VICP Clinical Update

Advisory Commission on Childhood Vaccines 12-2011

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Outline

- Medical Reviews/Analysis: 4th Q FY2011 – will do next time
- IOM Report on Adverse Effects of Vaccines and Update on changes to the Vaccine Injury Table (VIT)
- Rotavirus vaccines (RV) & Intussusception: Proposal for changes to the VIT
  - **Anna Jacobs, Esq. Office of General Counsel, HHS**
  - **Mary N. Rubin, M.D., Medical Officer (pediatrics), DVIC**

IOM Vaccine-AE Review History

- Charge to IOM 4/2009: Independent Review of the current epidemiological, clinical, and biologic literature
  - Frameworks for categorizing the evidence of causality
  - Describe the strength of evidence regarding biological mechanisms underlying theories when evidence is not enough for causal conclusions
  - Develop a report on the evidence regarding AEs associated with vaccines

- Additional Funding through ARRA/ISO/CDC September 2009 allowing addition of 4 more vaccines for review.

- The Final Report Released 8/25/11 followed by various briefings by the IOM Committee including presentation to the ACCV at our September Meeting by the Committee Chair.

IOM Vaccine-AE Review

- Vaccines Reviewed: Committee reviewed 8 vaccines, which constitute 12 of 16 vaccine combinations found in 92% of VICP claims
  - influenza (TIV, LAIV) *(H1N1 not included since charge was given prior to the Pandemic)*
  - hepatitis A (HAV) and hepatitis B(HBV),
  - human papillomavirus (HPV)
  - measles/mumps/rubella (MMR)
  - meningococcal (MCV4, MPSV4)
  - tetanus-containing (Tdap, Td, T, DTaP)
  - varicella virus (VZV, MMRV)

- Adverse Events (AEs) Reviewed: Working List of adverse events generated by DVIC medical staff based on the alleged injury petitions to VICP and current science with public input. The IOM Committee added 10 adverse events. The final Working List constituted 76 different AEs and 157 AE-vaccine combinations.

- Causality Framework: For each AE-vaccine relationship, IOM used 3 prongs and analyzed information from already published literature only.

1. Weight-of-Epidemiologic Evidence (4 levels – high, moderate, limited, and insufficient)
2. Weight-of-Mechanistic Evidence (4 levels – strong, intermediate, weak, lacking).
3. Causality Assessment: overall assessment taking 1 and 2 in combination.

- Causality Conclusions: FOUR Categories of Causation Evidence. Conclusions were consistent with literature, no surprises.

1. Convincingly Supports A Causal Relationship (14 AE-vaccine relationships)
2. Favors Acceptance of a Causal Relationship (4 AE-vaccine relationships)
3. Inadequate to Accept or Reject a Causal Relationship (134 AE-vaccine relationships)
4. Favors Rejection of a Causal Relationship (5 AE-vaccine relationships)

- Currently, this report is under HHS review via a public health task force (ISO- CDC, OGC and DVIC reviewers in 9 working groups)
- Our goal is for March 2012 ACCV Meeting - bring initial proposals for VIT update on 8 vaccines and the general category of injection-related injuries

Rotavirus Vaccines (RV) & Intussusception (IS)

- While IOM Review follow-up deliberations are on-going, we continue to monitor other vaccine AEs which may be a potential for VIT updates. Example - recent post-marketing surveillance publications on the second generation RVs and IS
- We established a separate RV Working Group (RVWG) - comprehensive review on the topic for possible proposal to update VIT
- RV- IS issues presented to ACCV as part of VICP clinical update in March 2011 and in September ACCV, there was an in-depth clinical presentation on this topic by Dr. Candice Smith
- Today (December 2011), RVWG team to present RVWG's proposed draft regulation to receive ACCV's comments and recommendation

RVWG Proposal to update the Vaccine Injury Table

Members

- Catherine Shaer, M.D.
- Mary Rubin, M.D.
- Candice Smith, M.D.
- Anna Jacobs, Esq.
- Rosemary Johann-Liang, M.D.

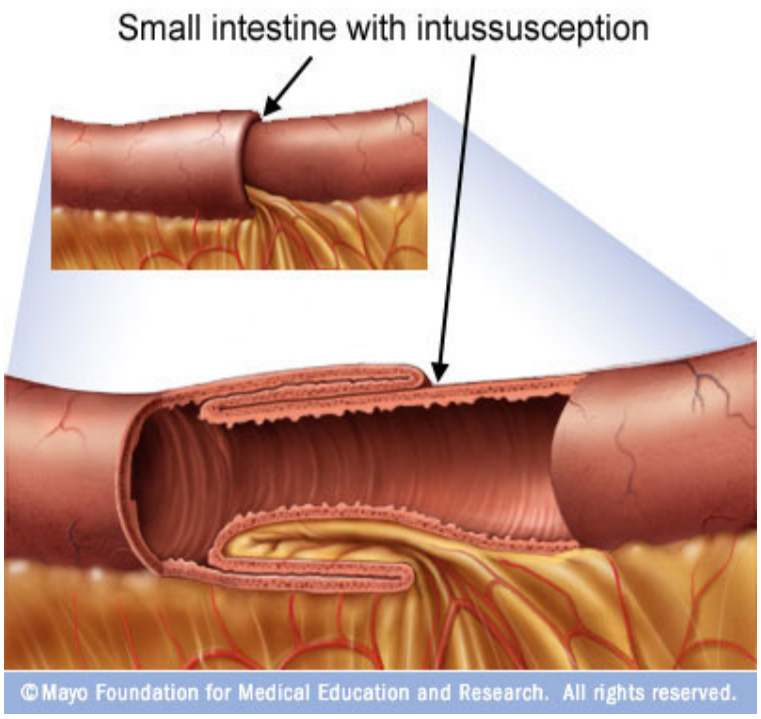
Outline

- RV and previous VIT legal history, ACCV "Guiding Principles" (AJ)
- Current published data on second generation RVs – summary caption September ACCV presentation (RJL)
- On-going study, proposed changes to VIT (MR)
- Summary/Presentation for ACCV (RJL)

Rotavirus Disease

- Rotavirus is the most common cause of acute, severe gastroenteritis
- May result in severe dehydrating diarrhea with fever and vomiting
- Virtually all children get rotavirus by age 5
- In developing nations, accounts for 500,000 deaths per year
- In U.S. caused 300,000 ER/Doctor visits each year and 50,000 hospitalizations

IS Characteristics



- Etiology not well defined
- Uncommon: Incidence ~1400 children each year in U.S.
- Most common reason for bowel obstruction in the first year
- Usually between 4 and 10 months of age
- Low incidence the first two months of life
- Peak risk 26-29 weeks old
- More common in males, Hispanics, African Americans

Naturally-occurring IS

- Intussusception incidence varies by region, more frequently in the West and Northeast than in the South and Midwest
- Associated with anatomic defects, multiple different infections
- Treated with contrast (barium) enema to reduce intussusceptions or surgical intervention (50/50)
- The need for surgery is a result of the time elapsed since the onset of symptoms. The need for surgery for successful reduction increases greatly if >5 hrs has elapsed.
- Morbidity and mortality low in U.S. (hospitalization usually 1-2 days)
- Recurrences do happen (10% of cases)

(AJ)

Vaccine Injury Table

- To qualify as a Table Injury, Petitioner must demonstrate:
  - Received a vaccine set forth in the Table
  - Sustained, or had significantly aggravated, any illness, disability, injury or condition set forth in the Table in association with the vaccine received, or died from the administration of the vaccine
  - First symptom or manifestation of the onset or of the significant aggravation of any such illness, disability, injury, or condition or the death occurred within the time period after vaccine administration set forth in the Table

42 U.S.C. § 300aa-11(c)(1)

Vaccine Injury Table

- "Qualifications and Aids to Interpretation" (QAI) define the injuries listed on the Table
  - "The following qualifications and aids to interpretation shall apply to the Vaccine Injury Table"

42 U.S.C. § 300aa-14(b), 42 C.F.R. § 100.3(b)

Regulatory Table Revisions

- By regulation, the Secretary may modify the Table
  - Add to or delete from the list of injuries, disabilities, illnesses, conditions, and deaths for which compensation may be provided
  - May change the time periods for the first symptom or manifestation of the onset or the significant aggravation of any Table injury or death

42 U.S.C. § 300aa-14(c)

- Regulatory table found at 42 C.F.R. § 100.3(a)

Regulatory Table Revisions

- Any modification of the Table shall apply only with respect to petitions for compensation filed after the effective date of the regulation.

  42 U.S.C. § 300aa-14(c)(4)

Regulatory Table Revisions

- Secretary may not propose a regulation to modify the Table unless
  - Secretary has first provided to the Advisory Commission on Childhood Vaccines (ACCV) a copy of the proposed regulation
  - Requested recommendations and comments by the ACCV
  - Afforded the ACCV at least 90 days to make such recommendations.

42 U.S.C. § 300aa-14(c)

Regulatory Table Revisions

- Statutory standard for adding vaccines:
  - When CDC recommends a vaccine for routine administration to children, the Secretary shall, within 2 years, amend Table to include such recommended vaccine

  42 U.S.C. § 300aa-14(e)(2)

- No statutory standard for adding or removing injuries.

ACCV Guiding Principles

- In 2006, the ACCV developed “Guiding Principles” for recommending revisions to the Table.
- The Table should be scientifically and medically credible
- Where there is credible scientific and medical evidence both to support and to reject a proposed change to the Table, the change should, whenever possible, be made to the benefit of petitioners

ACCV Guiding Principles

- Guidelines for what is “scientifically and medically credible”
  - If IOM study: conclusions of the IOM should be deemed credible but should not limit the deliberations of the ACCV.
  - For data sources other than IOM report, assess the relative strength. Also assess consistency if there is no IOM report. Consistency across multiple sources of evidence is an indication of credibility.

ACCV Guiding Principles

- Hierarchy of data sources (strongest to weakest)
  - Clinical laboratory data
  - Challenge/re-challenge data involving non-relapsing symptoms or diseases
  - Controlled clinical trials
  - Controlled observational studies (e.g., cohort and case control studies), including but not limited to studies based upon data from the Vaccine Safety Data link (VSD) database
  - Uncontrolled observational studies (e.g., ecological studies)
  - Case series
  - Data from passive surveillance systems, including but not limited to the Vaccine Adverse Event Reporting System (VAERS)
  - Case reports
  - Editorial articles on scientific presentations
  - Non-peer reviewed publications

ACCV Guiding Principles

- Additional factors that affect the relative strength of evidence (*e.g.*):
  - Methodological limitations
  - Potential bias
  - Potential confounding factors
  - Biologic coherence

- ACCV should request assistance from Division of Vaccine Injury Compensation in assessing the relative strength of evidence.

ACCV Guiding Principles

- Remain aware of policy considerations underlying the Table.
  - Awards to vaccine-injured persons are to be made quickly, easily, and with certainty and generosity.
  - Congress intended to compensate serious injuries
- If there is a split in credible scientific evidence, ACCV members should tend toward adding or retaining the proposed injury.

History of Rotavirus in the VICP

- August 31, 1998: FDA licensed live, oral, rhesus-based rotavirus vaccine ("Rota shield"), the only U.S.-licensed rotavirus vaccine on the market at that time.

- October 22, 1998: General category of Rotavirus vaccine added to Table. No condition specified.

- VAERS received reports of intussusceptions in infants receiving Rota shield after first dose.

History of Rotavirus in the VICP

- July 16, 1999: CDC recommended that health care providers and parents suspend use of Rota shield.
- CDC conducted epidemiological studies to determine association.
- Manufacturer voluntarily ceased further distribution of Rota shield.
- October 15, 1999: Manufacturer voluntarily withdrew the vaccine from the market and requested immediate return of all doses.

History of Rotavirus in the VICP

- October 22, 1999: ACIP reviewed data and concluded that intussusceptions occurs with significantly increased frequency in the first 14 days following administration of Rota shield. Withdrew its recommendation for use of Rota shield in infants.

- November 5, 1999: CDC adopted and published ACIP's decision in MMWR.

History of Rotavirus in the VICP

- July 13, 2001: Secretary published Notice of Proposed Rule Making.
  - Announced findings that intussusceptions could reasonably be determined in some circumstances to be caused by vaccines containing live, oral, rhesus-based rotavirus (Rota shield).
  - Proposed to amend the Table by adding:
    - Vaccines containing live, oral, rhesus-based rotavirus as a distinct category
    - Intussusception as covered injury
    - Time frame of 30 days

History of Rotavirus in the VICP

- July 25, 2002: Secretary published final rule adopting proposal
- August 26, 2002: final rule effective
- Revised Table:
  - Contained general category of rotavirus vaccines, with no associated injury.
  - Contained specific category of vaccines containing live, oral, rhesus-based rotavirus, with associated injury of intussusceptions, timeframe of 0-30 days.
    - Only applied to vaccines administered on or before August 26, 2002 (vaccine no longer administered after 1999)

History of Rotavirus in the VICP

- October 9, 2008: Secretary removed the specific category of vaccines containing live, oral, rhesus-based rotavirus from Table.
  - Rota shield was removed from the market on October 15, 1999. ACIP withdrew recommendation to use Rota shield on October 22, 1999.
  - Any claims could only have been for injuries sustained from vaccines administered before late 1999.
  - Statute of Limitations:
    - In the case of a Table revision, for injuries occurring before revision (August 26, 2002), 2 years to file, so long as the onset of injury or death occurred within 8 years preceding revision.

History of Rotavirus in the VICP

- If date of Table revision = August 26, 2002
- Then filing deadline = August 26, 2004
- Onset of injury or death must have occurred between August 26, 1994 and August 26, 2002.

History of Rotavirus in the VICP

- By October 9, 2008, the Secretary believed that any potential Table claim under the specific rotavirus category would have been time barred.

- Kept general rotavirus vaccine category, but removed live, oral, rhesus-based rotavirus vaccine category.

RV Update (3/2011 ACCV)

Rotary (RV1) data presented at ACIP 10/2010	Rotate (RV5) data presented at ACIP 10/2010
Live, attenuated derived from human strain, oral, 2-dose, initial license 2004, now in 100+ countries, FDA approval 2008. Close to 80 million worldwide but only ~3 million in US	Live, attenuated pentavalent vaccine - 5 re-assorted human & bovine rotaviruses , oral, 3-dose, FDA approval 2006, Majority ~34 million of ~40 million doses worldwide distributed in US
Prelicensure study: Rota 023 (n=31,673 Rotary vs. 31,552 placebo) : No increased risk of IS.	**Prelicensure study:** (n=72,324 total in 3 placebo-controlled trials): No increased risk of IS
Postmarketing: 1) Passive surveillance: VAERS – reports 2) US active surveillance: Vaccine Safety Data link (VSD) – unable to determine 3) GSK active surveillance: Mexico PASS (~1 million infants under surveillance over 2 year period) – interim study results suggest an increased risk of IS in the 31-day period following administration of the first dose of ROTARIX with RR:1.8 (99% CI 1.0, 3.1) 4) CDC active surveillance: Similar results as PASS in Mexico, but no increase in incidence ratio for IS in Brazil study 5) Australia surveillance (against expected IS# from historical control by region): no SS increase	**Postmarketing:** 1) Passive surveillance: VAERS – clustering of reports after Dose 1 2) Merck – observational study of 85,000 RV5 recipients - no SS increase 3) US Active surveillance: VSD (presented at ACIP 10/2010) Data through 5/31/2010, 21 cases but not chart confirmed. Total exposed 850,000 so limited power to detect small risk (RR <4). US experience – no evidence thus far of increased IS 4) Australia surveillance (against expected IS# from historical control by region): increased RR 1 – 7 days post dose 1 (age1 - <3 months, total exposed n=~110,000) – RR of 5.36 (95% CI 1.1, 15.4)
Labeling at time of FDA approval: Reports of IS cases have been made to VAERS. Changes to Labeling 9/2010 to Warnings and Precautions. PASS Final Report Due 2011	**Labeling** at time of FDA approval: Reports of IS cases have been made to VAERS. No recent labeling changes. VSD study on-going

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Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil

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ABSTRACT

BACKGROUND

Because postlicensure surveillance determined that a previous rotavirus vaccine, RotaShield, caused intussusception in 1 of every 10,000 recipients, we assessed the association of the new monovalent rotavirus vaccine (RV1) with intussusception after routine immunization of infants in Mexico and Brazil.

METHODS

We used case-series and case–control methods to assess the association between RV1 and intussusception. Infants with intussusception were identified through active surveillance at 69 hospitals (16 in Mexico and 53 in Brazil), and age-matched infants from the same neighborhood were enrolled as controls. Vaccination dates were verified by a review of vaccination cards or clinic records.

RESULTS

We enrolled 615 case patients (285 in Mexico and 330 in Brazil) and 2050 controls. An increased risk of intussusception 1 to 7 days after the first dose of RV1 was identified among infants in Mexico with the use of both the case-series method (incidence ratio, 5.3; 95% confidence interval [CI], 3.0 to 9.3) and the case–control method (odds ratio, 5.8; 95% CI, 2.6 to 13.0). No significant risk was found after the first dose among infants in Brazil, but an increased risk, albeit smaller than that seen after the first dose in Mexico — an increase by a factor of 1.9 to 2.6 — was seen 1 to 7 days after the second dose. A combined annual excess of 96 cases of intussusception in Mexico (approximately 1 per 51,000 infants) and in Brazil (approximately 1 per 68,000 infants) and of 5 deaths due to intussusception was attributable to RV1. However, RV1 prevented approximately 80,000 hospitalizations and 1500 deaths from diarrhea each year in these two countries.

CONCLUSIONS

RV1 was associated with a short-term risk of intussusception in approximately 1 of every 51,000 to 68,000 vaccinated infants. The absolute number of deaths and hospitalizations averted because of vaccination far exceeded the number of intussusception cases that may have been associated with vaccination. (Funded in part by the GAVI Alliance and the U.S. Department of Health and Human Services.)

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EDITORIAL

Rotavirus Vaccination and Intussusception — Act Two

Harry B. Greenberg, M.D.

The development of vaccines has been a triumph of modern medicine.[1] In addition to the eradication of smallpox and the near-eradication of polio, the past 30 years has seen an impressive decline in many vaccine-preventable diseases, including measles, hepatitis B virus, serious pneumococcal infection, hemophilus influenza, and, recently, rotavirus. Vaccination has been an enormously powerful force for health improvement because of the large societal benefits provided with remarkably small risks. However, some have expressed worry that current vaccines are dangerous and represent a considerable threat to the health of the recipients.[2] These concerns often do not include an analysis of the benefits as well as the risks of a given vaccine.

Rotavirus infection is the most important cause of severe diarrheal disease in young children. In less-developed countries, rotavirus accounts for more than 500,000 childhood deaths annually; in developed countries, rotavirus is an infrequent cause of death but a common cause of hospitalizations and outpatient visits. RotaShield, a rotavirus vaccine composed of four human×simian reassortants (RV4), was recommended for universal pediatric use in the United States in 1998. Within a year, after the vaccine had been given to more than 500,000 children, it was found to cause a transient increased risk of intussusception (estimated to occur in 1 child in 10,000) in the first 10 days after the initial vaccination. It was rapidly withdrawn from the market before there was an opportunity for a detailed public discussion of the risks and benefits surrounding its use.[3]

Two second-generation rotavirus vaccine candidates (one composed of five human×animal reassortants [RV5] and the other a monovalent attenuated human rotavirus vaccine [RV1]) were in development in 1999 and, after 7 additional years of study, were licensed in the United States and other countries. Both second-generation vaccines are efficacious, and both underwent extensive safety trials (together involving more than 130,000 subjects); no association with intussusception was detected in these trials.[4] In the 4 years since RV1 and RV5 were licensed, we have witnessed a substantial reduction in the rates of hospitalization and death from rotavirus in both developed and less-developed countries.[5] As part of the postlicensure safety follow-up, the possible effect of the widespread use of RV1 and RV5 on intussusception rates has been monitored in the United States and abroad. In this issue of the *Journal*, Patel et al.[6] report the results of safety assessments of RV1 in Mexico and Brazil.

RV1 was found to be associated with a small excess risk of intussusception (approximately 1 in 51,000 vaccinated children) in Mexico in the first week after the initial vaccination. The timing of the excess risk is similar to that originally seen with RV4 and corresponds to the peak timing of vaccine replication. A smaller excess risk was observed after the second RV1 dose, but this occurred during the second and third week after vaccination and its significance is unclear. Interestingly, in Brazilian children receiving RV1, a smaller excess risk of intussusception was observed (approximately 1 in 68,000 vaccinated children) and then only in the first week after the second dose. The reasons for these differences in timing and rate are not clear but might include the fact that in Brazil, but not in Mexico, the first dose of RV1 was administered with the oral poliovirus vaccine, which suppresses rotavirus vaccine replication. Recent preliminary studies from Australia also suggest a link between RV5 and intussusception.[7] Hence, we can infer from these studies that any orally administered live rotavirus vaccines will probably carry some detectable risk of intussusception, that the risks

RV Further Update

Rotary (RV1)	Rotate (RV5)
Live, attenuated derived from human strain, oral, 2-dose, initial license 2004, now in 100+ countries, FDA approval 2008. Worldwide market with small distribution in US.	Live, attenuated pentavalent vaccine - 5 re-assorted human & bovine rotaviruses , oral, 3-dose, FDA approval 2006, Majority are distributed in US.
Postmarketing: 1) Passive surveillance: VAERS – reports 2) US active surveillance: Vaccine Safety Data link (VSD) – unable to determine 3) GSK active surveillance: Mexico PASS (~1 million infants under surveillance over 2 year period) – interim study results suggest an increased risk of IS in the 31-day period following administration **of the first dose of ROTARIX with RR:1.8 (99% CI 1.0, 3.1)** 4) CDC active surveillance: Similar results as PASS in Mexico, but no increase in incidence ratio for IS in Brazil study Patel et al 2011 *(NEJM):* **Mexico: Incidence rate of 5.3** (3 – 9.3) **1 – 7 days after dose 1, not after dose 2**; **Brazil – Incidence rate of 2.6 (1.3-5.2) 1 – 7 days after dose 2, but not after dose 1.** 5) Australia surveillance (against expected IS# from historical control by region): **RR 1 – 7 days post dose 1 = 3.45 (0.7 – 10)**. **Not after 2nd dose.**	**Postmarketing:** 1) Passive surveillance: VAERS – clustering of reports after Dose 1 2) Merck – observational study of 85,000 RV5 recipients - no SS increase 3) US Active surveillance: VSD (presented at ACIP 10/2010) Data through 5/31/2010, 21 cases but not chart confirmed. Total exposed 850,000 so limited power to detect small risk (RR <4). US experience – no evidence thus far of increased IS. Final Publication Pending. *4) Buttery et al 2011 (Vaccine* journal): Australia surveillance (against expected IS# from historical control by region): increased **RR 1 – 7 days post dose 1 only** (age1 - <3 months, total exposed n=~110,000) – RR of 5.36 (95% CI 1.1, 15.4). **No increased RR with 2nd dose and decrease from expected case after 3rd dose.** 5) New study started for US data – Dr. Rubin to discuss

(MR)

Ongoing study

- FDA's Mini-Sentinel Post-Licensure Rapid Immunizations Safety Monitoring (PRISM) program
  - "Monitoring for intussusceptions after two rotavirus vaccines by the PRISM program" (Yih K et al)
  - Assess the risk of intussusceptions
  - RotaTeq and Rotary vaccines

Rotavirus PRISM study

- Protocol:

http://www.mini-sentinel.org/work_products/PRISM/Mini-Sentinel_PRISM_Rotavirus-Protocol.pdf

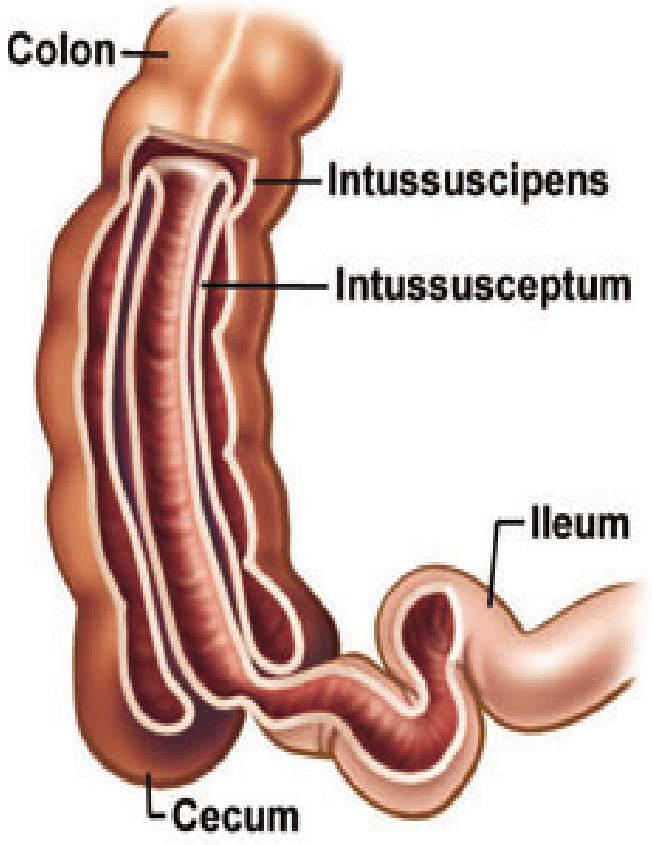
  - Method: self-controlled, case-centered and sequential methods
  - Population: Estimated 1 million infants
  - Study period: January 2004 – 2011
  - Results: Late 2012

Proposed Changes to the VIT

- Vaccine: Vaccines containing rotavirus
- Injury: Intussusception
- Time period: 0 – 21 days
  - publications show 1 – 7 days window
  - Proposing 0 – 21 days to be consistent with Guiding Principles.

  (Rota shield IS data showed 1 – 14 days window. VIT listed 0 – 30 days for that RV)

Qualifications and Aids to Interpretation (QAI)



Definition

- Invagination (telescoping)of the proximal segment into the distal segment
- Results in obstruction of the bowel passage, constriction of the mesentery and obstruction of the venous blood flow
- Characterized by sudden onset of colicky abdominal pain

42 CFR § 100.3

§ 100.3 Vaccine Injury Table.

(a) * * *

Vaccine Injury Table

Vaccine	Illness, disability, injury or condition covered	Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration
	* * * * * * *	
XI. Vaccines containing rotavirus	Intussusception	0 - 21 days.
	* * * * * * *	

QAI: Qualifications

- Intussusception occurs after the 1st or 2nd dose

- Absence of unrelated factors

QAI: Alternate Factors

- Infectious diseases
- Lead points
- Anatomic abnormalities
- Underlying conditions or systemic diseases

Literature Review and References (Credits: Dr. Chris Liacouras, Pediatric Gastroenterologist, Children's Hospital of Philadelphia)

Alternate Factors: Infectious Diseases

- Viral diseases
- Bacterial enteritis
- Enteric parasitic diseases

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Ramdial PK, Sing Y, Hadley GP, Chotey NA, Mahlakwane MS, Singh B. Paediatric intussusceptions caused by acquired immunodeficiency syndrome-associated Kaposi sarcoma. Pediatr Surg Int. 2010 Aug;26(8):783-7. Epub 2010 Jun 10.

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Nikolić H, Palčevski G, Saina G, Peršić M. Chronic intussusceptions in children caused by Ascaris lumbricoides.Wien Klin Wochenschr. 2011 May;123(9-10):294-6. Epub 2011 Apr 19.

Alternate Factor: Lead Points

- Intestinal masses
- Cystic structures
- Increased lymphoid tissue

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Draus JM Jr, Shelgikar CS, Buchino JJ, Bond SJ. Lipoma as a pathological lead point in a child with ileocolic intussusceptions. J Pediatr Gastroenterol Nutr. 2008 Sep;47(3):372-4

Woodruff SA, Sokol RJ. Colonic polyp as lead point for intussusceptions. J Pediatr Gastroenterol Nutr. 2007 Sep;45(3):279-80

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Alternate Factor: Bowel Abnormalities

- Congenital anatomic abnormalities
- Post – surgical changes
- Blood vessel abnormalities

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Alternate Factor: Underlying Conditions

- Inflammatory Bowel Disease
- Intestinal inflammation
- Tissue and small vessel edema
- Cystic Fibrosis
- Celiac disease

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VIT Qualifications and Aids to Interpretation

•* * (3) *Intussusception.* (i) For purposes of paragraph (a) of this section, intussusceptions means the invagination of a segment of intestine into the next segment of intestine, resulting in bowel obstruction, diminished arterial blood supply and blockage of the venous blood flow, which is characterized by a sudden onset of abdominal pain.

(ii) For purposes of paragraph (a) of this section, the following shall not be considered to be a condition set forth in the Table:

•Onset that occurs after the third dose of a vaccine containing rotavirus;
•Onset within one month after an infectious disease, including viral disease (such as those secondary to non-enteric or enteric adenovirus), bacterial enteritis (such as those with *Campylobacter jejuni* or *Salmonella typhi*), or enteric parasitic disease (such as from *Ascaris lumbricoides*) without regard to whether the organism of the infectious disease is known;
•Onset in a person with a pre-existing condition which causes lead points for intussusceptions such as intestinal masses and cystic structures (e.g., polyps, tumors, Meckel's diverticulum, lymphoma, or duplication cysts);
•Onset in a person with abnormalities of the bowel, including congenital anatomic abnormalities, anatomic changes after abdominal surgery, and other anatomic bowel abnormalities caused by mucosal hemorrhage, trauma, or abnormal intestinal blood vessels (such as Henoch Scholein purpura, hematoma or hemangioma); or
•Onset in a person with underlying conditions or systemic diseases associated with intussusceptions (such as cystic fibrosis, celiac disease, or Kawasaki disease).

(RJL)

Up-to-date analyses of VICP claims

- Data up to end of FY2011
  - 15 RotaTeq*/IS Claims reviewed
  - 11 males; 4 females
  - Age range 8 – 31 weeks
  - 5 after dose 1 only (onset 3-60 days); 5 after dose 2 (onset 3-64 days); 5 after dose 3 (onset 2–68 days)
  - 80% had surgical intervention (not just barium enema)
  - 53% had alternative factors (i.e. congenital malrotation)

** RotaTeq is the rotavirus vaccine mainly distributed in US up to now . As per CDC, Rotarix use will increase in the US.*

Summary

- Some, but not all, studies suggest a possible, very low risk of intussusceptions caused by the second generation rotavirus vaccines (mainly in Rotary studies and **after the first dose within the 1 – 7 days** post window).

- The level of risk observed in these studies is substantially lower than the risk of 1 case/5000-10,000 infants who received Rota shield vaccine and is probably closer to 1 case additional per 100,000 infants.

- The benefits outweigh any risk. Vaccines do prevent more than 50,000 hospitalizations and hundreds of thousands of office visits from the dehydration due to rotavirus disease in the United States.

Summary Continued

- Given the background of Rota shield and IS experience, given the new IS information in the literature regarding Rotary and RotaTeq, and given the guidance of the “Guiding Principles”, DVIC is pro-actively presenting a proposal to add IS to the VIT.
- Keep in mind however that there is an on-going US study which may give us more definitive answers (or not) end of next couple of years.
- As the statute requires, we have presented ACCV with a hard copy of the proposed regulation changes.
- We ask for ACCV recommendation with the following choices.

ACCV Recommendation Choices

1. ACCV concurs with the proposed amendment to the VIT and would like to move forward

2. ACCV does not concur with the proposed amendment to the VIT and would not like to move forward

3. ACCV would like to review the proposal further and not make a recommendation at this time but make a recommendation at a later ACCV meeting

4. ACCV would recommend that HHS wait for additional information from the US-PRISM study before making proposed revisions

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