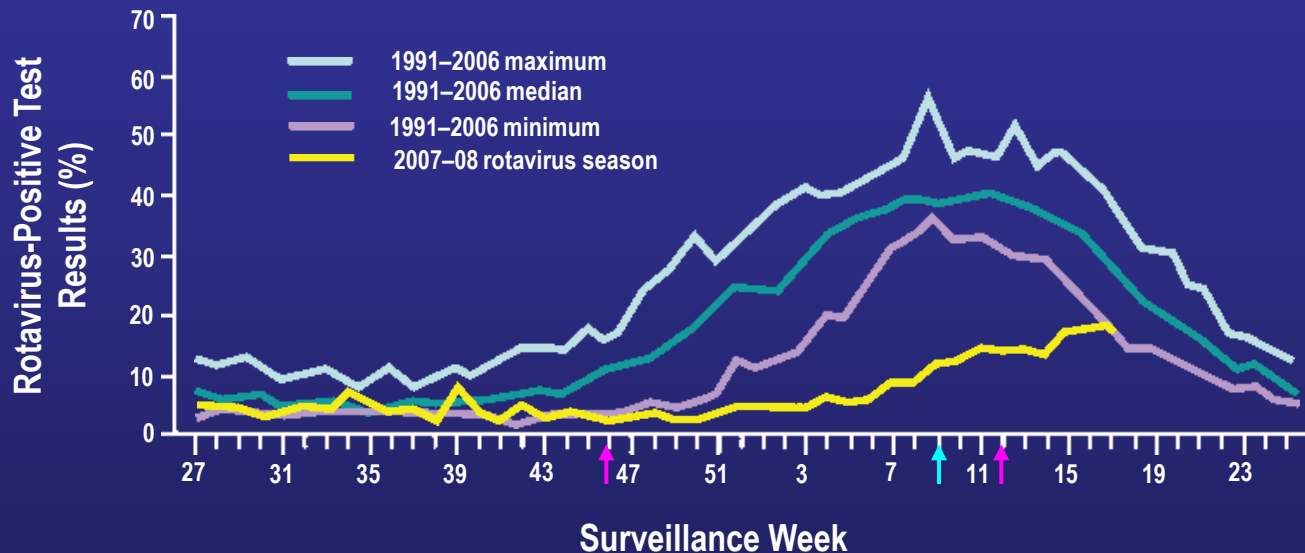
Local Hospital Studies Have Shown Marked Decrease of Rotavirus Cases in 2008 versus Previous Years



Total AGE and Rotavirus AGE cases in NVSN, January-April, 2006-2008



NREVSS Update: Data from 2007/08 Confirms the High Decrease of Rotavirus (RV) + Results

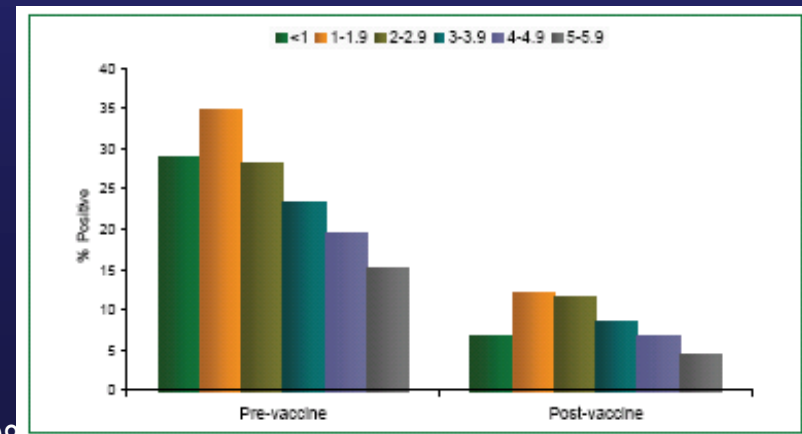
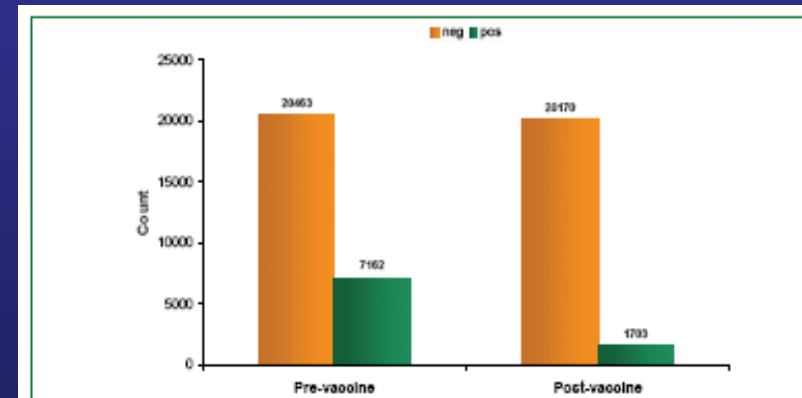


a2008 data current through week ending 3 May 2008. Data from July 2006–June 2007 were excluded from the (1991–2006) baseline data.

- the 2007–2008 rotavirus season appeared to begin 2 to 4 months later than the prior 15 rotavirus seasons from July 1991 to June 2006 and was diminished in magnitude.

National Diagnostics Laboratory Data

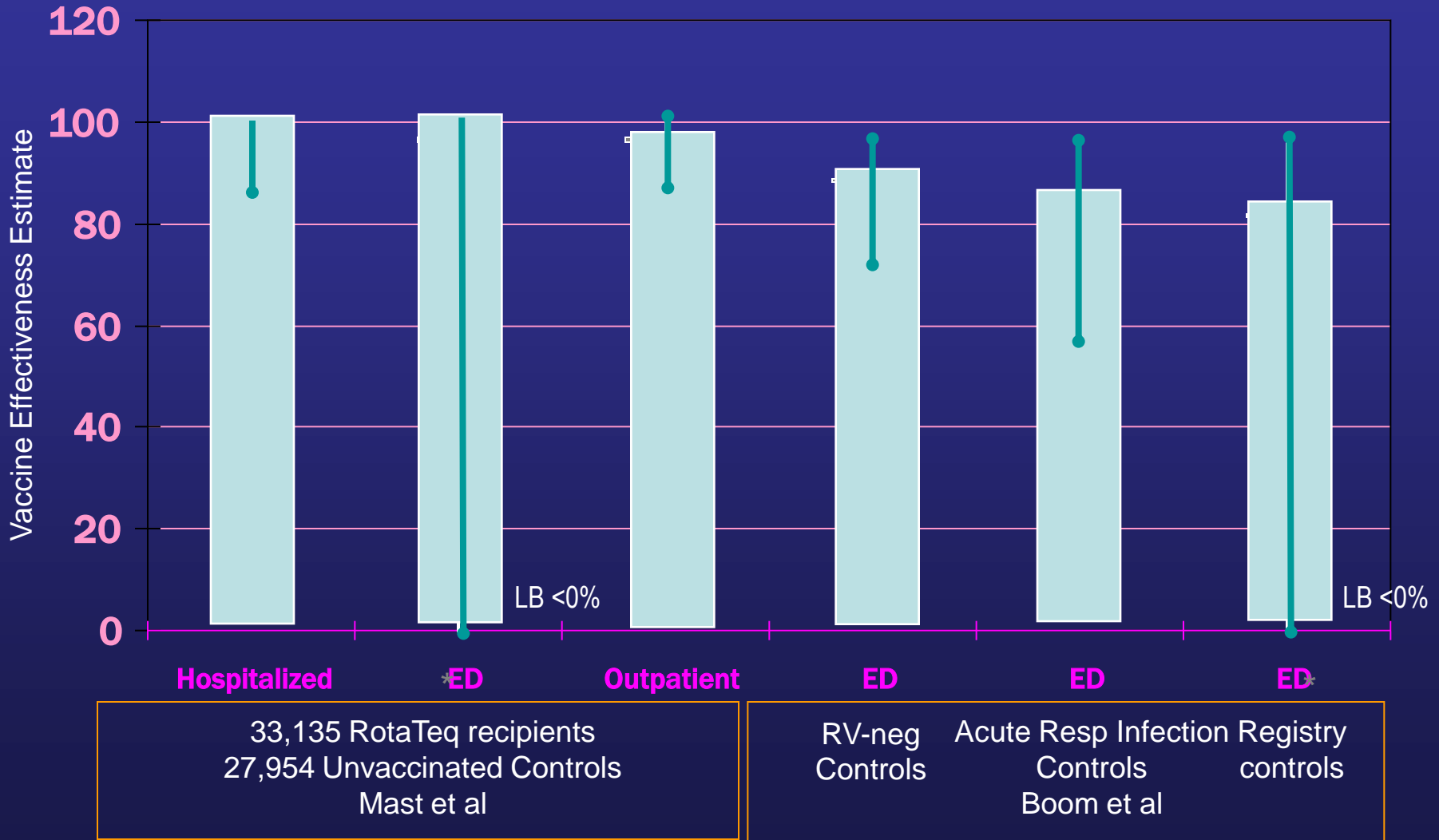
- QUEST Diagnostics -- Largest clinical diagnosis company covering more than half of US physicians
- Average of 27,625 rotavirus tests performed annually
- 76% reduction of RV prevalence rate in children <1 year for 2003-2006 vs. 2008
- Decline in every age group, including 2-5 years, unlikely to have been vaccinated



RotaTeq™ Comparative Effectiveness Studies

- High vaccine effectiveness shown
- Two study designs
 - 1. Case control study (Boom et al)
 - Local study at Texas Children's Hospital
 - 2. Prospective cohort study (Mast et al)
 - National study using insurance claims
 - Sample size of 61,000

Overview of RotaTeq® Effectiveness Studies (3 Doses) that used Control Groups (Estimates and 95% CI)



Studies Demonstrated 75-100% Reduction in Healthcare Costs Associated with RotaTeq™

| Data Source/ Location | Medical Setting | Years Evaluated | Reduction in RGE-Related Costs | Reduction in AGE-Related Costs | Savings in 2008 (US\$) |
|---------------------------------------|-----------------|---------------------------------|--------------------------------|--------------------------------|------------------------|
| National Claims Database ¹ | Hospital & ER | 2007-08 (vaccine vs no vaccine) | 100% | 78% | 100% |
| Kansas City, MO ² | Hospital | 2002-06 vs 2008 | 78-88% | <i>Not evaluated</i> | \$2.6-3.2 MM |
| New York State ³ | Hospital | 2005-07 vs 2008 | 75% | <i>Not evaluated</i> | \$3MM |

1. Mast TC et al. , IDSA/ICAAC, Washington DC, October 25-28, 2008

2. Harrison CJ et al. IDSA/ICAAC Washington DC October 25-28, 2008

3. Chang H et al. ACIP Atlanta October 22-23, 2008.

CDC Summary

Rapid Cycle Analysis of Pentavalent Rotavirus Vaccine Safety in the Vaccine Safety Datalink Population

Results

TABLE 2. RotaTeq utilization*.

| Vaccine Dose | # Administered (%) |
|--------------|--------------------|
| 1 | 87,381 (42) |
| 2 | 68,795 (33) |
| 3 | 51,445 (25) |
| Total doses | 207,621 |

* May 21, 2006 through May 31, 2008.

TABLE 3. Adverse event occurrence and risk.

| Event | Events observed | Events expected | Relative risk (RR) |
|-----------------------------|-----------------|-----------------|--------------------|
| Intussusception | 5 | 6.75 | 0.74 |
| Meningitis and Encephalitis | 8 | 13.08 | 0.61 |
| Seizures | 38 | 56.47 | 0.67 |
| Myocarditis | 0 | 0.41 | 0 |
| Gram negative sepsis | 3 | 5.65 | 0.53 |
| Kawasaki syndrome | 2 | 15 | 0.21 |

The LLR did not exceed the critical value for any outcome.

Discussions Regarding RotaTeq® and the Potential for Herd Immunity

- Data to support
 - Delay in seasonal rotavirus (RV) peak ^{1,2,3}
 - Less virus in circulation to assemble “critical mass” at usual time
 - Children too old to have received vaccine also demonstrate decreased RV prevalence ^{1,2,4}
 - Proportional reduction in RV is greater than proportion vaccinated ^{1,4}
 - Reduction in adults cases (small numbers)⁵
- Postulations why herd immunity may not be in effect
 - Even though RV does not always cause disease, it does cause infection so would not expect herd immunity
 - No studies conducted to specifically address this topic
 - Seasonality – Perhaps reductions due to anomalous low season

Merck - Nicaragua RotaTeq™ Partnership

Early Evidence of High Vaccination Impact (1)

- Reduction of Rotavirus Disease¹
 - 89% reduction in rate of rotavirus positive stool samples at primary health clinics in Leon District
 - 46% against rotavirus disease requiring admission or treatment with IV hydration
 - 58% against severe rotavirus diarrhea (Vesikari score of 11 or greater)
 - 77% against very severe rotavirus diarrhea (Vesikari score of 15 or greater).
- Mortality Rate Reduction for Acute Diarrhea²
 - Analysis of national health statistics
 - 3 doses vs 0 doses
 - 73% reduction : 3-11 month old children
 - 44% reduction: 7-11 month old children

1. Patel et al. JAMA 2009 2. Sanchez K. et al. 15th Annual Conference on Vaccine Research, April 27-29, 2009, Baltimore, MD

World Health Organization (WHO) Recommendations for Rotavirus Vaccination

“WHO strongly recommends the inclusion of rotavirus vaccination into the national immunization programmes of regions where vaccine efficacy data suggest a significant public health impact and where appropriate infrastructure and financing mechanisms are available...”¹

**RotaTeq[®] (Rotavirus Vaccine, Live, Oral, Pentavalent) is
on the WHO list of prequalified vaccines²**

1. World Health Organization (WHO). *Weekly Epidemiological Record*. 2007;82:285–296.

2. World Health Organization. Immunization Standards. http://www.who.int/immunization_standards/vaccine_quality/pq_suppliers/en/ Accessed October 2008.

RotaTeq®: Offers Comprehensive Protection Against Rotavirus

- The morbidity associated with rotavirus represents a significant burden in Israel
- RotaTeq™ provides high, long-lasting protection up to 3 years following a 3-dose regimen designed to mimic the natural course of protection^{1,5,6}
- Greater than 95% protection in preventing hospitalizations and ED visits across studies, regions, and populations (including premature infants)
- High and consistent protection against severe RVGE across clinical trials¹⁻⁴
- Good safety profile demonstrated in clinical trials and ~3 years post launch^{1,5,6}

1. Vesikari T, et al. *N Engl J Med*. 2006;354:23–33.

2. Clark HF, et al. *J Pediatr*. 2004;144:184–190.

3. Vesikari T, et al. *Vaccine*. 2006;24:4821–4829.

4. Block SL, et al. *Pediatrics*. 2007;119:11–18.

5. American Academy of Pediatrics. *Pediatrics*. 2007;119:171–182.

6. Vesikari T, et al. ICID, 2008. [Poster Presentation]

7. Vesikari T, et al. *Europaediatrics*, 2008. [Poster Presentation]



teşekkür ederim
Thank you

