“Does Less Ouch Equal Less Umph”?
Acetaminophen for the Prevention of Adverse Effects Associated with Childhood Immunizations and the Potential for Reduction in Immunogenicity

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Learning Objectives

1. Describe the processes of thermoregulation and fever production
2. Identify possible adverse effects associated with childhood immunizations
3. Describe the rationale for and against the use of prophylactic acetaminophen for prevention of adverse effects associated with childhood immunizations
4. Identify the possible reduction in immunogenicity associated with prophylactic acetaminophen on childhood immunizations.
I. Thermoregulation
   A. Integrated network of neural connections involving the hypothalamus, limbic system, lower brainstem, the reticular formation, spinal cord, and sympathetic ganglia
      i. “Preoptic area” is an important structure in thermoregulation
   B. Fever is a regulated rise in body temperature after an increase in the hypothalamic set point
      i. Thermoregulatory mechanisms are stimulated
      ii. Normal thermoregulation modulates at this higher set point

II. Pathogenesis of Fever
   A. Fever is defined as a controlled elevation of body temperature above normal range
      i. Normal body temperature range taken orally is 36.7°C to 37°C (98.7°F) higher than oral temperatures
      1. Normal rectal temperature are 0.6°C (1°F) higher than oral temperatures
      2. Axillary temperatures are 0.6°C (1°F) lower than oral temperatures
   B. Role of cytokines
      i. Produced from phagocytic cells in the blood or tissues
      ii. Intrinsic endogenous pyrogens (EPs)
         1. Include interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor (TNF), and various other pyrogenic cytokines
      iii. Trigger the release of other mediators such as prostaglandin E2 (PGE2) in the region of the “preoptic area” (includes the preoptic nuclei of the anterior hypothalamus and the septum)
         1. Fever produced by cytokines is most likely due to local release of prostaglandins in the hypothalamus
   C. Prostaglandin E2
      i. Synthesized from arachidonic acid, which is released from cell membrane lipid by phospholipase
      ii. Arachidonic acid is metabolized by two isoforms of the COX enzyme, COX-1 and COX-2.
         1. COX-2 is the key provider of PGE2 during pyrexia
      iii. Inhibiting central production of PGE2 is a well known mechanism of many antipyretic agents, such as acetaminophen.
III. Childhood Immunizations

A. From birth to the age of six years old, a child could receive a possible minimum of thirty immunization shots if following the CDC recommendation schedule

B. Associated with local and systemic adverse reactions
   i. Local—skin induration, swelling, tenderness, rash, and/or erythema at the site of injection
   ii. Systemic—fever, joint or muscle pain, fainting, seizures, and other central nervous system effects
   iii. Allergic—anaphylaxis

C. These reactions usually occur within the first 24-48 hours following immunization

D. The frequency of adverse effects can vary with different vaccines and formulations
   i. Diphtheria, Tetanus, Pertussis (DTP)
      1. Whole cell pertussis-containing vaccines combined with diphtheria and tetanus toxoids (DTwP)
         a. associated with high rates of injection-site reactions and neurologic adverse events, including febrile seizures, in the immediate post vaccination period

*Figure 1 Pathogenesis of Fever*
2. Acellular pertussis vaccines combined with diphtheria and tetanus toxoids (DTaP)\(^7\)
   a. developed to provide a less reactogenic alternative to DTwP

ii. Measles, Mumps, Rubella (MMR)
   1. Has been associated with an increased risk of febrile seizures during the first 7-14 days after vaccination\(^8\)

### Figure 2: Recommended Immunization Schedule for Persons Aged 0 Through 6 Years
United States 2011\(^9\)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>HepB</td>
<td>Birth, 1-2 months, 6-18 months</td>
</tr>
<tr>
<td>RV</td>
<td>2 months, 4 months, 6 months</td>
</tr>
<tr>
<td>DTaP</td>
<td>2 months, 4 months, 6 months, 15-18 months, 4-6 years</td>
</tr>
<tr>
<td>Hib</td>
<td>2 months, 4 months, 6 months, 12-15 months</td>
</tr>
<tr>
<td>PCV</td>
<td>2 months, 4 months, 6 months, 12-15 months</td>
</tr>
<tr>
<td>IPV</td>
<td>2 months, 4 months, 6-18 months, 4-6 years</td>
</tr>
<tr>
<td>MMR</td>
<td>12-15 months, 4-6 years</td>
</tr>
<tr>
<td>VAR</td>
<td>12-15 months, 4-6 years</td>
</tr>
<tr>
<td>HepA</td>
<td>12-23 months (x 2 doses)</td>
</tr>
</tbody>
</table>

Key: HepB=hepatitis B, RV= rotavirus, DTaP= diphtheria, tetanus, pertussis, Hib= Haemophilus influenza type b, PCV=pneumococcal, IPV=inactivated poliovirus, MMR= measles, mumps, rubella, VAR= varicella, HepA=hepatitis A

### E. Febrile Seizures

i. Seizure in infancy or childhood that is associated with fever, but with no evidence of intracranial infection, epilepsy, or other defined cause for the seizure.\(^10\)
   1. In children aged 6 months to 6 years, the incidence is 3-5% with a recurrence rate of 20-30%.\(^10\)

ii. Risk factors for recurrence include\(^10,11\):
   1. Number of febrile episodes
   2. Age
   3. Family history of febrile seizures

iii. Febrile seizures are usually benign, self limiting and not known to have adverse long-term consequences in otherwise healthy children\(^10,11\)

iv. Children who develop seizures with lower degrees of fever have a lower seizure threshold and therefore a higher recurrence rate of febrile seizure, while those with high fevers over 40°C have fewer recurrences\(^11\)
F. Prevention of Febrile Seizures
   i. Currently, the American Advisory Committee on Immunization Practices (ACIP) recommend the prophylactic use of antipyretics with an increased risk of febrile seizures\textsuperscript{12}
   ii. However, studies of children with previous febrile seizures have not demonstrated antipyretics to be effective in prevention of febrile seizures\textsuperscript{12,13}
   iii. Recurrence of febrile seizures is most likely due to associated risk factors for recurrence
      1. Antipyretics may have no role in preventing febrile seizures

IV. Acetaminophen
   A. Many physicians recommend the use of antipyretics before childhood immunizations to prevent adverse reactions of localized pain or fever
   B. Dose
      i. 10-15 mg/kg orally every 4 to 6 hours, with a maximum of 5 doses in 24 hours
   C. Adverse effects
      i. In the USA, acetaminophen-associated overdoses account for 56,000 emergency visits and 26,000 hospitalizations, with approximately 450 deaths each year. About 100 of these deaths are unintentional\textsuperscript{11}
   D. Prophylactic use for prevention of adverse effects\textsuperscript{12}
      i. Some studies show that prophylactic use of acetaminophen reduces the overall incidence of fever and other adverse effects, whereas others have shown no difference
      ii. In addition to possibly not providing any benefit for reducing fever associated with childhood immunizations, newer evidence is now suggesting that use of prophylactic acetaminophen may have negative effects on the immunogenicity of childhood vaccinations
### GENERAL STUDY OVERVIEW

<table>
<thead>
<tr>
<th>Title</th>
<th>The Risk of Seizures After Receipt of Whole-Cell Pertussis or Measles, Mumps, and Rubella Vaccine¹⁴</th>
</tr>
</thead>
</table>

#### Background
- The administration of diphtheria and tetanus toxoids and whole-cell pertussis (DTP vaccine and measles, mumps, and rubella (MMR) vaccine has been associated with seizures.
- The Vaccine Safety Datalink project is a population-based study of adverse events after childhood immunization in four large regional health maintenance organization (HMOs).

#### Objective
- To determine the relationship between DTP and MMR vaccine and first-time seizures

### METHODS

#### Study Design
- Data was pulled from the information provided by the Vaccine Safety Datalink project.
- Potential seizures were identified through the automated data systems of each HMO on the basis of visits classified according to ICD-9-CM codes.
  - Other methods included computerized data on anticonvulsant medications, referrals to neurology clinics, and electroencephalographic records.
- The following intervals used to assess exposure to DTP or MMR vaccine were based on the number of days since exposure:
  - Day of vaccination
  - 1-7 days after vaccination
  - 8-14 days after vaccination
  - 15-30 days after vaccination
- For nonfebrile seizure group: 0-7 days, 8-14 days, and 15-30 days (no seizures were recorded on the day of vaccination).

#### Patient Selection
- Inclusion: children less than 7 years old with first episode of seizure after DTP or MMR vaccination
- Exclusion: seizures that were due to an underlying disease process such as infection or trauma

#### Statistical analysis
- Stratified Cox proportional-hazards analysis to assess the association between immunization and the occurrence of a first seizure

### RESULTS

#### Data Collected
- 4 HMO: 6379 person-years of observation with 340,386 vaccinations with DTP vaccine and 137,457 with MMR vaccine
- 2281 possible seizures were identified; 1094 children were randomly selected; 716 with validated first-ever seizures
### Breakdown:
- **Febrile seizures:**
  - 487 (460 simple, 27 complex)
    - 42 occurred within 30 days after the receipt of DTP vaccine and 32 within 30 days after the receipt of MMR vaccine
    - 5 febrile seizures were verified as occurring on the same day the DTP vaccine given; 0 for MMR
- **Nonfebrile seizures:**
  - 137
    - 10 occurred within 30 days after DTP; 3 within 30 days after MMR
- **Infantile spasms or neonatal seizures:**
  - 36
- **Other causes:**
  - 56

#### Elevated risk of febrile seizures:
- **On the day of administration:** (RR 5.70; 95% CI 1.98-16.42)—adjusted for all variables
- **Risk did not persist and was not significantly elevated above baseline:** 1-7 days, 8-14 days, or 15-30 days after vaccination
- **Infants 0-12 months old:**
  - RR of seizures on the day of vaccination was 9.27; 95% CI 1.21-70.78
- **Children 13-24 months old:**
  - RR of seizures on the day of vaccination was 3.06; 95% CI 0.67 to 13.96
- **MMR vaccination:**
  - RR of febrile seizures of 2.83 from 8-14 days after vaccination; 95% CI 1.44 to 5.55, but was not associated with an elevated risk 0-7 days or 15-30 days after vaccination

### DISCUSSION

**Author's Conclusion**
- Significantly elevated risks of febrile seizures on the day of the administration of DTP vaccine and 8-14 days after the administration of MMR vaccine

**Reviewer's Critique**
- **Strengths**
  - Large sample of patients
  - Appropriate age groups to encompass all possible vaccinations
- **Limitations**
  - Febrile seizure definition not
  - Difference in methods of case ascertainment among the HMOs

### CONCLUSION

**Reviewer's Conclusion**
- Although the DTP and MMR vaccination are associated with an increased risk of febrile seizures, the benefits from vaccination does not outweigh risk
- The use of DTP has been replaced with the use of the diphtheria, tetanus, and acellular pertussis (DTaP) vaccine
## GENERAL STUDY OVERVIEW

<table>
<thead>
<tr>
<th>Title</th>
<th>Lack of Association Between Acellular Pertussis Vaccine and Seizures in Early Childhood[^15]</th>
</tr>
</thead>
</table>
| **Background**                                                       | • Seizures have been associated with receipt of the diphtheria-tetanus whole cell vaccine (DTP) as well as the measles-mumps-rubella (MMR) vaccine and/or measles-mumps-rubella-varicella (MMRV) vaccine  
• Limited studies have been conducted on the risk for seizures after receipt of the diphtheria-tetanus-acellular pertussis vaccine [DTaP] |
| **Objective**                                                       | • To assess the association between DTaP and seizures in early childhood |
| **METHODS**                                                         | **Study Design**  
• Used data from the Vaccine Safety Datalink (VSD) Project to obtain eligible subjects  
• To evaluate for potential confounders, information was also collected on administration of MMR and MMRV to eligible children during the observation period  
**Patient Selection**  
• Inclusion: children 6 weeks to 23 months who received the DTaP vaccination  
• Exclusion: if received DTP or had 2 consecutive DTaP doses given at an interval less than the recommended minimal interval in the catch up immunization schedule  
**Statistical Analysis**  
• Null hypothesis  
  • Incidence of seizures is not different in the 4 person-days after each DTaP dose compared with a control period temporarily unrelated to vaccination  
  • 2 methods to analyze data  
  • Risk interval cohort method (RIC)  
  • Self-controlled case series (SCCS)  

| **RESULTS**                                                        | **Data Collected**  
• 1997-2006  
  • N=433,654 children  
    • 222,470 males [51%]  
• Incidence was lowest at 3 months (582 seizures per 100,000 person-years) and highest was at 16 months (2004 seizures per 100,000 person-years)  
• The incidence of seizures outside the predefined exposed periods was not significantly different compared with the incidence of seizures for children who never received DTaP  
  • 1208 seizures per 100,000 person-years; 95% CI: 1180-1237 versus 1083 seizures per 100,000 person-years; 95% CI: 960-1223  
• 7191 seizures events involving 5205 patients: 112 seizures occurred |
<table>
<thead>
<tr>
<th>within 0-3 days of receiving DTaP</th>
<th>• Number of events 0-3 days after vaccination</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>o First dose series: n=28</td>
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<tr>
<td></td>
<td>▪ RIC: Adjusted incidence rate ratio (IRR) 0.99 (0.68-1.44)</td>
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<tr>
<td></td>
<td>▪ SCCS: Adjusted IRR 1.02 (0.70-1.50)</td>
</tr>
<tr>
<td></td>
<td>o Second dose series: n=20</td>
</tr>
<tr>
<td></td>
<td>▪ RIC: Adjusted IRR 0.72 (0.46-1.12)</td>
</tr>
<tr>
<td></td>
<td>▪ SCCS: Adjusted IRR 0.75 (0.48-1.17)</td>
</tr>
<tr>
<td></td>
<td>o Third dose series: n=24</td>
</tr>
<tr>
<td></td>
<td>▪ RIC: Adjusted IRR 0.87 (0.58-1.30)</td>
</tr>
<tr>
<td></td>
<td>▪ SCCS: Adjusted IRR 0.90 (0.60-1.35)</td>
</tr>
<tr>
<td></td>
<td>o Fourth dose series: n=40</td>
</tr>
<tr>
<td></td>
<td>▪ RIC: Adjusted IRR 0.89 (0.65-1.22)</td>
</tr>
<tr>
<td></td>
<td>▪ SCCS: Adjusted IRR 0.95 (0.69-1.29)</td>
</tr>
<tr>
<td></td>
<td>o All dose series: n=112</td>
</tr>
<tr>
<td></td>
<td>▪ RIC: Adjusted IRR 0.87 (0.72-1.05)</td>
</tr>
<tr>
<td></td>
<td>▪ SCCS: Adjusted IRR 0.91 (0.75-1.10)</td>
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</tbody>
</table>

**DISCUSSION**

**Author's Conclusion**

• Among children aged 6 weeks-23 months, no increased risk for seizures in the 0-3 days after DTaP vaccination was observed
• DTaP vaccine is not associated with acute seizure events and is safe for routine immunization in early childhood

**Reviewer's Critique**

• Strengths
  o Large population size
  o 2 methods of analysis
• Limitations
  o Only evaluated seizures that presented to the emergency department or in association with hospital discharge
  o Febrile seizure parameters not defined
  o Patient population excludes those who should receive their 5th dose at 4-6 years old

**CONCLUSION**

**Reviewer's Conclusion**

• DTaP vaccine is not associated with a significant increased risk for seizures, however cannot conclude that the risk for febrile seizures is not significant
• The risk of seizures associated with the 5th dose of the DTaP series should have been included
Prophylactic Acetaminophen in Febrile Seizures

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study Group</th>
<th>Study Design</th>
<th>Outcome</th>
<th>Key Result</th>
</tr>
</thead>
</table>
| Uhari et al (1995)| N=180       | Randomized double blind placebo controlled trial | Number of recurrence of FS   | a) 14 (25.4%)  
b) 9 (16.4%)  
c) 14 (25.4%)  
d) 18 (32.7%)  |
|                   | After first febrile seizure |                             |                              | No statistical difference           |
|                   | a) placebo + placebo       |                             |                              |                                     |
|                   | b) placebo + paracetamol    |                             |                              |                                     |
|                   | c) diazepam + paracetamol   |                             |                              |                                     |
|                   | d) diazepam + placebo       |                             |                              |                                     |
| Schnaiderman et al (1993)| N=104 | Randomized controlled trial | Early recurrence of FS       | a) 4 (7.5%)   
b) 5 (9.8%)   |
|                   | After first febrile seizure |                             |                              | No statistical difference           |
|                   | a) Paracetamol 4-hourly     |                             |                              |                                     |
|                   | b) Paracetamol PRN          |                             |                              |                                     |
| Von Esch et al (2000)| N=212 | Non-randomized controlled trial | Number of recurrence of FS   | a) 6.3%  
b) 12.2%  
ARR=5.9% (95% CI: -0.2-12%)  |
|                   | After first febrile seizure |                             |                              | No statistical difference           |
|                   | a) Ibuprofen or paracetamol |                             |                              |                                     |
|                   | b) No antipyretics          |                             |                              |                                     |
| Meremikwa et al (2002) | RCTs with paracetamol compared to placebo | Systematic review | Number of recurrence of FS | No evidence that paracetamol is effective in preventing FS |

GENERAL STUDY OVERVIEW

Title: A Randomized Placebo-Controlled Trial of Acetaminophen for Prevention of Post-Vaccination Fever in Infants


Background: • Fever is common following infant vaccinations.  
• Two randomized controlled trials demonstrated the efficacy of acetaminophen prophylaxis in preventing fever after whole cell pertussis vaccination, but acetaminophen has not been evaluated for prevention of fever following contemporary vaccines recommended for infants in the United States

Objective: • To evaluate the possible benefits of acetaminophen prophylaxis for the prevention of post-vaccination fever and other outcomes

Primary Outcome: • Rectal temperature > 38°C within 32 hours of vaccination

METHODS

Study Design: • Randomized, double blind, placebo-controlled trial of acetaminophen prophylaxis in children enrolled in Group Health Cooperative (a managed care organization)  
• Trial elected to stop enrollment due to the reported results of lower immune response in a randomized trial of acetaminophen prophylaxis in infants in the Czech Republic receiving a primary series of ten-valent pneumococcal nontypeable Haemophilus influenza protein D-conjugate vaccine co-administered with a combination of DTaP-HepB-IPV-Hib vaccine and oral human rotavirus vaccine
The results of this trial include the evaluation of 352 children enrolled prior to study cessation
- Parents completed a study diary and recorded the child's weight (measured at vaccination visit), time vaccinations were administered, and timing and volume of each dose of study medication administered. If they discontinued the study medication, they were asked to record the reason(s)
- Rectal temps were taken just prior to administration of the second, third, fourth and fifth doses of study medication, and to take a final rectal temp approx. 24 hours after vaccination, or 4 hours after the final dose of study medication (whichever was later)

### Patient Selection
- **Inclusion**: expected to receive 2 or more injected vaccines at an upcoming well child visit occurring after 6 weeks of age and before 10 months age
- **Exclusion**: children < 4 months of age who had a birth weight of <2500 grams or gestational age < 36 weeks

### Statistical Analysis
- Study sample size of 1000 children was selected to have 80% power to detect a 30% reduction in risk of the primary outcome of rectal temperature > 38 °C following vaccination
  - Assuming that 40% of children in the placebo group would have the primary outcome of >38 °C, a sample size of 897 would allow 80% power to detect a 30% reduction in risk of that outcome in the treatment group

### RESULTS

#### Data Collected
- n=352 (acetaminophen n=176; placebo n=76)
- Age range 12-42 weeks: ages grouped around the times of the four and six month vaccination
- Primary outcome
  - Acetaminophen 14% versus placebo 22% RR 0.66 (0.41-1.01); p=0.053
  - Acetaminophen group
    - 98% received at least 2 doses, 94% received at least 3 doses, 78% received at least 4 doses, and 33% received 5 doses
  - Placebo group
    - 98% received at least 2 doses, 91% received at least 3 doses, 76% received at least 4 doses, and 31% received 5 doses
- Children in the acetaminophen group were less likely to have the primary outcome of temperature >38 °C than children in the placebo group (p=0.05)
- Among children ≥24 weeks, there was a significant reduction in the risk of temp > 38 °C in the acetaminophen group compared with placebo (13% versus 25%; p=0.03)
  - This was not found amongst children <24 weeks (16% versus 18%; p=0.8)
### DISCUSSION

**Author's Conclusion**
- The risk of the primary outcome of temperature >38°C was lower in the acetaminophen group compared to placebo (15% versus 22%)
  - this difference was not statistically significant in the primary analysis of all subjects
  - A significantly lower risk of the primary outcome was found in the subgroup analysis of infants >24 weeks
- New information demonstrating an adverse effect of acetaminophen prophylaxis on vaccine immune response, as well as data indicating that the risk of febrile seizures is not increased following administration of DTaP vaccine, indicates that acetaminophen prophylaxis should not routinely be used for prevention of post-vaccination fever

**Reviewer's Critique**
- **Strengths**
  - Large population sample
  - Baseline characteristics similar in both groups
  - Included various childhood vaccination
- **Limitations**
  - Parent driven
  - Power not met due to early termination
  - Did not include older child population

### CONCLUSION

**Reviewer's Conclusion**
- Cannot conclude if the effects of prophylactic acetaminophen can significantly decrease the risk of developing fever as compared to placebo
- Early termination of the trial due to possible reduction in immunogenicity may further dissuade health care providers for recommending prophylactic acetaminophen
### GENERAL STUDY OVERVIEW

<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials¹⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Funding</strong></td>
<td>GSK</td>
</tr>
</tbody>
</table>

#### Background
- Although fever is part of the normal inflammatory process after immunization, prophylactic antipyretic drugs are sometimes recommended to allay concerns of high fever and febrile convulsion
- However, evidence lending support to this is scarce

#### Purpose
- To assess the effect of the prophylactic administration of paracetamol at the time of vaccination and within the next 24 hours on the rate of febrile reactions and vaccine responses in infants after primary vaccination with a ten-valent pneumococcal nontypeable H.influenza protein D-conjugate vaccine (PHiD-CV) co-administered with the hexavalent diphtheria-tetanus-3 component acellular pertussis-hepatitis B-inactivated poliovirus types 1,2, and 3-H influenza type b vaccine (DTPa-HVB-IPV/Hib) and oral human rotavirus vaccine (HVR), followed by a booster dose of PHiD-CV plus DTPa-HBV-IPV-Hib

#### Primary Objective
- Primary and booster studies:
  - To measure the reduction in febrile reaction at 38°C or greater on day 0-3 when prophylactic paracetamol (PP) was administered compared with no prophylactic paracetamol (NPP)

#### METHODS
- Two consecutive phase 3, randomized, controlled, open label studies in 10 centers in the Czech Republic from Sep 18, 2006 to April 10, 2007
- Children enrolled were randomly assigned (1:1) into 2 groups:
  - One group received three doses of PP administered every 6-8 hours within the first 24 hours after each vaccine dose
  - One group received NPP
- The control group did not receive a placebo drug
- Booster doses of PHiD-CV and DTPa-HVB-IPV/Hib, with or without prophylactic paracetamol, were administered between 12 and 15 months of age
- When the primary vaccination immunogenicity results became available, the administration of PP at the time of booster vaccination was discontinued via a protocol amendment
- The prophylactic antipyretic treatment consisted of three doses of paracetamol given via suppositories within the first 24 h after each vaccine dose
- Study staff gave the first administration of PP immediately after
vaccination. The second and third administrations were done at home every 6-8 hours
- The dose of paracetamol was based on body weight: 80 mg per administration for infants weighing between 4.5-6.9 kg; 125 mg per administration for infants weighing ≥7 kg
- At booster vaccination, same dose was given to infants weighing 7-8.9 kg and those ≥9 kg received four administrations of 125 mg paracetamol each within 24 h
- Primary vaccine doses of PHiD-CV and DTPa-HVB-IPV/Hib were administered to all participants at 3,4 and 5 months of age. HRV was administered at 3 and 4 months of age
- Temperature was measured rectally on the evening of the day of vaccination, the morning and the evening of the first day after vaccination, and in the evening of the 2nd and 3rd days after vaccination; the highest temp was recorded for each day of collection
- Blood samples were collected before the first dose and 1 month after primary vaccination, and before and 1 month after the booster dose
  - ELISA analysis
    - Geometric mean antibody-concentrations (GMCs)
    - Opsonophagocytic activity (OPA) titers (geometric mean titers [GMTs])

### Patient Selection

- Inclusion: healthy infants aged 9-16 weeks at time of enrollment and 12-15 months at time of boosting
- Exclusion: use of prophylactic antipyretic therapy required for reasons unrelated to the study; contraindication to paracetamol treatment, previous vaccination against pathogens targeted by PHiD-CV, DTPa-HVB-IPV/Hib, and HRV

### RESULTS

#### Data Collected

- Primary vaccination group
  - 459 participants enrolled and vaccinated
  - PP group: n=226; NPP group: n=233
- Booster group
  - 414 participants in the booster study
    - Paracetamol before amendment: n=178, paracetamol after amendment: n=27, no paracetamol before amendment: n=172, no paracetamol after amendment: n = 37
  - The percentage of children with temp of 38°C or greater after at least one dose was significantly lower in the PP group than in the NPP group
    - 94/226 (42%) after the primary vaccination and 64/178 (36%) after booster vaccination versus 154/233 (66%) after primary vaccination and 100/172 (58%) after booster vaccination
    - Primary vaccination group difference 24.5% (95% CI 15.49-33.11)
    - Booster vaccination group difference 22.18% (95% CI...
For each vaccine dose, the percentage of participants with temp > 38 °C was 40-50% less in the PP group versus the NPP group.

The effect of PP was greatest after the first dose: 50/226 (22%) participants in the PP group had temp >38 C versus 117/223 (50%) in the NPP group
- Group difference 28.9% (95% CI 19.52-36.27)

**Immunogenicity Data (Primary vaccination group):**

- Before the first vaccine dose, seroprotection and seropositivity rates and antibody GMCs and GMTs were within the same range in group receiving or not receiving PP (data not shown in article)
- PHiD-CV was immunogenic for all pneumococcal vaccine serotypes.
  - For each serotype apart from 6B and 23F, at least 95.7% of children reached antipneumococcal antibody concentrations of 0.2 mcg/mL or greater after primary vaccination
- The percentage of children with antibody concentrations of 0.2 mcg/mL or greater against serotype 6B was significantly lower in the PP group than in the NPP group, as were antipneumococcal antibody GMCs against all ten vaccine serotypes
- The percentage of children with OPA titres of 8 or greater was significantly lower in the PP group than in the NPP group for serotypes 1,5, and 6B
- For other serotypes at least 91.6% of participants had OPA titers > 8 in both groups
- Lower opsonophagocytic activity titres (GMTs) were recorded in the PP group for most serotypes, with significant differences for serotypes 1 and 5
- After primary vaccination, at least 96% of children had seroprotective antibody concentrations against H.influenzae type b, diphtheria, tetanus, hep b and the three acellular pertussis antigens, and all children were seropositive for poliovirus types 1,2,3
  - However, lower seroprotection rates against H.influenzae type b (at the 0.15 mcg/mL and 1 mcg/mL cutoffs) and lower GMCs for antibodies against Haemophilus type b, diphtheria, tetanus, and pertactin were recorded in the PP group than in the NPP group
  - The antirotavirus IgA seroconversion rates and antibody GMCs were within the same range in both groups

**Immunogenicity Data (Booster group):**

- Before the booster dose, lower antibody GMCs were detected for all vaccine serotypes in the PP group, than in the no PP group, with fewer children with antibody concentrations of 0.2 mcg/mL or greater for most vaccine serotypes
- Similarly, OPA activity GMTs and seropositivity rates were lower in the PP group for most serotypes (apart from 9V), although for several serotypes these differences were not statistically significant
**DISCUSSION**

**Author’s Conclusion**
- Prophylactic paracetamol significantly reduced inflammatory febrile and local pain reactions, but had no effect on the occurrence of fever greater than 39.5°C.
- Conversely, PP significantly reduced several vaccine antibody responses independently from its effect on fever.

**Reviewer’s Critique**
- **Strengths**
  - Large sample size
  - 2 randomized controlled trials
- **Limitations**
  - Antibody response data not the primary outcome
  - Vaccine combination formulations not available in the United States (US)
  - Paracetamol suppositories used; not available in the US
  - Both studies were not blinded; control group did not receive placebo drug

**CONCLUSION**

**Reviewer’s Conclusion**
- Prophylactic administration of paracetamol at the time of vaccination may reduce the antibody response of several vaccinations.
- A need for a randomized placebo-controlled trial to analyze the effects of prophylactic acetaminophen on recommended childhood vaccinations available in the US.
VI. Conclusion

A. The older formulation of diphtheria, tetanus, and whole pertussis vaccine (DTP) along with measles, mumps, rubella (MMR) vaccine has been associated with an increased risk of febrile seizures

B. The newer formulation of diphtheria, tetanus, and acellular pertussis vaccine is not associated with an increased risk of seizures

C. Prophylactic use of acetaminophen for prevention of febrile seizures and other adverse effects has not been shown to be effective

D. Newer evidence has shown that use of prophylactic acetaminophen may actually reduce antibody response against various immunizations

E. Recommendations
   i. The use of prophylactic acetaminophen may help reduce the pain and discomfort associated with vaccinations, but will not reduce the risk of febrile seizures
   ii. Use of acetaminophen may be used on an “as needed” basis after vaccination
### Recommended Immunization Schedule for Persons Aged 0 Through 6 Years—United States • 2011

For those who fall behind or start late, see the catch-up schedule

<table>
<thead>
<tr>
<th>Vaccine ▼</th>
<th>Age ▶</th>
<th>Birth</th>
<th>1 month</th>
<th>2 months</th>
<th>4 months</th>
<th>6 months</th>
<th>12 months</th>
<th>15 months</th>
<th>18 months</th>
<th>19–23 months</th>
<th>2–3 years</th>
<th>4–6 years</th>
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<tbody>
<tr>
<td>Hepatitis B¹</td>
<td>HepB</td>
<td>HepB</td>
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<td>HepB</td>
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<tr>
<td>Rotavirus²</td>
<td></td>
<td></td>
<td>RV</td>
<td>RV</td>
<td>RV²</td>
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</tr>
<tr>
<td>Diphtheria, Tetanus, Pertussis³</td>
<td>DTaP</td>
<td>DTaP</td>
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<td>Haemophilus influenzae type b⁴</td>
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</tr>
<tr>
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<td></td>
<td>IPV</td>
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<td>Influenza (Yearly)</td>
</tr>
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<td>Measles, Mumps, Rubella⁸</td>
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<td>MMR</td>
<td>see footnote⁸</td>
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<td>Varicella⁹</td>
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<td>Varicella</td>
<td>see footnote⁹</td>
<td>Varicella</td>
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<td>Hepatitis A¹⁰</td>
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<td>HepA (2 doses)</td>
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<td>HepA Series</td>
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<td>Meningococcal¹¹</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>MCV4</td>
</tr>
</tbody>
</table>

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¹ For children born on or after 1990: 3 doses
² For children born on or after 2010: 2 doses
³ For children born on or after 2010: 2 doses
⁴ For children born on or after 2010: 3 doses
⁵ Includes PCV13 or PCV15
⁶ Includes IPV or OPV
⁷ Annual dose
⁸ MMR is recommended only once
⁹ Varicella: For children born on or after 1995
¹⁰ MMR is recommended only once
¹¹ MenACWY conjugate vaccine (MCV4): For children born on or after 2006

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Range of recommended ages for all children

Range of recommended ages for certain high-risk groups
## Appendix B

**Catch-up Immunization Schedule for Persons Aged 4 Months Through 18 Years Who Start Late or Who Are More Than 1 Month Behind—United States • 20**

The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child’s age.

### Persons Aged 4 Months Through 6 Years

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Minimum Age for Dose 1</th>
<th>Minimum Interval Between Doses</th>
<th>Dose 1 to Dose 2</th>
<th>Dose 2 to Dose 3</th>
<th>Dose 3 to Dose 4</th>
<th>Dose 4 to Dose 5</th>
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</thead>
<tbody>
<tr>
<td>Hepatitis B&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Birth</td>
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</tr>
<tr>
<td>Rotavirus&lt;sup&gt;2&lt;/sup&gt;</td>
<td>6 wks</td>
<td></td>
<td>4 weeks</td>
<td>8 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria, Tetanus, Pertussis&lt;sup&gt;3&lt;/sup&gt;</td>
<td>6 wks</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
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<td>Haemophilus influenza type b&lt;sup&gt;4&lt;/sup&gt;</td>
<td>6 wks</td>
<td></td>
<td>4 weeks</td>
<td>8 weeks&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>Pneumococcal&lt;sup&gt;5&lt;/sup&gt;</td>
<td>6 wks</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated Poliovirus&lt;sup&gt;6&lt;/sup&gt;</td>
<td>6 wks</td>
<td></td>
<td>4 weeks</td>
<td>4 weeks&lt;sup&gt;2&lt;/sup&gt;</td>
<td>6 months&lt;sup&gt;4&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Measles, Mumps, Rubella&lt;sup&gt;7&lt;/sup&gt;</td>
<td>12 mos</td>
<td></td>
<td>4 weeks</td>
<td>4 weeks&lt;sup&gt;2&lt;/sup&gt;</td>
<td>6 months&lt;sup&gt;4&lt;/sup&gt;</td>
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<tr>
<td>Varicella&lt;sup&gt;8&lt;/sup&gt;</td>
<td>12 mos</td>
<td></td>
<td>3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A&lt;sup&gt;8&lt;/sup&gt;</td>
<td>12 mos</td>
<td></td>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> Birth

<sup>2</sup> 4 weeks

<sup>3</sup> 6 months

<sup>4</sup> 8 weeks

<sup>5</sup> 8 weeks (as final dose)

<sup>6</sup> 8 weeks (as final dose)

<sup>7</sup> 12 months

<sup>8</sup> 12 months

This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months.

This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.
References