Are We Getting WHOOPed by Pertussis? 
Coughing Up the *Whole* Story

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**LEARNING OBJECTIVES**

1. Describe the characteristics of *Bordetella pertussis* infection  
2. Recognize the epidemiological trends of pertussis infection in the United States  
3. Evaluate the gaps in the current immunization program  
4. Propose a strategy to halt the current trend of pertussis infection
I. Introduction\textsuperscript{1,2}
   A. First epidemic of whooping cough described by DeBaillou in 1578
   B. Sydenham first used the term *pertussis* (intense cough) in 1670
   C. The Chinese later described the “cough of 100 days”
   D. In 1900 Bordet and Gengou isolated *Bordetella pertussis* from the sputum of an infant
   E. Current epidemiological trends suggest the once believed vaccine-preventable illness is on the rise
      i. Substantial morbidity among all ages infected and risk of death for infants

II. Etiology and Microbiology\textsuperscript{1}
   A. *B. pertussis* is a motile, aerobic small gram-negative coccobacilli
   B. Fastidious and slow-growing
      i. Special growth requirements necessary
      ii. Difficult to culture, highly affected by timing and technique
   C. Only pathogen causing epidemic pertussis and 95\% of sporadic pertussis

III. Transmission\textsuperscript{1,3}
   A. Exclusively a human pathogen with no known animal reservoir
   B. Highly contagious in susceptible individuals via inhalation of aerosol droplets
      i. High basic reproduction number (Ro): 12 to 17 secondary illnesses per case
      ii. Up to 90\% of household contacts develop a clinical case following exposure
   C. Vaccination reduces transmission even from symptomatically infected individuals

IV. Pathogenesis\textsuperscript{1,2}
   A. Infection is limited to the ciliated epithelium of the respiratory tract
      i. Attaches to ciliated cells of the respiratory system
      ii. Evades host defenses through inactivation pathways of immune response
      iii. Results in inflammation and mucous production of bronchial epithelium
   B. Few systemic symptoms because it does not disseminate in the circulation

V. Clinical Presentation\textsuperscript{1,2,4,5}
   A. Infection is divided into three separate stages distinguished by symptoms
      i. Catarrhal stage: begins 7-10 days after exposure
         1. Non-distinct symptoms of a common upper respiratory tract infection
         2. Typically lasts one to two weeks
         3. Highly contagious period
      ii. Paroxysmal stage: hallmark cough of classic pertussis
         1. Spasms of uncontrollable bursts of coughing in a single expiration
            a. Classic pertussis seen in the young and/or unimmunized
            b. Infants with “apparent life-threatening event” +/- whoop
         2. Inspiratory whoop caused by inspiration against a partially closed glottis
         3. Post-tussive vomiting of mucous plugs
      iii. Convalescent stage
         1. Gradual recovery with mean duration of cough lasting 36 to 48 days
         2. Relapse or subsequent infection not uncommon
   B. Adults and adolescents often present with only a persistent cough
      i. May express sensation of suffocation with each episode
      ii. Atypical presentation is often unrecognized
iii. ≥5 asymptomatic cases for each one symptomatic pertussis case

![Disease Progression: Pertussis](image)

**Figure 1:** Disease progression of classic pertussis.
Available at: http://www.cdc.gov/pertussis/about/signs-symptoms.html.

VI. Complications¹⁻²,⁴,⁶
A. Secondary bacterial pneumonia in up to one-quarter of infants and children
B. Death
   i. Highest (~1%) among infants who have not completed the primary vaccination series
C. Seizures and encephalopathy are rare
D. Pneumothorax, subdural hematoma, hernia possible with severe paroxysms

VII. Diagnosis¹⁻²,⁴,⁷
A. CDC pertussis case definitions
   i. Clinical (probable) case
      1. Cough lasting ≥14 days AND
      2. Paroxysmal cough, whoop, or post-tussive vomiting
   ii. Confirmed case
      1. Cough of any duration AND positive *B. pertussis* culture
      2. Clinical case AND positive PCR assay OR confirmed epidemiologic link
         a. Nasopharyngeal (NP) aspirate or posterior NP swabs preferred
         b. Culture most specific; PCR most sensitive and quicker results
         c. Serology usually positive upon onset of classic symptoms
B. Reportable to the National Notifiable Diseases Surveillance System (NNDS)

![Optimal Timing for Diagnostic Testing](image)

**Figure 2:** Diagnosis Confirmation.
Available at: http://www.cdc.gov/pertussis/clinical/diagnostic-testing/diagnosis-confirmation.html
VIII. Treatment\textsuperscript{1,2,8}
A. Macrolides early in the course of infection reduces duration, severity, and transmission (See Appendix A)
B. Antibiotics are recommended for all close contacts regardless of age and immunization status

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**Vaccines for *Bordetella pertussis* Prevention**

I. Vaccines\textsuperscript{1,2,4,9-11}
A. Simulate natural response of adaptive immunity and immune memory
   i. Exposure to a foreign antigen mounts an immune response
      1. Cell-mediated phagocytosis by macrophages
      2. Antibodies (Ab) produced by plasma cells
         a. Antibodies are imperative for vaccine-induced resistance to disease
            i. Neutralize the antigen and facilitate pathogen removal
         b. Immunologic memory allows long term protection through an accelerated response upon re-exposure to the pathogen
B. Classified by the inoculated pathogen type
   i. Live-attenuated vaccine
      1. Weakened pathogen replicates without causing significant disease
      2. High-level immune response mimics that of natural infection
      3. Ex. measles, mumps, and rubella vaccine
   ii. Inactivated vaccine
      1. Not alive, does not replicate, cannot cause disease
         a. Killed by chemical, heat, or radiation
         b. Always requires multiple doses to activate protective immunity
      2. Whole-cell
         a. Whole, inactivated pathogen containing many antigens
      3. Fractional (acellular)
         a. Purified toxins or subunits of the pathogen
         b. Ex. tetanus and diphtheria toxoid, acellular pertussis vaccine
II. Pertussis Vaccines\textsuperscript{1,2,4,11}
A. Whole-cell vaccine (wP)
   i. Developed by Drs. Pearl Kendrick and Grace Eldering in Michigan in the 1930s
      1. Recommended for use nationally by the 1940s
   ii. Combined with diphtheria and tetanus toxoid (DTwP)
   iii. Effective, however concerns about high incidence of adverse reactions
      1. Case reports of potential vaccine-associated encephalopathy, coma, and death
      2. Injection-related reactions in 20-50%
      3. Persistent crying (greater than with diphtheria and tetanus toxoid (DT) alone)
B. Acellular vaccine (aP, ap)
   i. Developed by Sato and colleagues of Japan in 1981
   ii. Replace DTwP in the 1990s
      1. Retains efficacy
         a. Reported as 85% for children and 92% for adolescents and adults
2. Decreases side effects by removing reactive antigens, such as bacterial lipopolysaccharide (LPS)
   a. Side effects similar to control, but increase with successive doses
   b. Extensive limb swelling in 3% of patients
iii. Only pertussis vaccine class currently available in the United States
   1. All are formulated with the tetanus toxoid and diphtheria vaccine (DT, Td)
   2. Also combined with inactivated polio virus and hepatitis B or Haemophilus b vaccine
iv. Individual vaccines have variable antigen types and quantities (See Appendix B)
   1. DTaP: high antigen quantity of diphtheria, tetanus toxoid, and pertussis to elicit an adequate immune response in children
      a. Toddlers and pre-school aged (1992)
      b. Primary infant series (1997)
   2. Tdap: low antigen quantity of diphtheria and pertussis
      a. Single dose for adolescents (2005), catch-up for age 7-10 (2010)
         i. Substitute for one decennial tetanus-diphtheria vaccine (Td)
      c. Infant contacts and Tdap naïve pregnant women (2011)
      d. Tdap naïve adults age >65 (2012)

III. Pertussis Vaccination Schedule for Children, Adolescents, and Adults\textsuperscript{12,13}

<table>
<thead>
<tr>
<th></th>
<th>2 mo</th>
<th>4 mo</th>
<th>6 mo</th>
<th>15-18 mo</th>
<th>4-6 yr</th>
<th>7-10 yr</th>
<th>11-12 yr</th>
<th>13-18 yr</th>
<th>&gt;19 yr</th>
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<tbody>
<tr>
<td>DTaP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tdap</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X\textsuperscript{a}</td>
<td>X\textsuperscript{b}</td>
<td>X\textsuperscript{c}</td>
<td>X\textsuperscript{d}</td>
<td></td>
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<tr>
<td>Td</td>
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</tbody>
</table>

\textsuperscript{a}Not fully vaccinated against pertussis; \textsuperscript{b}No record of Tdap; \textsuperscript{c}Single dose in Tdap naïve; \textsuperscript{d}Td booster every 10 years

Epidemiology and Current Trends of Pertussis

I. Epidemiology\textsuperscript{1,2,11,14-22}
   a. The pre-vaccination era
      i. Major childhood illness and leading cause of death from communicable disease
         1. Primarily affected children age 1 to 10
         2. Peaks of 260,00 cases in 1934 and 9,000 deaths in 1923
         3. More deaths than measles, scarlet fever, diphtheria, poliomyelitis, and meningitis combined
      ii. Cyclical peaks in pertussis cases every 3 to 5 years
   b. The vaccination era
      i. Dramatic decrease in cases after whole-cell pertussis vaccine introduced
         1. Incidence declined from 150/100,000 to <1/100,000 by the 1980s
         2. Nadir of 1010 cases and 7 deaths in 1976
      ii. Gradual increased incidence over the past 20 years
         1. Peaks still occur every 3 to 5 years
iii. Annual reported cases of pertussis

![Figure 3: Annual reported cases of pertussis in the United States, 1922-2010. Adapted from Clark et al. Trends Microbiol. 2012.](image)

iv. Increased incidence in adolescents and adults by the 2000s
   1. 34% of cases in 2004 were in adolescents 11 to 18 years old
      a. The Tdap vaccination recommended in 2005 resulted in a 50% decrease in cases by 2009

v. Adults and adolescents recognized as reservoirs for transmission to infants
   1. Seldom diagnosed, but up to one-third of patients experiencing a prolonged cough is believed to be pertussis
   2. U.S. incidence estimated between 800,000 and 3.3 million cases yearly

vi. Majority of cases in unimmunized infants <2 months
   1. Highest risk for complications, hospitalization, and death
      a. Deaths have dramatically increased over the past three decades
         i. 1980-89: 38
         ii. 1990-99: 68
         iii. 2000-09: 152

c. Comparison to other vaccine preventable diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Annual Average Pre-vaccine Cases</th>
<th>2010 Cases</th>
<th>Decrease (%)</th>
<th>Coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertussis</td>
<td>200,752</td>
<td>27,550</td>
<td>86.3</td>
<td>84.6</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>21,053</td>
<td>0</td>
<td>100</td>
<td>84.6</td>
</tr>
<tr>
<td>Tetanus</td>
<td>580</td>
<td>26</td>
<td>95.6</td>
<td>84.6</td>
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<td>Measles</td>
<td>530,217</td>
<td>23</td>
<td>99.9</td>
<td>91.6</td>
</tr>
<tr>
<td>Mumps</td>
<td>162,344</td>
<td>2,612</td>
<td>98.4</td>
<td>91.6</td>
</tr>
<tr>
<td>Rubella</td>
<td>47,745</td>
<td>0</td>
<td>100</td>
<td>91.6</td>
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<tr>
<td>Polio (paralytic)</td>
<td>16,316</td>
<td>0</td>
<td>100</td>
<td>93.9</td>
</tr>
<tr>
<td>Smallpox</td>
<td>29,005</td>
<td>0</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type b and unknown (&lt;5yr)</td>
<td>20,000</td>
<td>246</td>
<td>98.7</td>
<td>94</td>
</tr>
</tbody>
</table>

*Table 2: 20th century annual morbidity and 2010 cases of vaccine preventable diseases. Adapted from Centers for Disease Control and Prevention. Summary of Notifiable Diseases-United States, 2010 and National, State, and Local Area Vaccination Coverage Among Children Aged 19-35 months-United States, 2011.*
d. Pertussis outbreaks in the United States
   i. Endemic pertussis with frequent outbreaks
   ii. California, 2010
      1. 9,156 cases (23.4/100,000), highest incidence in 52 years
         a. Ten deaths reported, all in infants
   iii. Washington, 2012
      1. 4,272 reported cases (63.5/100,000) by 10/20/12, highest incidence since 1942, and
         an 850% increase from 2011
         a. Incidence highest in infants <1 year and children aged 10, 13, 14

![Figure 4](image)

**Figure 4:** Number and incidence of confirmed and probable pertussis cases among persons aged ≤19 years, by patient age and vaccines received—Washington, January 1-June 16, 2012. Adapted from MMWR Morb Mortal Wkly Rep. 2012;61(28):517-22.19

iv. 41 states with >2-fold increase in pertussis cases compared to 2011
   1. Age-specific incidence mirrors that of Washington
   2. 36,078 cases as of November 17, 2012
   3. 12 states with incidence greater than 20/100,000

v. Texas, 2012
   1. 1,653 cases as of November 17, 2012 (128% increase compared to 2011)
   2. 6 of the 16 nationwide pertussis deaths in 2012 from Texas

e. Epidemics among countries using acellular pertussis vaccine
   i. United Kingdom
      1. 6,121 cases as of October 1, 2012 (7 times more than 2008 peak)
   ii. Australia
      1. Infection rate as high as 1:550 in 2011 (182/100,000)
      2. Incidence almost identical to 1953 when the vaccination was introduced
Identifying Reasons for Increased Pertussis Incidence

I. Vaccination Rates
   a. 12 to 17 secondary cases from one case introduced into susceptible population
      i. Goal of vaccination is Ro < 1 to halt transmission
      ii. Theoretical vaccination rate required to halt transmission is 1-(1/Ro)
         1. 92% to 95% of population must be protected to develop herd immunity
         2. Assumes vaccine is effective
   b. Population pertussis vaccination rates in the United States
      i. Children aged 19 to 35 months (2011)
         1. ≥3 doses: 95.5%
         2. ≥4 doses: 84.6%
         3. Bexar County: 90.2% and 77% respectively
      ii. Adolescents aged 13 to 17 years (2011)
         1. ≥1 Tdap on or after age 10: 78.2%
            a. Significant increase from 2010 (68.7%)
         2. Bexar County: 85.2%
      iii. Adults ≥19 years (2010)
         1. Td or Tdap previous 10 years: 64.0% (19-49 yr); 63.4% (50-64 yr); 53.4% (≥65 yr)
         2. Tdap among adults with tetanus vaccine in the previous 10 years: 8.2%

II. Increased Awareness
   a. Media attention on vaccine safety after reports of substantial side effects
      i. Increased public awareness and reporting of pertussis symptoms
   b. Physicians becoming more aware of atypical presentation in adolescents and adults

III. B. pertussis PCR Confirmation
   a. Less time sensitive to symptom presentation
   b. Faster confirmation compared to culture
   c. Increased sensitivity
      i. PCR is 70-99% sensitive vs. 12-60% for culture

IV. Waning Immunity of Pertussis Vaccination
   a. Acellular pertussis vaccine has previously been reported as efficacious
      i. However, limited durability led to Tdap booster recommendations
   b. Recent outbreaks suggest a large number of vaccinated children are being infected
      i. Three studies identify a gap in the immunization schedule where children inadequately protected
   c. Witt et al
      i. San Rafael Kaiser Permanente Medical Center, 2010
         1. Any patient age 0-18 years of age with cough ≥1 week underwent PCR analysis
         ii. No difference in attack rates among 2-7 and 8-12 year olds whether vaccinated or un/undervaccinated
            1. Significantly lower rates in children aged <8 and >12 years vs. children aged 8-12 years
            2. 55/58 (95%) of pertussis cases in children aged 10-12 years had received ≥5 doses of vaccination
         iii. Vaccine effectiveness of 41%, 24%, and 79% for patients 2-7 years, 8-12 years, and 13-18 years respectively
         iv. Vaccine is effective, but a hole in coverage exists after the 5th dose
d. Winter et al. All pertussis cases reported to California Department of Public Health, 2010
   1. Probable and confirmed cases using CDC definitions
   2. 9,156 pertussis cases in 2010
      1. Incidence highest among infants <6 months
      2. 10 deaths reported, all infants ≤2 months
      3. High disease rate in 7-10 year olds
         a. 79% had received 5 doses of DTaP
            i. 5th dose most often administered around 4 years of age
         b. Step-wise increase incidence from age 7-10; step-wise decreased incidence ages 11-14
            i. Suggests immunity after 5th dose may wane prior to booster at age 11-12
         ii. Disease incidence decreases as Tdap coverage increases


<table>
<thead>
<tr>
<th>Purpose</th>
<th>• To assess risk of pertussis in children relative to the time since 5th DTaP dose</th>
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<tbody>
<tr>
<td>Design</td>
<td>• Multicenter, case-control study</td>
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<td></td>
<td>• Kaiser Permanente health system, California</td>
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<tr>
<td>Population</td>
<td>• Inclusion: received a pertussis PCR test between 1/2006 and 6/2011</td>
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<td>• Exclusion: born before 1999; received Tdap or any pertussis-containing vaccine after 5th DTaP dose, but before PCR test; PCR test within 2 weeks after 5th DTaP dose; previous pertussis</td>
</tr>
<tr>
<td>Cohorts</td>
<td>• Cases: children PCR-positive for <em>B. pertussis</em> and negative for <em>B. parapertussis</em> who received 5th DTaP dose between age 47 and 84 months and before PCR</td>
</tr>
<tr>
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<td>• PCR-negative controls: children PCR-negative for <em>B. pertussis</em> and <em>B. parapertussis</em> who received 5th DTaP dose before PCR</td>
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<td>• Matched controls: PCR-negative children of the same sex and age, same race or ethnic group, and attended same clinic as PCR-positive cases</td>
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<tr>
<td>Analysis</td>
<td>• Primary analysis: PCR-positive cases vs. PCR-negative controls</td>
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<td>• Secondary analysis: PCR-positive cases vs. matched controls</td>
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<tr>
<td>Results</td>
<td>• Overall Incidence:</td>
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<td>o 27,912 PCR assays performed regardless of age</td>
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<td></td>
<td>▪ 1,512 (5.4%) positive for <em>B. pertussis</em></td>
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<tr>
<td></td>
<td>▪ 95% cases occurred from January 2010 to June 2011</td>
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<tr>
<td></td>
<td>• Age &lt;1 year: 115 cases per 100,000 person-years</td>
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<td></td>
<td>• Age 5: 29 cases per 100,000 person-years</td>
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<td></td>
<td>• Age 10-11 years: 226 cases per 100,000 person-years</td>
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<td></td>
<td>• Age &gt;12 years: sharp decrease in case incidence</td>
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<tr>
<td></td>
<td>• Study Population:</td>
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<td></td>
<td>o Children aged 4-12</td>
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<td></td>
<td>▪ 58% continuously enrolled in health plan from age 1 month to date of PCR or seventh birthday</td>
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<td></td>
<td>• 99% vaccine coverage with 5 DTaP doses</td>
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<td>▪ 277 children PCR-positive for <em>B. pertussis</em></td>
</tr>
<tr>
<td></td>
<td>▪ 3,318 PCR-negative controls</td>
</tr>
<tr>
<td></td>
<td>▪ 6,086 matched controls</td>
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</tbody>
</table>
Waning Effectiveness:
- Time since 5th DTaP dose significantly longer for PCR-positive cases
  - PCR-positive cases 1699 days (CI 1627-1772) vs. PCR-negative cases 1028 days (CI 1003-1053); p<0.001
- Odds ratio for pertussis after 5th dose=1.42 per year (CI 1.21-1.61)

Authors’ Conclusions
- Risk of pertussis increased by 42% each year after 5th DTaP dose
- Pertussis incidence highest in children aged 8 to 11 years who had received the full five-dose DTaP series
- DTaP protection may be less enduring than DTwP protection
- Sharp drop in pertussis cases as percentage of children who received all 5 childhood doses as DTaP decreased

Strengths
- Integrated healthcare system with centralized laboratory confirmation and precise vaccine history
- Older age associated with increasing proportion of positive PCR

Weaknesses
- CDC definition for case determination using symptoms not used
- Cases were only confirmed by PCR assays
- No unvaccinated population to allow absolute vaccine efficacy calculation

Take Home Points
- Children aged 8 to 11 years are largely unprotected and serve as a reservoir for *B. pertussis* infection
- The transition from DTwP to DTaP appears to be associated with an increased incidence of pertussis among children who received only DTaP

Comparing Acellular vs. Whole-Cell Pertussis Vaccine

I. Transition from Whole-Cell to Acellular Pertussis Vaccine
   a. Sheridan et al\(^ {32} \)
      i. Queensland, Australia
         1. Sustained epidemic with highest incidence in children aged 6 to 11 years
      ii. DTaP available in 1996 and replaced public funded primary series in March 1999
      iii. Compared pertussis reporting rates by primary vaccination in 1998 birth cohort
         1. DTwP only, DTaP only, or mixed schedule
      iv. 58,223 children born in 1998 identified in the Queensland Vaccination Register
         1. 40,694 (70%) with ≥3 doses of pertussis-containing vaccine during first year
         2. 267 pertussis cases reported between 1999 and 2011
               i. Single vaccine primary course
                  1. Greater pertussis risk with DTaP compared to DTwP (RR 2.53; CI 1.06-6.07)
            b. Outbreak (2009-2011): 242 cases
               i. Single vaccine primary course
                  1. Greater pertussis risk with DTaP compared to DTwP (RR 3.29; CI 2.44-4.46)
               ii. Mixed vaccine primary course
                  1. Greater pertussis risk with mixed course compared to DTwP
                     a. DTaP primed (RR 3.61; CI 1.79-6.67)
                     b. DTwP primed (RR 1.78; CI 1.20-2.63)
II. Vaccine Efficacy Trials of the 1990s

a. Occurred in four countries without a pertussis vaccination schedule
   i. Various antigenic DTaP vaccines evaluated against DTwP
b. World Health Organization (WHO) case definition (1991) for efficacy trials
   i. Paroxysmal cough lasting ≥21 days AND
   ii. Confirmation by culture, serology (significant rise in Ab), or household contact with confirmed case within 28 days before or after onset of illness
c. Stehr et al

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Purpose</td>
<td>• Assess the absolute vaccine efficacy of DTaP vs. DTwP</td>
</tr>
<tr>
<td>Design</td>
<td>• Double-blind, multicenter randomized study (Germany) plus open study arm (DT)</td>
</tr>
<tr>
<td>Population</td>
<td>• Inclusion: healthy infants aged 2 to 4 months enrolled between 5/1991 and 1/1993</td>
</tr>
</tbody>
</table>
| Methods | • Interventions: vs. DT
   - Blinded arm: DTaP [4 component] vs. DTwP
     - 4 doses: 2-4 mo, 2nd and 3rd dose >6 wk after the prior dose, and 15-18 months of age
   - Open study arm: DT
     - 3 doses: 2-4 mo, 2nd >6 wk later, and 15-18 months of age
- Definitions:
  - Typical pertussis: cough ≥21 days + paroxysms, whoop, or post-tussive vomiting (PWV) + culture, serology (significant increase in IgA or IgG to pertussis toxin), or epidemiological link
  - Mild and typical pertussis: cough ≥7 days with or without PWV + same confirmation criteria
- Surveillance:
  - Illness: parent-driven reporting of all cough illnesses by any family member; monitored biweekly by phone; MD visited all persons with any cough ≥7 days to obtain culture and blood sample; blinded central investigator visited any person with a cough illness ≥14 days to make a diagnosis
  - Adverse events: parents kept a reaction diary for 3 days after each dose; long-term follow-up monitored by telephone every 2 weeks |
| Analysis | • Cases included for vaccine efficacy starting 2 weeks after third dose |
| Results | • Study Population:
  - DTaP (n=4025), DTwP (n=3957), DT (n=1615)
  - Mean follow-up: DTaP (2.13 yr), DTwP (2.13 yr), DT (1.81 yr)
- Incidence:
  - 238 total cases with cough ≥7 days in which *B. pertussis* identified
    - 154 cases met typical pertussis case definition |
| Absolute Vaccine Efficacy (%) of DTaP and DTwP |
| | DTaP | DTwP |
| Typical Pertussis | 83 (CI 76-88) | 93 (CI 89-96) |
| Mild and Typical Pertussis | 72 (CI 62-79) | 83 (CI 76-88) |
Illness:
- Mean duration of cough
  - DTaP (33 days) vs. DTwP (32 days) vs. DT (47 days)
- Cases with paroxysms, whoop, or post-tussive vomiting
  - DTaP (62%) vs. DTwP (46%) vs. DT (92%)

Adverse Events:
- Discontinued due to adverse events
  - DTwP (2.2%) vs. DTaP (0.8%) vs. DT (0.2%)
- Local reactions more common after all doses of DTwP
  - Erythema and induration
- Minor systemic events more common after all doses of DTwP
  - Fever, fussiness, drowsiness, and anorexia
- Severe adverse events rare

### Absolute Vaccine Efficacy (%) of DTaP and DTwP After 3 and 4 Doses

<table>
<thead>
<tr>
<th></th>
<th>3 Doses</th>
<th>4 Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTaP</td>
<td>DTwP</td>
</tr>
<tr>
<td>Typical Pertussis</td>
<td>78 (CI 60-88)</td>
<td>93 (CI 83-97)</td>
</tr>
<tr>
<td>Mild and Typical Pertussis</td>
<td>62 (CI 38-77)</td>
<td>78 (CI 62-88)</td>
</tr>
</tbody>
</table>

Authors’ Conclusions
- DTwP has significantly greater efficacy than DTaP against typical pertussis
- DTwP established protective immunity quicker than DTaP
- Vaccination altered the course of disease in children with vaccine failure
- Most precise estimate of efficacy is determined by any cough regardless of duration

Strengths
- Suspected cases all followed by 3 blinded central investigators following a protocol
- Evaluation of mild and typical cases is more sensitive for pertussis cases
- Four dose vaccine regimen used

Weaknesses
- Blinding of central investigator occasionally broken inadvertently by the parent
- Unblinded DT group

Take Home Points
- DTwP significantly more effective than DTaP against typical pertussis
- Vaccine failures have a mitigated disease course as compared to DT
- Minor reactions and discontinuation occurred more frequently with DTwP

e. Summary of other absolute vaccine efficacy trials
### Absolute Vaccine Efficacy Trials: DTaP vs. DTwP

<table>
<thead>
<tr>
<th>1st Author Year Location</th>
<th>Design</th>
<th>Vaccines</th>
<th>Absolute Vaccine Efficacy (%)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Simondon 1997 Senegal    | DB, RCT Household contact | • DTaP [2 component]  
• DTwP (3 doses: 2, 4, 6 mo) | Mild Pertussis: 31  
Typical Pertussis: 74 | • Age-specific rate-ratio indicates waning immunity with DTaP  
• Small sample size of unvaccinated group |
| Schmitt 1996 Germany     | Household contact | • DTaP [3 component]  
• DTwP (3 doses: 3, 4, 5 mo) | Mild Pertussis: 88  
Typical Pertussis: 89 | • Only 75 evaluable contacts in the DTwP arm resulting in one case of pertussis  
• Significantly more index cases in the DTwP arm vs. DTaP arm were treated with erythromycin |
| Liese 1997 Germany       | Case control analysis with prospective observational study | • DTaP [2 component]  
• DTwP (3 doses: 2, 4, 6 mo) | Mild Pertussis: 80  
Typical Pertussis: 93 | • Vaccine used based on parent or guardian choice  
• DTwP efficacy did not differ appreciably based on the presence of paroxysms |
| Greco 1996 Italy         | DB, prospective cohort | • DTaP [3 component]  
• DTaP [5 component]  
• DTwP (3 doses: 2, 4, 6 mo) | Mild Pertussis: 79  
Typical Pertussis: 84 | • Level of protection from DTwP was much lower than anticipated  
Although serologic responses have not been shown to correlate with protection, DTwP produced minimal response compared to previous data |
| Gustafsson 1996 Sweden   | DB, prospective cohort | • DTaP [2 component]  
• DTaP [5 component]  
• DTwP (3 doses: 2, 4, 6 mo) | Mild Pertussis: 42  
Typical Pertussis: 59 | • Efficacy of DTwP was much lower than expected, as was found in Greco et al  
• DTaP [5 component] efficacy against typical pertussis was sustained over 2 years, while DTwP declined sharply |

### Relative Vaccine Efficacy Trials: DTaP vs. DTwP

<table>
<thead>
<tr>
<th>1st Author Year Location</th>
<th>Design</th>
<th>Vaccines</th>
<th>Relative Risk</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Olin 1997 Sweden         | DB, RCT | • DTaP [2 component]  
• DTaP [3 component]  
• DTaP [5 component]  
• DTwP (3 doses: 3, 5, 12 mo) | Mild Pertussis: --  
Typical Pertussis: -- | • DTaP [2 component] unblinded due to poor efficacy  
• DTaP [5 component] and DTwP had similar efficacy  
• Each more effective than DTaP [3 component] |

Table 3: DTaP vs. DTwP Vaccine Efficacy Trials

Mild pertussis: confirmed *B. pertussis* with cough ≥ 21 days; Typical pertussis: confirmed *B. pertussis* with paroxysmal cough ≥ 21 days  

*aDTwP Connaught vaccine;  
*confirmed B. pertussis with cough ≥ 1 day;  
*confirmed B. pertussis with or without cough;  
DB=double blinded; RCT=randomized control trial
f. Vaccine efficacy is variable depending on study design, surveillance, case definition, and specific vaccine used
   i. High-efficacy DTwP had more protective efficacy than most DTaP vaccines and similar efficacy to five-component DTaP
   ii. One lot of the Connaught DTwP vaccine had surprisingly poor protective efficacy
      1. This vaccine enjoyed widespread use in the United States at the time
   iii. Observer bias is a confounding factor of all efficacy trials
      1. No perfect case definition that is sensitive and specific
      2. Inflated efficacy likely seen with vaccines that decrease symptoms of disease, but do not prevent illness

V. Reactogenicity\textsuperscript{1,27,33}
   a. National Childhood Encephalopathy Study (NCES)
      i. Evaluated the relationship between DTwP and neurologic injury
         1. Risk of encephalopathy 1 in 140,000 vaccinations
         2. Artifact due to inclusion of nine children with febrile convulsions
   b. U.S. Institute of Medicine
      i. No evidence to support pertussis vaccine causing permanent neurological damage
   c. Canadian Immunization Monitoring Program, Active (IMPACT) Surveillance Network
      i. No evidence of encephalopathy after >6.5 million doses of DTwP
      ii. No such entity as “pertussis vaccine encephalopathy”
   d. Cochrane Review, 2011
      i. Review of 52 safety trials
      ii. No cases of encephalopathy were observed in 81,601 acellular and 32,161 whole-cell vaccine recipients
      iii. No difference in risk of death between acellular and whole-cell vaccine
      iv. Acellular vaccine less likely to cause febrile convulsions and hypotonic-hyporesponsive episodes during the primary series
         1. No cases of hypotonic-hyporesponsive episodes observed after any booster dose
   e. Acellular vaccine is superior to whole-cell vaccine with regard to selected minor reactions

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>% Infants with Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTaP</td>
</tr>
<tr>
<td>Redness</td>
<td>34.7</td>
</tr>
<tr>
<td>Swelling</td>
<td>24.3</td>
</tr>
<tr>
<td>Pain\textsuperscript{a}</td>
<td>6.9</td>
</tr>
<tr>
<td>Fussiness\textsuperscript{b}</td>
<td>17.1</td>
</tr>
<tr>
<td>Use of Antipyretic</td>
<td>55.9</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>42.7</td>
</tr>
<tr>
<td>Anorexia</td>
<td>21.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12.6</td>
</tr>
</tbody>
</table>

\textbf{Table 4}: Percent of infants with reported reaction within three days after the three-dose primary series pertussis vaccination. Adapted from Decker et al. Pediatrics. 1995.\textsuperscript{42}

\textsuperscript{a}Protested to touch or cried when leg moved; \textsuperscript{b}Prolonged crying with refusal to play or persistent, inconsolable crying

i. Whole-cell priming and acellular vaccine boosting
   1. Fewer minor adverse events than a full whole-cell or acellular vaccine series
VI. Whole-Cell Pertussis Vaccine-Induced Immunity

a. Search for a correlate of immunity
   i. Unlike other vaccine-preventable diseases, no correlation between specific Ab titers and protection against pertussis infection is understood
      1. Circulating Ab may not reflect what is happening the local mucosal surface in the lung, and may not be the sole determinant of disease protection

b. Natural *Bordetella pertussis* infection
   i. Selectively primes a cell-mediated response directed by phagocytic cells
      1. Important for bacterial clearance following primary infection

c. Murine model
   i. T-cell response affected by vaccination type
      1. wP selectively primes a cell-mediated response pathway
      2. aP induces Ab production
   ii. Short-term protective immunity
      1. Complete bacteria clearance occurs within 5-7 days in wP immunized mice
      2. Does not occur for >14 days in aP immunized mice
   iii. Long-term protective immunity
      1. Circulating Ab undetectable 9 months after immunization, yet memory T- and B-cell response present
      2. Superior protection of wP suggests that cell-mediated immunity accounts for long-term immunity against pertussis

d. Human model
   i. aP primed children had an Ab response similar to the murine model
      1. aP booster significantly enhanced this response
   ii. wP immunization selectively primed cell-mediated response in infants who are intrinsically defective for this response
      1. Similar response as natural infection

e. Components of wP (ex. LPS) responsible for reactogenicity, also likely contribute to vaccine efficacy

f. Data suggest cytokine secretion may be formulated by the first pertussis vaccines received
   i. Linked epitope suppression may “lock in” future immune response
   ii. First 6 months of life is key for initiation of this polarization

VII. Emerging Strains of *Bordetella pertussis*

a. Increased selection for *B. pertussis* strains with antigens not in DTaP
   i. Isolates collected in prolonged Australian epidemic
      1. Significant increase since 2008 compared to isolates from 2000-2007
   ii. Same mutations identified in Chinese and European epidemics

b. However, not see in Denmark where single component DTaP has been used for years

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**Strategies: Where Do We Go From Here?**

I. Historical Perspective

a. Despite the current trend, the national incidence is ~1/23 the incidence of the 1940-50s
   i. However, the pertussis vaccination program is losing ground

II. Improving the Pertussis Vaccine

a. Whole-cell vaccine
   i. Historical evidence of effectiveness in the pediatric population
      1. No experience with adolescents and adults
ii. Warnings of permanent neurological disorders have been debunked
   1. Mild adverse events significantly more common
   2. Major contributor of side effects is believed to be LPS

iii. Future development of a whole-cell pertussis vaccine that retains effectiveness, but has less minor reactions

b. Acellular Vaccine
   i. Evidence of waning immunity and increased pertussis outbreaks
   ii. Only a five-component vaccine demonstrated similar efficacy to DTwP
   iii. Future development of an acellular pertussis vaccine
      1. Increase number of antigens to simulate natural infection
      2. Genetically purified LPS

c. Challenges
   i. Regulatory pathway to licensure is a substantial hurdle
   ii. All countries now vaccinate against pertussis, so it is not feasible to conduct a traditional efficacy trial
   iii. Antibody responses of new vaccines must therefore be bridged to previous vaccines
      1. Even though no direct correlation between Ab and immunity has been identified

III. Optimize the DTaP schedule

a. Goal to eradicate the circulation of *B. pertussis*
   i. Immunization program must include all ages to eliminate the reservoir

b. Infants
   i. Aggressive primary series prevents more than 95% of all illness
   ii. Unvaccinated and under-vaccinated infants remain vulnerable
      1. Tdap now recommended for pregnant women and infant contacts
      2. Immunization of newborns at birth
         a. Initial studies show Ab titers similar between 0, 1, 2 month and conventional 2, 4, 6 month regimens, with good tolerability
   iii. Whole-cell priming, followed by DTaP boosters

c. Children
   i. Current trends identify a “hole” in coverage between age 7 and 11
      1. Serves as a reservoir for transmitting infection to infants
   ii. Optimize the vaccination schedule to eliminate the gap
      1. Delay the 5th dose or move up the Tdap dose
      2. Add an extra dose to cover this age group
         a. Tdap now recommended for catch-up in 7 to 10 year olds
         b. No other immunizations in the schedule administered at this age
   iii. Whole-cell priming, followed by DTaP boosters

d. Adolescents
   i. Tdap dose in 11-12 year olds has substantially decreased cases in adolescents
   ii. May see waning immunity as whole-cell primed adolescents diminish

e. Adults
   i. Physicians are becoming more aware of atypical pertussis in adults
   ii. The public is largely unaware of the significance of pertussis in adults and the need to vaccinate
      1. One-time Tdap dose now recommended for all adults
      2. High risk individuals: pregnant mothers, infant contacts, healthcare workers, elderly
   iii. Due to vaccine efficacy and waning immunity, lifetime protection likely warranted
      1. Tdap booster has proven to be immunogenic in adults 10 yr after prior dose
2. One simulation suggests decennial vaccine is cost-effective using current adult incidence
   a. Cost-effectiveness ratios < $50,000 per quality-adjusted life year saved
3. Evaluation of adult pertussis cases yielded substantial direct and indirect costs
   a. Mean direct medical costs of $326
   b. Mean nonmedical costs of $447
   c. 61% of adults missed a mean of 9.8 days from work
      i. Residual cough 94 days after cough onset
iv. Low vaccination rates remain a hindrance of effectively decreasing the reservoir

IV. Increase Vaccination Rates
   a. Pediatric and school-based immunization programs have aggressively targeted children and adolescents
      i. Healthy People 2010 goal for 90% of children immunized with four doses DTaP
      ii. State mandates have steadily increased Tdap coverage in adolescents
   b. No broad scale strategy in place to provide Tdap to adults
      i. Each exposure of an adult to a healthcare provider is an opportunity to assess vaccination status
      ii. Awareness campaigns needed for practitioners and the public
      iii. Reminder-recall systems
      iv. Work-related immunization programs

Summary

I. Bordetella pertussis in 2012
   a. Steady increasing trend in pertussis cases has highlighted the inadequacy of the current vaccination program
   b. Waning immunity of acellular pertussis vaccines has left preadolescents vulnerable to disease and reservoirs for transmission
   c. Limited duration does not imply limited impact, as children are largely protected from severe disease and death
   d. Research should focus on the improving the efficacy of the pertussis vaccine, to include the exploration of a modified whole-cell vaccine
   e. Reducing the burden of disease requires the promotion to a highly vaccinated population
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   vaccinated (primed) and unvaccinated (unprimed) young children with pertussis. Clin Vaccine Immunol. 
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### Appendices

#### Appendix A

**Recommended Treatment and Post-Exposure Prophylaxis for Pertussis**

<table>
<thead>
<tr>
<th>Age ≤1 mo</th>
<th>Age 1-5 mo</th>
<th>Children ≥6 mo</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td><strong>Azithromycin</strong></td>
<td><strong>Azithromycin</strong></td>
<td><strong>Azithromycin</strong></td>
</tr>
<tr>
<td>10mg/kg/d PO x 5 days</td>
<td>10mg/kg/d PO x 5 days</td>
<td>10mg/kg/d PO on day 1; 5mg/kg/d PO days 2-5 (Max 500mg on day 1)</td>
<td>500mg PO on day 1; 250mg PO on days 2-5</td>
</tr>
<tr>
<td>Erythromycin 40-50mg/kg in 4 divided doses PO x 14 days</td>
<td>Erythromycin 40-50mg/kg in 4 divided doses PO x 14 days</td>
<td>Erythromycin 2g/d in 4 divided doses x 14 days</td>
<td>Erythromycin 2g/d in 4 divided doses x 7 days</td>
</tr>
<tr>
<td>Clarithromycin 15mg/kg in 2 divided doses PO x 7 days</td>
<td>Clarithromycin 15mg/kg in 2 divided doses PO x 7 days</td>
<td>Clarithromycin 15mg/kg/d in 2 divided doses PO x 7 days (Max 1g per day)</td>
<td>Clarithromycin 1g/d in 2 divided doses x 7 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Alternate</strong></th>
<th><strong>TMP-SMX</strong></th>
<th><strong>TMP-SMX</strong></th>
<th><strong>TMP-SMX</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>8mg/kg/d (TMP) in 2 divided doses PO x 14 days</td>
<td>8mg/kg/d (TMP) in 2 divided doses PO x 14 days</td>
<td>320mg (TMP) in 2 divided doses PO x 14 days</td>
<td></td>
</tr>
<tr>
<td><em>Infants ≥2 mo</em></td>
<td>(Max 2g per day)</td>
<td>(Max 2g per day)</td>
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</tbody>
</table>

Adapted from MMWR 2005;54(RR 14):1-16.

#### Appendix B

**Acellular Pertussis Vaccines Available in the United States (0.5 mL dose)**

<table>
<thead>
<tr>
<th>DTaP</th>
<th>Tdap</th>
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<tbody>
<tr>
<td><strong>Tripedia®</strong></td>
<td><strong>Adacel™</strong></td>
</tr>
<tr>
<td><strong>Daptacel®</strong></td>
<td><strong>Boostrix®</strong></td>
</tr>
<tr>
<td><strong>Infranrix®</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Pentacel®</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Kinrix®</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Pediarix®</strong></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Age</strong></th>
<th><strong>Tripedia®</strong></th>
<th><strong>Daptacel®</strong></th>
<th><strong>Infranrix®</strong></th>
<th><strong>Pentacel®</strong></th>
<th><strong>Kinrix®</strong></th>
<th><strong>Pediarix®</strong></th>
<th><strong>Adacel™</strong></th>
<th><strong>Boostrix®</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Dose(s)</strong></td>
<td>6 wk-7 yr</td>
<td>6 wk-7 yr</td>
<td>6 wk-7 yr</td>
<td>6 wk-5 yr</td>
<td>4 yr-6 yr</td>
<td>6 wk-7 yr</td>
<td>11-64 yr</td>
<td>&gt;10 yr</td>
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<tr>
<td><strong>PT (µg)</strong></td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
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<tr>
<td><strong>FHA (µg)</strong></td>
<td>23.4</td>
<td>10</td>
<td>25</td>
<td>20</td>
<td>25</td>
<td>25</td>
<td>2.5</td>
<td>8</td>
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<tr>
<td><strong>PRN (µg)</strong></td>
<td>23.4</td>
<td>5</td>
<td>25</td>
<td>20</td>
<td>25</td>
<td>25</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td><strong>FIM 2/3 (µg)</strong></td>
<td>3</td>
<td>8</td>
<td>3</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>3</td>
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<tr>
<td><strong>D (Lf)</strong></td>
<td>6.7</td>
<td>15</td>
<td>25</td>
<td>15</td>
<td>25</td>
<td>25</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>T (Lf)</strong></td>
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<td>5</td>
<td>10</td>
<td>10</td>
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<tr>
<td><strong>Addition</strong></td>
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<td>IPV</td>
<td>IPV</td>
<td>HBV, IPV</td>
<td></td>
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</tbody>
</table>

Adapted from Long et al. *Principles and Practice of Pediatric Infectious Diseases*, 4th Ed. 2012.

FHA: filamentous hemagglutinin; FIM 2/3: types 2 and 3 fimbriae; HBV: hepatitis B vaccine; Hib: *Haemophilus b* vaccine; IPV: inactivated polio virus vaccine; LF: flocculation unit; PRN: pertactin; PT: pertussis toxin.