Safety Considerations for Neonatal Vaccine

Adverse Events in the Neonatal Period

Marie R. Griffin MD MPH
Vanderbilt University School of Medicine
Department of Preventive Medicine

Objectives

- Safety considerations for serious adverse events
- Review serious adverse events that occur in the neonatal period
- Review data on specific vaccine-disease relationships
- Consider study designs for assuring confidence in vaccines

Confidence in Vaccines and Vaccine Programs

- Assure
  - Safe and effective vaccines
  - Perception as well as reality of safety
- Be proactive about collecting safety data
- Be proactive about responding to safety concerns

Serious Adverse Events

- Numbers needed to prove immunogenicity/efficacy may be insufficient to give confidence about absence of rare but serious adverse effects
  - Large clinical trials necessary
    - Confidence in safety
    - Examine more serious disease outcomes

Perception of causality more likely if:

1. Adverse events closely follow vaccination
   - DTP vs MMR
2. Adverse event follows a reaction to a vaccine
   - High fevers, seizures, local reactions
3. Adverse event has no known cause
   - SIDS, autism
4. Data are insufficient to determine causality

Serious Adverse Events in Neonatal Period

- Sudden Unexplained Death Syndrome
  - SIDS
  - Other unexplained deaths
- Seizures
- Other neurologic disorders

Infant Mortality 2002 7/1000 live births

- Neonatal: <28 days = 4.7/1000
  - **0-7 days 3.7/1000**
  - 7-27 days 0.9/1000
- Postneonatal
  - 28 days-11 months 2.3/1000

Source NCHS http://www.cdc.gov/nchs/products/pubs/pubd/hestats/infantmort/infantmort.htm

Causes of Neonatal Deaths

Cause of Death (1989)	%	
Congenital Anomalies	24	5-10/10,000
Low Birth Weight	15	
Respiratory Distress S	14	
Complications of birth	10	
Perinatal infection	3	≤ 1/10,000
Hypoxia/Birth Asphyxia	3	
Sudden Infant Death	2	

Special Considerations of Neonatal Period: Deaths

- SIDS
  - 2 weeks to 1 year
  - Peak 2-3 months
  - "back to sleep" decreased rate: 5/10,000
  - Not uniform in all groups
  - Neonatal period: <1/10,000
- Sepsis deaths also rare
  - Can't ignore fevers

Neonatal Deaths after Hepatitis B Vaccine

- Background to FDA VAERS Report
  - At time of licensing: 2000 infants 0-12 months
    - No serious reactions or death
- 1991-1998: 1771 reports of events following vaccine given in neonatal period
  - 18 deaths
    - Mean age vaccination 12 days
    - Median time to symptoms/death 2 days
      - 12 SIDS (6-28 days), 3 infection, 1 each ich, accidental suffocation, chd

Source: Niu et al Arch Pediatr Adolesc Med 1999

Parent Report: previously healthy baby

"Nicholas was given a **hepatitis B** shot ..on the 13th day of his life. Nicholas cried on and off for most of the night. ..the next day, he was still crying on and off… and into the evening. The next morning, his mother found him dead in his crib. From the way he looked, he had been dead for several hours."

SIDS and DTP (plus OPV): vaccinated vs unvaccinated

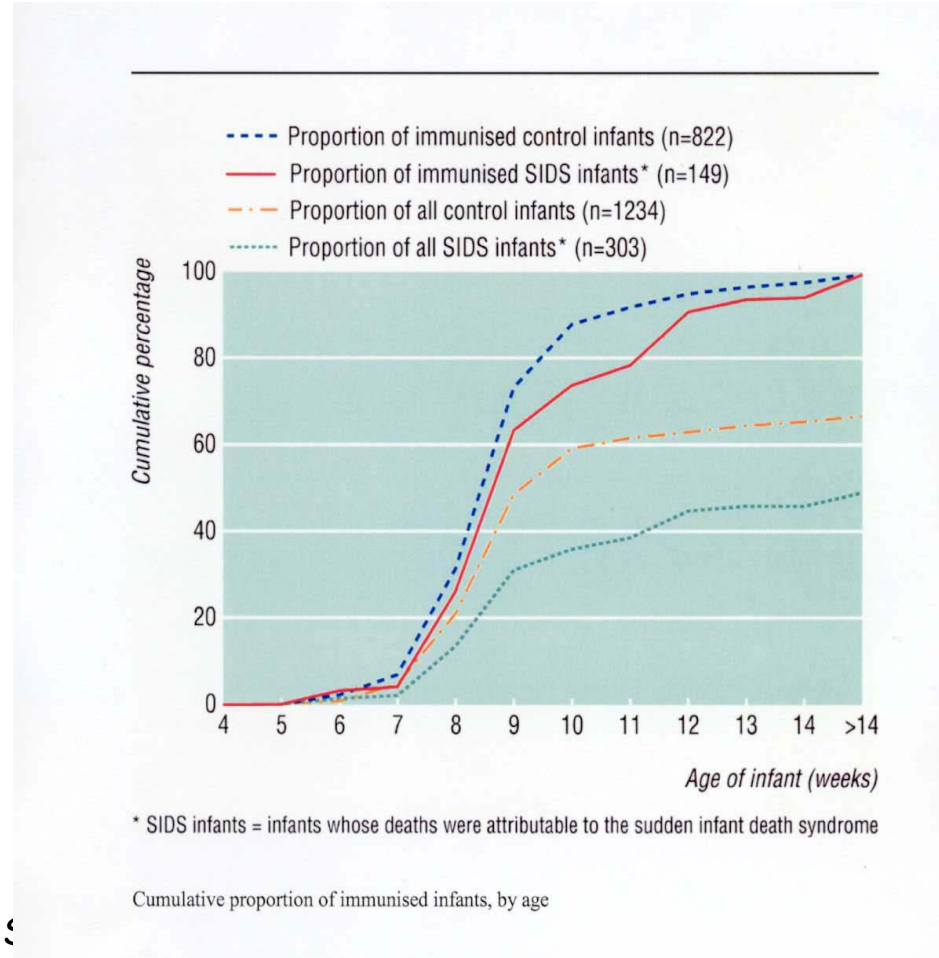
- Most observational studies that compared children dying of SIDS to population controls found "protective effect" of vaccination
  - RR 0.2 to 0.7

National SIDS Case Control Study (Hoffman et al 1987)

- Population-based, parental interviews, matching and control for multiple factors
- Vaccinated vs Unvaccinated
  - N=716 SIDS RR=0.6
- Timing of Vaccination
  - N=285 SIDS RR=0.8
  - 1% of cases had DTP vaccine within 24 hours of death

SIDS and Routine Infant Immunization (Fleming 2001)

- 325 SIDS,
  - RR 0.47 for vaccination
  - RR 0.67 with additional control for "sleeping environment"
- 149 vaccinated SIDS
  - 5% cases and controls vaccinated within 48 hours of death/index date



Cumulative proportion of immunised infants, by age

SIDS Summary

- Rare in neonatal period
- Good evidence for lack of an association with DTP
- Some spontaneous reports with Hepatitis B vaccine
- Observational studies suggest that it is difficult to "control for" factors associated with immunization
  - Healthy vaccinee effect
  - Unmeasured factors associated with vaccination

Neonatal Seizures

- About 1/1000
- More common in 1st 10 days
- Rarely generalized: focal; subtle: chewing, pedaling, ocular movements; tonic; clonic; myoclonic
- Some benign: familial and "5th day fits"
- 20%-50% develop epilepsy
- Often sign of underlying neurologic disorder

Febrile Seizures and Infantile Spasms

- Febrile seizures: 4/100
  - 1st febrile seizure 6 months to 3 years
  - Peak 14-18 months
  - Familial, no permanent neurologic damage
  - Epilepsy risk increased if prolonged, focal features, recur in 24 hours
- Infantile spasms
  - 0.2-0.6/1000
  - Peaks 3-8 months
  - Characteristic EEG

Data for DTP(OPV), MMR

- Febrile seizures
  - DTP and MMR increase
- Afebrile seizures
  - DTP and MMR not associated
- Infantile spasms
  - DTP "triggers" not causal
- Neonatal seizures
  - No data

Seizure Summary

- Fevers associated with vaccines result in an increase in febrile seizures
- Vaccines may also trigger manifestations of other neurologic disorder e.g. infantile spasms
- Little known about vaccines and neonatal seizures

Chronic neurologic disorders following vaccination

- Coincidental
- Trigger/unmasking
  - Seizures or encephalopathy could be first manifestation of underlying neurologic disorder
- Causal

DTP and Acute Encephalopathy

- IOM
  - Most evidence from NCES (2 million vaccinated children)
  - Complex seizures and encephalopathy 3 times higher in 7 days following DTP (n=30 cases; 26 previously "normal")
- Agreed with NCES authors "consistent with a causal association"
  - 0 to 10.5 per million doses

Chronic neurologic disorder

- Subset 7/26 (27%) with acute encephalopathy who were previously "normal" were impaired on follow up
  - Insufficient evidence for causal relation (IOM, 1991)
  - Balance of evidence supports causal relationship if chronic disorder follows acute encephalopathy (IOM, 1994)

Implications for neonatal vaccines

- If first manifestation of underlying neurologic disease occurs post vaccine
  - Precedent for considering vaccine causal
  - Evidence of other known cause (e.g. intracerebral hemorrhage) less likely to be attributed to vaccine

Fever
Neonatal Hepatitis B Vaccine

- CDC web site
  - Fevers: 7% children, 1% adults
- Linder:fever day 0-3 after birth dose
  - Switch to birth dose 1991 → 1992
  - Excess 3.2/1000 with temp >38°C

Retrospective Review: Fever day 0-3

Birth Dose:	*No*	*Yes*
N children	5010	5819
Temp 37.5-38°C	0	18
Temp >38°C	27	50
Explained fever	13	15
Unexplained fever	14	35
Temp >38°C per 1000	5.4	8.6

Linder et al Arch Dis Child Fetal Neonatal Ed 1999

Why be concerned about fever?

- Increased morbidity/cost
  - Sepsis work-up
  - Need to include in cost analyses
- Fevers may "unmask" underlying neurologic problems

Summary

- Neonatal period time of increased risk for
  - Death
  - First manifestation of serious underlying neurologic/developmental problems
- Causal associations difficult to distinguish
  - Coincidence
  - Unmasking

Conclusions: Neonatal Vaccination

- Evidence for vaccinating in the neonatal period should be solid and benefits demonstrable
- Clinical trials best for evaluating safety as well as efficacy
- Consistent findings from methodologically strong observational studies helpful

Small-Moderate Sized Clinical Trials

- Collect information on adverse events in a uniform way
  - Brighton collaboration: fever, convulsions
- Determine consistency between studies
- Estimate more rare events from looking at several studies

Large Clinical Trials

- Licensed vaccines:
  - accelerated vs usual schedules
- New vaccines:
  - Efficacy for serious disease
    - prevnar: invasive disease
  - Safety
    - rotavirus: intussusception

Observational Studies

- Need to be supported if too late to do clinical trials
- VAERs
  - Most helpful in alerting for possible problem
  - Less helpful in providing reassurance of no problem

Challenges

- Clinical trials
  - Best controls?
  - Unblinded if randomize to alternate schedule
- Observational studies
  - Vaccinated vs unvaccinated
    - Difficult in well-vaccinated population
  - Accelerated vs usual schedule
    - Bias?—healthier children immunized earlier
  - Studies of "timing" of events
    - Difficult to study chronic events

Opportunities

- Large vaccine clinical trials are being done
  - Rotavirus, prevnar, shingles
- Uniform criteria for adverse events are being developed
- Serious events with unknown cause are decreasing e.g. SIDS, many neurologic disorders
- Recognition of need for research into serious problems in childhood
  - SIDS, autism, mental retardation