Proposed Recommendations from the ACIP Rotavirus Vaccines Working Group

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Overview

- Background
- Proposed recommendations
  - Main
    - General concepts
    - Proposed wording
  - Additional
    - General concepts
    - Proposed wording

Rationale for Rotavirus Vaccination in US

- Primary public health measure for prevention of severe rotavirus disease
- Vaccination early in life to mimic child's first natural infection
  - Will not prevent all subsequent disease
  - Should prevent most cases of severe rotavirus disease and sequelae
    - Physician visits, dehydration, hospitalizations, deaths

US Rotavirus Disease Burden

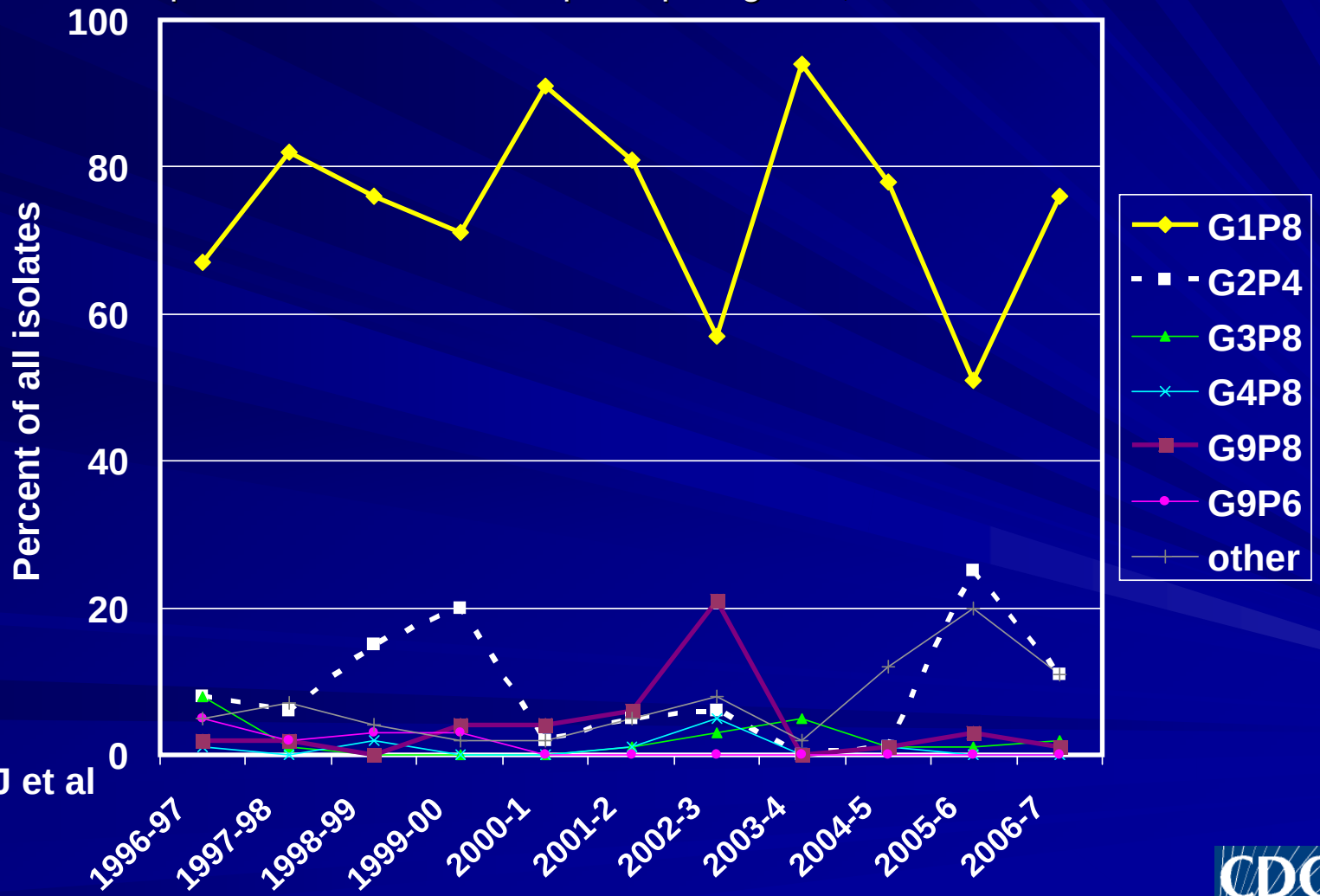
Estimated for one US birth cohort followed to age 5 yrs

Deaths	30
Hospitalizations	67,000
ED visits	214,000
Outpatient visits	424,000
Episodes with home care	2,281,000

WIddowson MA et al Pediatrics 2007; 119:684-93

Rotavirus Strains in the US 1996-2007

Convenience sample of isolates from ~12 participating labs, in different US areas



Gentsch J et al

Proposed Recommendations
General Approach by Working Group

- Review available data
  - Summarize in statement
- Draft recommendations to provide guidance for providers
  - Consider programmatic aspects

Proposed Recommendations
General Approach by Working Group

- Two different vaccine products now available in US
  - Are there circumstances where ACIP would state one product is recommended or preferred over the other product?

Rotavirus Vaccines

	RV5 (RotaTeq)	RV1 (Rotarix)
Vaccine composition	Bovine-human strain reassortant G1x WC3 G2x WC3 G3x WC3 G4x WC3 P1A[8] x WC3	Human strain G1P1A[8]
Doses in series in major trials	3	2
Major trials **--Safety**	Large: REST 11 countries (48% US/Puerto Rico) (33% Finland)	Large: 023 Latin America: 11 countries (+ 3% Finland)
Major trials **--Efficacy**	REST --Large: healthcare utilization --Smaller substudy: clinical efficacy	Large: 023 Latin America Smaller: 036 Europe 6 countries (74% Finland)

Major Clinical Trials
Vaccine Efficacy

	RotaTeq REST	Rotarix 023 Latin Am	Rotarix 036 Europe
Severe Rota GE	G1-G4; Clark>16 **98% (88, 100)**	Vesikari≥11 **85% (71, 93)**	Vesikari≥11 **96% (90, 99)**
Rota Hosp	Hosp G1-G4 **96% (90, 98)**	**85% (70, 94)**	**100% (82, 100)**
Any Rota GE	Any G1-G4 **74% (67, 80)**		**87% (80, 92)**

Major Clinical Trials

Type specific vaccine efficacy

	RotaTeq REST	Rotarix 023 Latin Am	Rotarix 036 Europe
G1P8	Hosp/ED use **95% (92, 97)**	Vesikari≥11 **91% (71, 98)**	Vesikari≥11 **96% (85, 100)**
G3P8	Hosp/ED use **93% (49, 99)**	Clinical **88% (8, 100)**	Vesikari≥11 **100% (45, 100)**
G4P8	Hosp/ED use **89% (52, 98)**	Clinical **VE not calc**	Vesikari≥11 **100% (65, 100)**
G9P8	Hosp/ED use **100 (67, 100)**	Clinical **91% (62, 99)**	Vesikari≥11 **95% (78, 99)**

Major Clinical Trials
Type specific vaccine efficacy

	RotaTeq REST	Rotarix 023 Latin Am	Rotarix 036 Europe
G2P4	Hosp/ED use **88% (<0, 98)**	Vesikari≥11 **45% (-81, 88)**	Vesikari≥11 **75% (-386, 100)**
	Any severity **63% (3, 88)**		
		To age 24m Clinical **39% (-112, 84)**	Through 2nd rota season Vesikari≥11 **86% (24, 99)**

Rotavirus Vaccines

	RV5 (RotaTeq)	RV1 (Rotarix)
Shedding of virus --Measured by Ag detection		7 Phase II/III studies 26-152 infants/study Post Dose 1 ~Day 7: 50 –80% ~Day 15: 19–64% ~Day 30: : 0–24% ~Day 60: 0–3% Post Dose 2 ~Day 7: 4–18% ~Day 15: 0–16% ~Day 30: : 0–1% ~Day 45: 0%

Rotavirus Vaccines

	RV5 (RotaTeq)	RV1 (Rotarix)
Shedding of virus --Live virus detection	1-2 Phase III studies ~100 infants/assessment Post Dose 1 Day 4-6: 13% Post Dose 2 Day 4-6: 0% Post Dose 3 Day 4-6: 0% Range of detection: Days 1 to 15 after a dose	2 Phase II studies Virus detected in ~46% of 46 antigen-positive stools Post Dose 1 (estimated) Day 7: 25%
	Transmission not studied	Transmission not studied

Rotavirus Vaccines

	RV5 (RotaTeq)	RV1 (Rotarix)
Data in premature infants		
--Safety	Post-hoc Gest age 25-36 weeks Serious adverse events studied in 1005 RV5 ; 1061 placebo Solicited adverse events studied in ~120 RV5 ; ~120 placebo	Post-hoc Gest age <37 weeks Serious adverse events studied in 134 RV1 ; 120 placebo
--Efficacy	Post-hoc Gest age <37 weeks Studied in 73 RV5 ; 78 placebo 764 RV5 ; 818 placebo	

Rotavirus Vaccines

	RV5 (RotaTeq)	RV1 (Rotarix)
Age of series completion	6 months	4 months
Vaccine delivery system	No latex	Contains latex

General Concepts of Main Proposed Recommendations

Proposed Recommendations
Routine Administration

- Safety and efficacy demonstrated for both RV5 and RV1 in clinical trials
- Vaccines differ in composition and schedule of administration
- No preference for RV5 or RV1

Proposed Recommendations

Overview of ages and intervals

	RV5 (RotaTeq)	RV1 (Rotarix)
Number of doses in series	3	2
Recommended ages for doses	2, 4 and 6 months	2 and 4 months
Minimum age for Dose 1	6 weeks	
Maximum age for Dose 1	14 weeks 6 days	
Minimum interval between doses	4 weeks	
Maximum age for last dose	8 months 0 days	

Proposed Recommendations

Ages in Trials vs. Proposed Recommendations

	RV5 (RotaTeq)	RV1 (Rotarix)
Minimum age for Dose 1	6 weeks	6 weeks
Maximum age for Dose 1	12 weeks 0 days **14 weeks 6 days**	LA: 12 weeks 6 days 1 country: 13 wks 6 days EU: 14 weeks 6 days **14 weeks 6 days**
Interval between doses	4–10 weeks **Min. interval : 4 weeks**	1–2 months **Min. interval: 4 weeks**
Maximum age for last dose	32 weeks 0 days **8 months 0 days**	24 weeks 6 days **8 months 0 days**

Proposed Recommendations
Interval between doses

	RV5 (RotaTeq)	RV1 (Rotarix)
Interval between doses	4–10 weeks **Min. interval : 4 weeks**	1–2 months **Min. interval : 4 weeks**

The minimum interval between doses of rotavirus vaccine is 4 weeks.

Proposed Recommendations
Interval between doses

	RV5 (RotaTeq)	RV1 (Rotarix)
Interval between doses	4–10 weeks **Min. interval : 4 weeks**	1–2 months **Min. interval : 4 weeks**

State minimum interval is 4 weeks

- For RV5
  - No change from way 2006 ACIP recommendation is likely interpreted "Subsequent doses should be administered at 4-10 week intervals…"
  - Data from limited number of infants in RotaTeq trial who received vaccine doses >10 weeks apart
- Harmonization of recommendations whenever reasonable is programmatically advantageous

Proposed Recommendations
Maximum age Dose 1

	RV5 (RotaTeq)	RV1 (Rotarix)
Maximum age for Dose 1	12 weeks 0 days **14 weeks 6 days**	LA: 12 weeks 6 days 1 country: 13 wks 6 days EU: 14 weeks 6 days **14 weeks 6 days**

The first dose of rotavirus vaccine should be administered from age 6 weeks through age 14 weeks 6 days. Vaccination should not be initiated for infants aged 15 weeks 0 days or older.

Proposed Recommendations
Maximum age Dose 1

	RV5 (RotaTeq)	RV1 (Rotarix)
Maximum age for Dose 1	12 weeks 0 days **14 weeks 6 days**	LA: 12 weeks 6 days 1 country: 13 wks 6 days EU: 14 weeks 6 days **14 weeks 6 days**

RV1: Used maximum age from European efficacy trial

- Limit on maximum age for Dose 1 impacts ultimate coverage with rotavirus vaccines

Proposed Recommendations
Maximum age Dose 1

	RV5 (RotaTeq)	RV1 (Rotarix)
Maximum age for Dose 1	12 weeks 0 days **14 weeks 6 days**	LA: 12 weeks 6 days 1 country: 13 wks 6 days EU: 14 weeks 6 days **14 weeks 6 days**

RV5: Expansion of maximum age for Dose 1 by 2 weeks from 2006 recommendation
("12 weeks"; likely interpretation 12 weeks 6 days)

- Available data (trial, U.S. post-marketing) do not indicate RV5 is associated with intussusception in the age groups recommended for vaccination.
  - No safety data (trial, post-marketing) for Dose 1 in infants much older than those covered in 2006 recommendation.
- Harmonization

Proposed Recommendations
Maximum age Last Dose

	RV5 (RotaTeq)	RV1 (Rotarix)
Maximum age for last dose	32 weeks 0 days **8 months 0 days**	24 weeks 6 days **8 months 0 days**

All doses of rotavirus vaccine should be administered by age 8 months 0 days.

Proposed Recommendations
Maximum age Last Dose

	RV5 (RotaTeq)	RV1 (Rotarix)
Maximum age for last dose	32 weeks 0 days **8 months 0 days**	24 weeks 6 days **8 months 0 days**

RV5: Expansion of maximum age for last dose by ~2 weeks from 2006 Recommendation

"32 weeks"; likely interpretation 32 weeks 6 days

8 months 0 days = ~34 weeks 6 days

- For providers, determining if infant is aged ≤8 months 0 days much simpler than determining if infant is aged ≤32 weeks.
- Available data (trial, U.S. post-marketing) do not indicate RV5 is associated with intussusception in the age groups recommended for vaccination.

Proposed Recommendations
Maximum age Last Dose

	RV5 (RotaTeq)	RV1 (Rotarix)
Maximum age for last dose	32 weeks 0 days **8 months 0 days**	24 weeks 6 days **8 months 0 days**

RV1: Expansion of maximum age for last dose by ~10 weeks, from that used in trials.

(8 months 0 days = ~34 weeks 6 days)

- Data from trial do not suggest RV1 is associated with intussusception in the age groups studied.
- Background rates of intussusception similar at ages 24−34 weeks.
- If mixed (or potentially mixed) series allowed and 3 doses recommended, 8 month age limit is practical.
- Harmonization

Proposed Recommendations

Interchangeability of products in vaccine series

Allowing “mixing” in series

- No data available or expected
- WG opinion: mixed series
  - Not expected to pose additional risk
  - May be more effective than incomplete series with one product
- Programmatic: practical requirement

Proposed Recommendations

Interchangeability of products in vaccine series

Give 3 doses of rotavirus vaccine if any dose in series was RV5 or product unknown

- No data available or expected
- Follows general concept of ACIP Hib vaccine recommendations for mixed series

Proposed Wording of Main Recommendations

Proposed Wording-1
Routine Administration

ACIP recommends routine vaccination of US infants with rotavirus vaccine. Two different rotavirus vaccine products are licensed for use in infants in the United States, RotaTeq (Merck) (RV5) and Rotarix (GSK) (RV1). The products differ in composition and schedule of administration. Rotavirus vaccine efficacy studies demonstrated 85%–98% protection against severe rotavirus disease and 72%–87% protection against any rotavirus disease (see pages xx). ACIP expresses no preference for RV5 or RV1.

Yellow text = wording change from 2006 ACIP recommendations

DISCUSSION

VOTE

Proposed Wording-2
Routine Administration

RV5 is to be administered orally in a 3-dose series with one dose at ages 2, 4, and 6 months. RV1 is to administered orally in a 2 dose series with one dose at ages 2 and 4 months (Table 8). The first dose of rotavirus vaccine should be administered from age 6 weeks through age 14 weeks 6 days; the maximum age for the first dose is 14 weeks 6 days. Vaccination should not be initiated for infants aged 15 weeks 0 days or older because of insufficient data on safety of the first dose of rotavirus vaccine in older infants. The minimum interval between doses is 4 weeks. All doses should be administered by age 8 months 0 days.

Proposed Wording-3
Routine Administration

Table 8

	RV5 (RotaTeq; Merck)	RV1 (Rotarix; GSK)
Number of doses in series	3	2
Recommended ages for doses	2, 4 and 6 months	2 and 4 months
Minimum age for Dose 1	6 weeks	
Maximum age for Dose 1	14 weeks 6 days	
Minimum interval between doses	4 weeks	
Maximum age for last dose	8 months 0 days	

Proposed Wording-4
Interchangeability of Rotavirus Vaccines

ACIP recommends that the rotavirus vaccine series be completed with the same product whenever possible. There are no studies that address the interchangeability of the two rotavirus vaccine products. However, there are no theoretical reasons to expect that risk of adverse events would be increased if the series contained more than one product, compared to risk of adverse events of a series containing only one product. Further, although it is possible that effectiveness of a series that contained both products could be reduced compared to a complete series with one product, the effectiveness of a series that contained both products may be greater than an incomplete series with one product. *cont'd*

Proposed Wording-5
Interchangeability of Rotavirus Vaccines *cont'd*

Therefore, ACIP recommends that vaccination not be deferred because the product used for previous doses is not available or is unknown. If the product used for a previous dose(s) is not available or is unknown, the provider should continue or complete the series with the product available.

If any dose in the series was RV5 or the vaccine product is unknown for any dose in the series, a total of three doses of rotavirus vaccine should be given. The minimum interval between rotavirus vaccine doses is 4 weeks. All doses should be given by age 8 months 0 days.

DISCUSSION

VOTE

General Concepts of Additional Proposed Recommendations

Proposed Recommendations

Contraindications

- History of severe allergic reaction after previous dose or to vaccine component
  (same as 2006 recommendation)

- Infants with severe (anaphylactic) allergy to latex should not receive RV1
  - RV5 may be preferred over RV1 for infants at high risk of acquiring latex allergy (e.g., infants with spina bifida or bladder exstrophy)

Proposed Recommendations
Simultaneous administration

	2006 recommendations	Changes in 2008 recommendations
Administration of rotavirus vaccine with other vaccines for infants	Can be administered with DTaP, Hib, IPV, Hep B and PCV7	No change State General Recs support administration of inactivated influenza vaccine

Proposed Recommendations

Precautions

	2006 recommendations	Changes in 2008 recommendations
Altered immunocompetence		
--General	Providers consider risks and benefits	Consultation also advised
--HIV-exposed/infected	Old wording in statement: data insufficient to support vaccination	Wording updated to that approved by ACIP, June 2007 (=support vaccination)

Proposed Recommendations

Precautions

	2006 recommendations	Changes in 2008 recommendations
Acute gastroenteritis	Moderate to severe GE: defer until improved Mild GE: OK to vaccinate	No change No change
Moderate-to-severe acute illness	Defer until recovery from acute phase	No change
Pre-existing chronic gastrointestinal diseases	Benefits>risks	No change
Previous history of intussusception	Providers consider risks and benefits	No change

Proposed Recommendations
Special situations

	2006 recommendations	Changes in 2008 recommendations
Premature infants	Providers consider benefits and risks; Benefits>risks	Benefits>risks
	ACIP supports vaccination if clinically well and discharged from hospital	No change
		Rationale provided for not vaccinating in NICU, nursery

Proposed Recommendations

Special situations

	2006 recommendations	Changes in 2008 recommendations
Infants in household with immuncompromised person	Can be vaccinated	No change States shedding more common and lasts longer after RV1 than after RV5
Infants in household with pregnant woman	Can be vaccinated	No change from intent (wording now….. should be vaccinated like other infants)

Proposed Recommendations

Special situations

	2006 recommendations	Changes in 2008 recommendations
Regurgitation of vaccine	Do not readminister dose	No change
Hospitalization after vaccination	Follow universal precautions	No change
Recent receipt of antibody-containing product	Defer vaccination for 42 days, if possible	Administer vaccine at any time Rationale provided

THANK YOU

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