Intussusception in Asia
What is known?

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Rotashield  Rotavirus Vaccine

• Human rhesus tetravalent re-assortant (RRV-TV)
• 1998 licensed in the U.S.
• National immunization Program was suspended in June 1999
• >500,000 infants of 3.8-4 million birth cohort had received at least one dose of vaccine
• Voluntarily withdrawn by manufacturer October 1999
• IS risk was estimated at 1 in 10,000 to 30,000 vaccinees
Implications for development of other rotavirus vaccine candidates and for vaccine implementation strategies

Clinical trials
- Size of trial >60,000 infants to identified a risk of <1 in 30,000
- Baseline incidence of intussusception in the region
- Development of a surveillance system for the early detection of intussusception

*Large pre-licensure clinical trials of Rotarix (RRV1 - GSK) and RotaTeq (RRV 5- Merck) showed NO association with Intussusception*

Preparation for introduction of rotavirus vaccines
- Recommendations for timing of routine immunisation and catch-up immunisation
- Strengthening/development of Post-marketing Surveillance Systems
Post-licensure data from “early introducer” countries

• USA
  • Vaccine Safety Datalink (VSD)
    – Collaboration between CDC and 8 managed care organizations (3% US pop)
    – 786,725 total doses of RV5 (including >300,000 first doses) – No association with increased incidence of IS
    – Unable to rule out a risk of 1-2 in 100,000
    – (Shui, et al; 2012)
  • Hospital discharge data
    – No detectable increase in hospital discharges for US infants after 2006
    – (Zickafoose et al; 2012)
  • Vaccine Adverse Events Reporting System (VAERS)
    Difficult to interpret due to limited data on the doses of vaccine delivered and ascertainment of IS cases incomplete
  • Manufacturer sponsored study using a large claims database:
    – No association observed (Rotateq) but unable to detect a low level of risk
    – (Mast C. Advisory Committee on Immunization Practices Meeting October 2010)

• Europe
• Brazil
• Mexico
• Australia
Post-licensure data from “early introducer” countries

- USA
- Europe
  - Manufacturer sponsored study
    - Increase in IS cases in vaccinated infants (RV1) compared with expected baseline incidence
    - 29 cases vs 3-11.2 expected within 7 days dose 1
      (Benninghoff B. 9th International Rotavirus Symposium 2010)
- Brazil
- Mexico
- Australia
Post-licensure data from “early introducer” countries

- USA
- Europe
- Brazil
  - Self controlled case series and case-control study
    - active sentinel site surveillance and age/neighborhood matched controls
    - No increase in IS observed following first dose of RV1
    - Increased risk of 1 in 76,000 vaccinated infants 1-7 days following second dose of RV1
    - Evidence of benefit of vaccination – hospitalizations/deaths
    - ?role of co-administration with OPV
      - (Patel M et al NEJM 2011)
- Mexico
- Australia
Post-licensure data from “early introducer” countries

- **Mexico**
  - Self controlled case series and case-control study
    - active sentinel site surveillance and age/neighborhood matched controls
    - Increased risk of ~1 in 52,000 vaccinated infants in 1-7 days post-dose 1 RV1
    - Evidence of benefit of vaccination – hospitalizations/deaths
    - Mexico and Brazil combined data
      » an additional ~100 cases due to vaccination
      » Prevention of 80,000 hospitalisations, 1,300 deaths/year
      *Patel M et al NEJM 2011*
  
- **PASS (post-marketing active surveillance study)**
  - Mexican Institute of Social Security and manufacturer sponsored (GSK)
  - Interim analysis suggests a clustering of IS cases following dose 1 RV1, analysis continuing
  - (Colindres R. Advisory Committee on Immunization practices Meeting 2010)
Post-licensure data from “early introducer” countries

- **Australia**

  PAEDS (Paediatric Active Enhanced Disease Surveillance) and APSU (Australian Paediatric Surveillance Network) Intussusception Study

  - **Active surveillance** (*July 2007 – December 2008*)
    - Increase IS observed vs baseline following dose 1
    - RV1  
      - Dose 1: 1-7 d  
        - RR 3.5 (0.7, 10.1)
    - RV5  
      - Dose 1: 1-7 d  
        - RR 5.3 (1.1, 15.4)
      - Dose 1: 1-21 d  
        - RR 3.5 (1.3, 7.6)

  (Buttery J, Danchin M et al, Vaccine 2011)

  - **Self controlled case series n= 274 IS cases** (*July 2007- December 2009*)
    - RV1  
      - Dose 1: 1-7 d  
        - RI 3.89 (1.53, 9.89)  
        - p.004
      - Dose 2: 1-7 d  
        - RI 2.98 (1.41, 6.32)  
        - p.004
    - RV5  
      - Dose 1: 1-7 d  
        - RI 4.12 (1.26, 13.48)  
        - p.02
      - Dose 1: 8-21 d  
        - RI 3.60 (1.53, 8.50)  
        - p.003

  1 -2 per 100,000 additional cases in post-vaccination risk window

  (www.tga.gov.au)
How do we interpret this data?

- A small risk of intussusception (~1-2 per 100,000 vaccinated infants) detected in some settings
- Identified following dose 1 of both currently licensed vaccines
- Increased risk noted in the immediate post-vaccination risk window
- Is there still an increased risk at 2 years of age?
- Level of risk is significantly lower than that observed with Rotashield
- The benefits of vaccinated has been considered to outweigh the risk of IS
- What will the risk of IS following vaccination be increased in populations with a high baseline risk of IS? (Vietnam, China) or in countries where there is no/minimal baseline IS data
- What factors may increase or decrease the risk of IS? (OPV)
Clinical features of intussusception reflect the pathophysiology

1. Abdominal or rectal mass
2. Blood in the stool
3. Abdominal pain
4. Intestinal obstruction
5. Vomiting
6. Lethargy, pallor
7. Irritability
8. Shock
Transient, asymptomatic intussusception

- Momentary dysrhythmic contractions resulting in a function abnormality of peristaltic activity
- Frequency underestimated
- Incidentally noted at:
  - surgery
  - endoscopy
  - ultrasound
- Distinguishing features:
  - no lead point
  - normal wall thickness
  - < 3.5 cm length
  - non-dilated proximal segment
  - normal vascularity on color Doppler
  - reduces spontaneously
- Ileoceleal valve “simple intussusception”
  - O’Donnell et al. Anat Rec 2009, 292:254-
## Incidence of intussusception in infants in Asia

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Possible explanations for observed regional differences in IS incidence

- Genetic
- Cultural
- Exposure to infection
- Environmental
- Therapeutic practices
- Methods of diagnosis
- Access to healthcare services

Incidence of acute intussusception in infants & children per 1,000 live-births or children <1 year

[Map showing incidence rates with color coding: No current data, < 0.49, 0.5 – 1.0, 1.0 – 1.99, 2.00 – 2.99, Preliminary data > 10]
Clinical characteristics of children presenting with Intussusception in Asia

Gender
- Male predominance in all published reports
- 9:1 in 2 studies from India

Age
- <2 months of age rare
- Peak age 4-8 months

Ethnicity
- 10 X increase in Ethnic Malays compared to Indian Malays attending a major hospital in KL (Laidin et al 1982)
Clinical characteristics of children presenting with Intussusception in Asia

Clinical Presentation

– Prior respiratory infection or acute gastroenteritis/diarrhea
  • Taiwan: Fever, Resp and/or Gastro ~ 63% (Hsu et al 1998)
  • Indonesia: Gastro 61%, Resp 51% (van Heek 1999)
  • Korea: Gastro 10%, Resp 21% (Kim 1989)

– Classical “triad” = Vomiting, rectal bleeding and abdominal pain

– Clinical Signs
Clinical characteristics of children presenting with Intussusception in Asia

Clinical Presentation

– Prior respiratory infection or acute gastroenteritis/diarrhea

– Classical “triad” = Vomiting, rectal bleeding and abdominal pain
  • Taiwan 81% (Pang 1989)
  • Korea 66% (Kim 1989)
  • India 50-65% (Rattan 2000, Jain 1990)
  • Malaysia 10% (Laidin 1982)
  • Hong Kong 14% (Peh 1991)

– Clinical Signs
Clinical characteristics of children presenting with Intussusception in Asia

Clinical Presentation

- Prior respiratory infection or acute gastroenteritis/diarrhea
- Classical “triad” = Vomiting, rectal bleeding and abdominal pain

- Clinical Signs
  - Rectal blood in 50-82% studies reporting this sign
  - Abdominal distension 38-94%
  - Abdominal mass 19-78%
## Treatment patterns of children with Intussusception in Asia

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Treatment patterns of children with Intussusception in Asia

Surgery

Radiological reduction (liquid or air)

First line therapy in China, Vietnam, Hong Kong, Korea, Japan, Taiwan

Success rate in China (6396 cases over a 13 yr period at Shanghai Children’s Hospital) 95% - complications few, deaths 0.03% (Guo 1986)
Outcome of children with Intussusception

**Intestinal resection**
- Higher delayed presentation >48 hours
- Varies between region
- Incidence ranges 0-15%
  - Vietnam 2%
- Average resection length
  - Vietnam ~ 20cm (range 10-30cm)

**Mortality**
- >X10 higher when presentation >48 hours
- Varies widely from:
  - region to region
  - Level of hospital
  - Era of reporting
- Incidence ranges 0-58%
  - Indonesia 20% (Dewi 2012*)
  - Japan 3% (Kato 1969)
  - Vietnam 0% (Bines 2006)
  - India 0-58% (various 1968-2000)
Etiological associations with intussusception in children in Asia

Infections

- Adenovirus
  - Taiwan (Hsu 1998)
  - Vietnam (Bines 2006)
- Yersinia pseudotuberculosis
  - Korea (Koo 1996)
- Ascaris lumbricoides
  - Burma (Thein-Hraing 1990)
- Bacillary dysentery
  - India (Jain 1990)
  - India 52% treated with anti-diarrheal agents (Yadav 1986)

“Mobile” caecum

- Korea:
  - 88% IS cases > 2yr
  - 10/14 subacute/chronic IS (Dietrick 1965)

Increased serum gastrin and cAMP levels

- China (Jin 1996)
Bacterial Enteritis as a Risk Factor for Childhood Intussusception: A Retrospective Cohort Study

Cade M. Nylund, MD, Lee A. Denson, MD, and James M. Noel, MD

Objective  To assess the relationship between bacterial enteritis and intussusception.

Study design  The Patient Administration Systems and Biostatistics Activity database from January 2002 to December 2005 was examined for clinic visits or hospital admission to a Department of Defense medical facility for children age 0-5 years. The study included the International Statistical Classification of Diseases and Related Health Problems diagnosis-related group (DRG) codes for infections with Yersinia enterocolitica, Escherichia coli, Shigella species, Salmonella species, and Campylobacter. Identified patients were then assessed for the intussusception DRG code for 0-180 days postinfection. The total number of children enrolled in military treatment facilities in the same age group (denominator) was obtained.

Results  Bacterial enteritis significantly increased the relative risk of intussusception. An increased risk was found following infection with Salmonella, E. coli, Shigella, and Campylobacter. The relative risk for intussusception following any bacterial enteritis was 40.6 (95% confidence interval = 28.6-57.5; P < .0001).

Conclusions  Bacterial enteritis is a significant risk factor for the subsequent development of intussusception in children. (J Pediatr 2010;156:761-5).
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Recurrent intussusception is not rare in infants

• 598 patients < 2 years with intussusception over a 2 year period at the National Hospital of Pediatrics, Hanoi

• At 6 months following the primary episodes
  – Estimated recurrence rate 14%
  – 15 (2.5%) between 3 - 10 recurrences

• Pathological lead point was rare

• 1st presentation more severe

• Anatomical pattern similar in ⅓ but more distal progression of apex in primary episode

Justice et al, 2011: J Paediatrics and Child Health
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**Intussusception in infants in Asia**
Development of tools to assist countries planning to implement rotavirus vaccines

- Brighton Collaboration Clinical Case definition for Intussusception
- WHO Generic Protocols
  - Baseline Epidemiology of Intussusception
  - Post-marketing surveillance for the safety of rotavirus vaccines
- WHO Document: Acute intussusception in infants and children